Pharmaceutical Research, Vol. 25, No. 11, November 2008 (© 2008)
DOI: 10.1007/s11095-008-9675-3

Research Paper

Manipulation of Corticosteroid Release from a Transiently Supersaturated Topical Metered Dose Aerosol Using A Residual Miscible Co-Solvent

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Received May 8, 2008; accepted June 19, 2008; published online July 31, 2008

Purpose. The creation of supersaturation transiently after application overcomes the issue of drug instability. However, if the solvents used to drive supersaturation evaporate too quickly, drug recrystallisation or rapid film drying can occur which will inhibit drug release. As such the effects of a residual solvent, poly(ethylene glycol) 400 (PEG), on the release, mobility and supersaturation kinetics of a transiently supersaturated formulation were studied.
Materials and Methods. Metered dose aerosol (MDA) formulations consisting of hydrofluoroalkane 134a, ethanol, poly(vinyl pyrrolidone) K90, beclomethasone dipropionate (BDP), and 0%, 5% or 10% *w/w* PEG were prepared in canisters sealed with metered dose valves and tested for release and adhesion over time.
Results. The addition of 10% PEG to the MDA formulation resulted in a significant reduction ($p < 0.05$) in steady state drug release rate (230.4 ± 17.3 μg/cm^2/h for 0% PEG MDA, 83.6 ± 4.9 μg/cm^2/h for 10% PEG MDA). The presence of PEG caused a delay in dose depletion (2 h for 0% PEG MDA versus 4 h for 10% PEG), retarded supersaturation kinetics and increased film drying time.
Conclusion. Whilst equivalent amounts of BDP were released, the residual solvent altered the drug release profile to achieve more constant delivery.

KEY WORDS: aerosol; beclomethasone dipropionate; corticosteroids; diffusion; *in vitro* models; percutaneous drug delivery; solubility; supersaturation.

INTRODUCTION

Designing a dosage form that efficiently delivers a drug into the skin is not trivial as the outermost layer of this topical surface, the s*tratum corneum* (SC) is a highly effective barrier (1). The problems of penetrating the SC are exacerbated by the fact that many conventional topical formulations such as creams and ointments do not allow effective drug release, and as a consequence a high percentage of the drug administered to the topical site can remain trapped in the formulation, unavailable to penetrate into the skin (2, 3).

Supersaturation of a drug in a topical vehicle is a simple, cost-effective and safe strategy to improve percutaneous drug delivery. The increased concentration of drug in a vehicle above saturation leads to a greater thermodynamic activity, which proportionally increases the rate at which the drug can pass through the skin (4). However, by definition, the drug in supersaturated formulations is physically unstable and precipitation will occur well within the shelf-life of a pharmaceutical product (typically a minimum of 18 months) even in the presence of excipients included to prevent crystal nucleation (5). The reduction of solubilised drug caused by precipitation diminishes the drug thermodynamic activity and therefore reduces the potential enhancement capability of the delivery system (6). To avoid this problem, novel formulations have been developed that become supersaturated only after dosing onto the skin and not whilst stored in the original formulation reservoir. These supersaturated systems use high levels of volatile organic solvents that evaporate after actuation to increase the concentration of drug on the skin. Examples of novel formulations containing high amounts of evaporative organic solvents include foams (7, 8), alcoholic gels (9, 10) and sprays (11–13). High levels of organic solvents in all these formulations evaporate and drive the drug into the skin.

Sprays, in particular metered dose aerosols (MDA), are attractive vehicles to induce drug supersaturation as they are cosmetically acceptable and lack dosing variability. These sprays commonly consist of volatile propellants and co-solvents that evaporate after dosing. Volume reduction of a solution caused by evaporation can induce supersaturation post dose application; this is commonly known as 'transient supersaturation' due to its highly dynamic nature. Leichtnam *et al.* (2006) previously reported an attempt to generate a transiently supersaturated formulation containing testosterone for transdermal drug delivery. However, the testosterone present in the saturated system containing ethanol (EtOH), water, hydrofluoroalkane (HFA) and propylene glycol co-solvent was shown to quickly form drug crystals upon application (Leichtnam *et al.*, 2006). Rapid post-dosing crystallisation resulted in a reduction of drug thermodynamic

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activity and as a result very little permeation enhancement when compared to a saturated drug solution was reported (14). Morgan *et al.* (1998) also found no improvement in plasma concentrations of testosterone and estradiol in swine using MDAs without penetration enhancers (15). However, the limiting factor in these studies was the inability to maintain drug supersaturation after dose actuation for an appropriate amount of time to increase in flux (15).

Given the nature of MDA formulations, the combination of excipients and volatile solvents can be manipulated to give a wide range of physical characteristics after the dose is applied to the skin. Typically these formulations begin as a light mousse or gel upon dosing and then decrease in mass as the solvent is lost until eventually a thin film is formed upon the skin. Solvents from the formulation can be lost after dose application via two routes: either by evaporation or absorption into the skin. As the solvent is lost from the formulation the nature of the applied film changes and release of the drug is altered. In some cases the enhanced delivery has been reported as a consequence of solvent evaporation and this has been attributed to a heightened level of drug thermodynamic activity in the formulation and/or the 'solvent drag' effect which aids partitioning into the skin (16). The decrease in solvent volume after application can also result in a reduction in the amount of drug release due to rapid film formation causing a decrease in mobility and/or drug precipitation (17). It is possible that with the addition of appropriate non-volatile residual solvents to MDA that evaporation of the volatile components can be altered and as a result drug release from the remaining formulation manipulated (18, 19). However, the rational inclusion of residual solvents into volatile transiently supersaturated systems requires a greater understanding of the their influence upon both drug saturation and mobility in the formulation.

The aim of this study was to investigate how the addition of a residual solvent could modulate the characteristics of a topical film and influence the release of drug from a MDA. The release profile of BDP from MDA formulations containing a volatile propellant HFA 134a, a film forming polymer poly(vinyl) pyrrolidone (PVP) K90 and co-solvent EtOH was compared to identical MDAs containing different concentrations of a residual, non-evaporative solvent (PEG 400). The effect of the PEG 400 upon both the kinetics and degree of saturation (DS) after actuation was calculated based on the solubility of BDP in EtOH and PEG 400. A probe tack test was employed to measure physical changes in the film by determining the relationship between dose depletion and adhesion as a function of time.

MATERIALS AND METHODS

Materials

BDP was purchased from Airfilco (High Wycombe, UK) and was used as received. EtOH (99.7–100% *v/v*) and poly (ethylene glycol) 400 (average molecular weight of 400 g/mol) were purchased from BDH (Lutterworth, UK). Acetonitrile (ACN) (HPLC grade) was from Fisher Scientific (Loughborough, UK). Poly (vinyl pyrrolidone) (PVP K90, average molecular weight 360,000 g/mol) was purchased from Fluka (Buchs, Switzerland). Solkane 1,1,1,2-tetrafluoroethane (HFA) 134a propellant was kindly donated by Solvay (Hanover, Germany). Regenerated cellulose membrane (RCM, 12–14 k molecular weight cut-off) was purchased from Medicell International (London, UK).

Metered Dose Aerosol Preparation

PVP K90 and BDP were weighed directly into a 10 mL Purgard® canister made of clear glass and safety coated in polypropylene (Adelphi Tubes, Haywards Heath, UK) at the desired weight/weight ratios. PEG 400 (if appropriate) and EtOH were subsequently weighed into the canister, and a 13 mm magnetic follower was added. The canister was sealed with a 50 μl metered valve (Bespak Europe Ltd, Milton Keynes, UK). This was left to stir overnight to allow the polymer to solvate and equilibrate. The HFA 134a was pressure-filled into the sealed glass canister using an MDA filler (Model # 2016, Pamasol Willi Mader AG, Pfäffikon, Switzerland) until the desired weight was obtained. The MDA was stirred for 24 h and complete dissolution of the polymer into the other components was defined as a soluble system whereas the appearance of precipitate in the mixture was defined as an insoluble mixture.

In Vitro Drug Release

The release experiments were carried out in individually calibrated upright Franz cells (MedPharm Ltd, Guilford, UK) with an average receiver volume of 10.8 cm^3 and an average surface area of 2.1 cm^2. RCM was soaked in deionised water (DiH_2O, conductivity 0.5–1 μS) for 30 min at 70°C and then rinsed with DiH_2O to remove any impurities. The membrane was cut to fit the Franz cell with scissors, mounted and sealed between the two chambers of the cell with a 13 mm magnetic flea in the receiver chamber. The cell was inverted and filled immediately with a previously sonicated receiver fluid composed of 70:30 ACN:DiH_2O (BDP was stable in this solution over the time of the experiment; data not shown, and had a saturated solubility of ~20 mg/mL). The high proportion of organic solvent in this RF was required to maintain sink (20, 21). The cells were checked for leaks by inversion and placed on a submersible stir plate in a pre-heated water bath set at 37° C to obtain 32°C at the membrane surface (22). The cells were left to equilibrate for 1 h prior to application of the donor phase, which consisted of an infinite dose of 30 actuations of an MDA formulation, equivalent to 1.2 mg of BDP (whereby one actuation is equivalent to 40 μg of BDP). An infinite dose of these formulations were examined to investigate the supersaturation kinetics after dose actuation only; it was not anticipated that a large dose would be applied in a clinical setting. Further work is necessary to understand the mechanisms of action of the MDAs at smaller, more therapeutically relevant amounts. Drug diffusion through the membrane and into the receiver fluid was monitored by removal of 1 mL samples out of the Franz cell sampling arm. These samples taken from the Franz cells were placed into an HPLC vial without dilution, and the sample volume was replaced with 1 mL of thermostatically regulated receiver fluid. The cumulative amount of drug (μg) penetrating the unit surface area of the membrane (cm^2) was corrected for sample removal and plotted against time (h). Steady-state

release rate was calculated using the line of best fit over at least five time points with a linearity of $R^2 \geq 0.97$. The thickness of the RCM membrane was measured before and after the release rate experiment using a Vernier micrometer (Starrett, Jedburgh, UK) set at low torque. Five thickness measurements were made in randomly selected membrane sections.

HPLC Analysis

Quantitative determination of the BDP was performed using a reverse phase HPLC system consisting of a 600E pump, a 996 PDA Detector, Waters™ 717 Plus Autosampler coupled with Millennium[32] Software, version 4.0 (Waters, Milford, MA, USA). The mobile phase was 70:30 ACN: DiH_2O set at a flow rate of 1.0 mL/min. BDP was separated using a Nova-Pak® C18 150 mm×4 μm stationary phase (Waters, USA) at room temperature with a 100 μL injection volume and UV detection at 254 nm. Average BDP retention times was 3 min and calibration curves were constructed from the peak height of known standard concentrations, prepared by serial dilution (peak height was shown to have superior accuracy and precision compared to peak area). The HPLC method had a 0.8 μg/mL limit of detection and was shown to be 'fit for purpose' in terms of accuracy, precision and linearity in accordance to the limits described by the International Conference on Harmonisation guidelines, data not shown (23).

Adhesion Testing

Thirty actuations of the MDA formulations were applied to one well in a 24 well polystyrene multi-dish plate (Nunc, Roskilde, Denmark). This plate was super-glued (UHU glue, UK) to the base of a single column, bench mounted Testing Machine LF 500 (Lloyd Instruments, Hants, UK). The force of adhesion was measured using the food category, single stickiness method which was predefined within the NEXYGEN ™ Materials Test and Data Analysis Software (version 4.5.1, Lloyd Instruments, Hants, UK). At three intervals after dose application (0.5, 2, and 4 h) a flat probe was driven into the sample at a speed of 1 mm/min until a force of 10 N was applied and this was held for 60 s. The probe was reversed out of the sample at the same speed and the pull-off force created by the pull on the load cell in the base was measured until the probe broke away from the sample. This force was defined as the adhesive force, measured in Newtons (N).

Evaporation and Degree of Saturation Calculation

Thirty actuations from an MDA were applied to a tared weigh boat (usable surface area of 6 cm^2) in a balance and monitored for weigh loss after application by recording the sample weight at multiple time points over 48 h. As there was a known amount of BDP applied, the concentration and thus DS could be determined by the weight loss using Eq. 1:

$$\frac{\left(\frac{WD_{App}}{WF_t - WF_{Final}}\right)}{C_{SS}} = DS \quad (1)$$

where WD_{App} was the mass of the drug applied, WF_t was the mass of the formulation at time t, WF_{Final} as the final mass of the formulation after 48 h (24) and $C_{SS,}$ was the saturated solubility of drug in the solvent mixture at time t. In this study, the C_{SS} was not constant over the course of the experiment, because the amount of EtOH decreased with time while the amount of (liquid) PEG 400 remain unchanged. In order to determine the total mass of PEG applied by each MDA the final mass of the film at 48 h was multiplied by the initial percentage of PEG 400 in the formulation. The EtOH mass at each time point was determined by subtraction of the EtOH loss (assumed to be equal to formulation weight loss after 1 min) from the total EtOH mass. This allowed the EtOH and PEG ratio to be determined at each time point of the weight loss profile, and the saturated solubility (determined experimentally) of these co-solvent mixtures were used in Eq. 1 for the DS calculation. Saturated solubility of the drug in appropriate ratios of PEG 400 and EtOH was determined by adding excess BDP to the co-solvent solution which was stirred for 24 h in sealed containers at room temperature (21°C). The solution was centrifuged at 14,000 rpm for 30 min (Biofuge pico Heraeus Instruments, Hanau Germany), the supernatant was diluted and assayed by HPLC using the method previously described.

RESULTS AND DISCUSSION

The MDA formulations employed in this study consisted of an active ingredient (BDP), a film-forming polymer (PVP K90), a propellant (HFA 134a), and volatile co-solvent (EtOH). To this blend of excipients PEG 400 was added in an attempt to control drug release. It was anticipated that upon application of the MDA to a topical surface the evaporation of the volatile propellant and co-solvent would lead to a formulation volume decrease, an increase in drug concentration and the formation of a supersaturated semi-solid film. Accurate interpretation of drug release data from the formulations undergoing this process using RCM was facilitated by the assessment of membrane dehydration effects which could have been induced by the co-solvent blend of PEG/PVP/EtOH (25). Measurements of membrane thickness in the absence (51.0±4.2 μm) and presence of PEG (48.0±2.7 μm for 5% PEG and 46.0±2.2 μm for 10% PEG) indicated that variation of the co-solvent polymer mixture did not induce a diffusional path length alteration. Thus these differences in the release rate of the drug were assumed to be as a consequence of the formulation excipient effects upon the drug and not an artifact of the experimental method.

The release rate of BDP from a MDA without a residual co-solvent across the RCM was 230.4±17.3 μm/cm^2/h (Table I). The fastest release from the rapidly drying PVP/EtOH film was within the first 1.5 h, but this rate slowed between 1.5–2 h and release stopped within 2 h (Fig. 1). The addition of PEG to the MDA formulation was shown to slow the release rate (from 230.4±1.73 μg/cm^2/h for 0% PEG to 172.0±21.1 μg/cm^2/h for 5% PEG, and to 83.6±4.9 μg/cm^2/h for 10% PEG) and extend the time to dose depletion (2 h for 0% PEG, 3 h for 5% PEG and 4 h for 10% PEG, Fig. 1). However, the total amount of drug released from all three MDAs over the 4 h experiments was not significantly different ($p>0.05$), indicating that the addition of PEG only affected the rate and not the extent of drug release. It was hypothesised that PEG influenced the drug release profile in two different ways: (1) by altering the

Table I. List of Metered Dose Aerosol Formulations Containing Poly(Vinyl Pyrrolidone), Beclomethasone Dipropionate, Ethanol, and Hydrofluoroalkane 134a with Two MDAs Containing Poly(Ethylene Glycol) 400. Steady state drug release through a regenerated cellulose membrane and the membrane thickness of the RCM after the release study was completed at 4 h. Mean of $n=5\pm$one standard deviation

	Excipients (% *w/w*)						
Formulation	PVP K90	BDP	PEG 400	EtOH	HFA 134a	Steady state release rate (μg/cm^2/h)	Membrane thickness (μm)
0% PEG MDA	2.52	0.09	0	10.00	87.39	230.4±17.3	51.0±4.2
5% PEG MDA	2.15	0.09	5.00	10.00	82.76	172.0±21.1	48.0±2.7
10% PEG MDA	3.36	0.09	10.00	10.00	76.55	83.6±4.9	46.0±2.2

RCM Regenerated cellulose membrane, *MDA* metered dose aerosol, *PVP K90* poly(vinyl pyrrolidone), *BDP* beclomethasone dipropionate, *EtOH* ethanol, *HFA* hydrofluoroalkane, *PEG* poly(ethylene glycol)

saturation kinetics and (2) by increasing the drug mobility within the film.

The weight loss profiles of the MDA formulations after application were determined as a function of time to assess supersaturation kinetics (Fig. 2). As in previous work, there were two obvious gradients in the weight loss profiles, one immediately post dose application and a second after approximately 1 min (24). The 0% PEG MDA displayed the most rapid weight loss from 10 s to 1 min after the last spray was actuated at −197±14 mg/min and the 10% PEG MDA was the slowest at −112±15 mg/min (linearity of these gradients were $R^2>0.9$ for both). This period of rapid weight loss post dose actuation was considered to be a consequence of HFA 134a evaporation as it has a lower enthalpy of vaporisation (19.6 kJ/mol) (26) compared to other volatile solvent EtOH (42.3 kJ/mol) (27). The slower rate of weight loss between 10 s to 1 min for the 10% PEG MDA was probably a result of the different formulation composition, as the addition of 10% PEG in this formulation was compensated by a 10% reduction in HFA 134a. An increase in the most viscous excipient in the formulation, PEG (105–130 cP PEG, 0.22 cP HFA, 1.22 cP EtOH (28)) may have hindered HFA diffusion through this solvent mixture. If the access of HFA to the air/liquid interface post application was retarded then depletion of HFA at the interface could occur and evaporation as a result weight loss slowed.

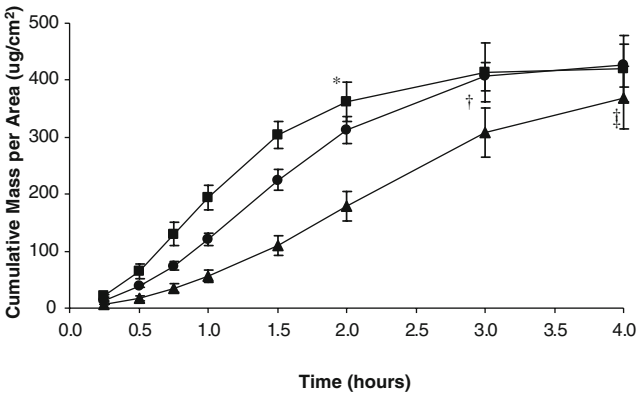

Fig. 1. Beclomethasone dipropionate release profiles from metered dose aerosol formulations containing 0% (*filled square*), 5% (*filled circle*) and 10% (*filled triangle*) *w/w* polyethylene glycol (PEG) 400; the dose depletion time point from each formulation is indicated by (*asterisk*) for the 0% PEG, (*dagger*) for 5% PEG, and (*double dagger*) for 10% PEG MDAs. Mean of $n=5\pm$one standard deviation.

The weight loss determined in the second sector of the profile (i.e. from 5 to 30 min) for all three of the MDAs was statistically equivalent ($p>0.05$) with weight loss rates of −3.9± 0.1 mg/min, −3.7±0.2 mg/min and −3.7±0.2 mg/min for 0% PEG, 5% PEG, and 10% PEG MDAs respectively ($R^2>$ 0.96). Previous work has shown that formulation weight loss as a consequence of EtOH evaporation from a saturated solution occurs at approximately 6 mg/min (24). Although the weight loss that was thought to be due to EtOH evaporation in this experiment was slower than previously observed, these small but significant differences could have been a result of a change in the ambient conditions. During EtOH loss it was again assumed that the viscosity of the formulations was changing, but as the process was occurring at a rate nearly two orders of magnitude slower than that in the first sector of evaporation it was assumed that the air/liquid interface depletion of EtOH did not occur. The final weights of the three formulations indicated that PEG did not evaporate and this was probably as a consequence of its comparatively high boiling point of 250°C (29). The MDA spray formulation with the highest concentration of PEG, 10% PEG MDA, was the heaviest at 240 min due to the fact a large proportion of residual film that remained at this time point was comprised of PEG.

Once the HFA 134a had completely evaporated from the 0% PEG MDA, the BDP was left in a solution containing PVP K90 and EtOH. The amount of EtOH continuously decreased post dose application until the formulation was completely dry. This process was found to take approximately 90 min after the last spray was actuated from the MDA, as after this time no more weight loss was observed (final weight of 0.036±0.001 g from 90 to 240 min which remained statistically unchanged up to 48 h ($p>0.05$)). It was hypothesised that once the film was dry the viscosity of the film would be high, and as a result drug mobility was lessened and hence release would be poor. The BDP release profile confirmed this hypothesis. However, dose depletion occurred at approximately 120 min post dose application and at this time point 45% of the drug had passed through the membrane. Therefore although dose depletion could have been as a consequence of the lack of drug availability at the membrane interface, due to poor mobility in the film, it was more likely to be a consequence of an inadequate concentration of drug remaining on the apical surface of the membrane due to the highly efficient release (Fig. 1). The drug release profile of the films was therefore probably controlled by a combination of physical properties and evaporation (thus

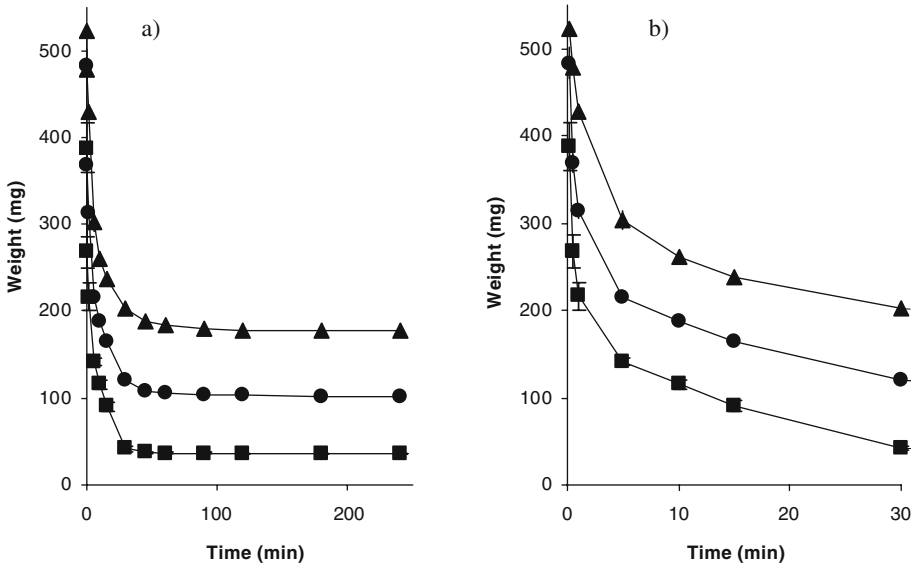

Fig. 2. Weight loss of the metered dose aerosol formulations containing 0% *w/w* poly(ethylene glycol) (PEG) 400 (*filled square*), 5% *w/w* PEG 400 (*filled circle*), and 10% *w/w* PEG 400 (*filled triangle*) MDAs, whereby **b** is an expansion to show the two rate gradients over 30 min of the full data set **a**. Points represent mean of $n=3\pm$one standard deviation (in most cases the standard deviation is too small to be seen).

supersaturation kinetics) in the early part of the release profile.

The saturation kinetics for the three MDA formulations were very different as a consequence of the altered evaporation profiles and film compositions after loss of the HFA (Fig. 3). The MDA formulation containing 0% PEG was subsaturated and took approximately 30 min to become supersaturated whereas the MDA formulations containing 5% and 10% PEG were not supersaturated until approximately 45 and 60 min post dose application, respectively. There was no significant difference ($p>0.05$) between the final DS value for the 0% PEG MDA and the 5% PEG MDA (both were approximately six times supersaturated), but the MDA containing 10% PEG only reached a final DS of approximately three. The addition of PEG to the formulations resulted in a PEG/PVP/EtOH mixture in the film compared to the PVP/EtOH film from the 0% PEG MDA, thus altering the solubility profile of BDP in these systems. The solubility of BDP in PEG was 28.9 mg BDP/g PEG while the solubility of BDP in EtOH was 46.9 mg/g. This meant that as the EtOH evaporated from the MDA formulations containing PEG, the BDP was solubilised by the remaining PEG solution which caused the reduction in drug saturation. In addition to the slower volume change in the PEG solutions, this was the cause of the DS saturation kinetics being relatively slower.

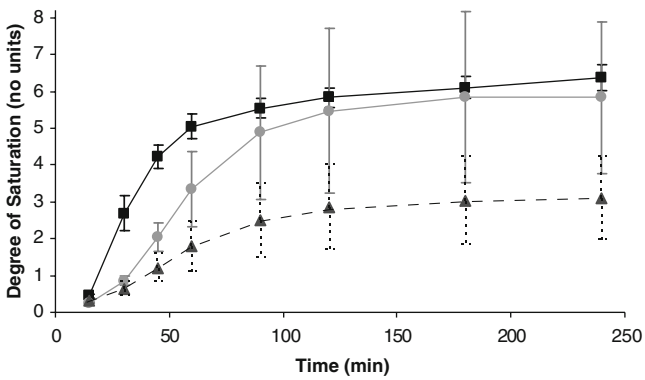

Fig. 3. The supersaturation kinetics for the metered dose aerosols containing 0% *w/w* poly(ethylene glycol) (PEG) 400 (*square*), 5% *w/w* PEG 400 (*circle*), and 10% *w/w* PEG 400 (*triangle*) MDAs. Points represent a mean of $n=3\pm$one standard deviation.

The physical characteristics of topical dosage forms are often assessed via rheological characteristics as these parameters often relate to the ease of product use, physical stability, and the feel upon the skin. In addition, the rheology of a semi-solid can provide some information on the drug mobility in the formulation. However, due to the experimental method limitations, it is difficult to assess the rheological properties of dynamic films. As a consequence several specific film physical characterisation tests have been previously developed and reported in the literature including: abrasion resistance (30), elongation (31), swelling and water uptake (31, 32) and adhesion (31, 33, 34). Adhesion is an important characteristic for topical film formulations as they need to remain in contact with the skin during dose application, and this measure can also provide an indication of the fluidity of a film. Due to the speed at which measurements could be made, in the current study adhesion was used as a parameter to monitor the dynamic properties of the transiently supersaturated film over time.

Tackiness has previously been defined as the capability of a material to form a strong adhesive bond with another surface during a short contact time (35). The most common test performed to measure tackiness is the peel test, which assesses the force necessary to pry a film from another object, e.g. a tablet or a pressure sensitive adhesive (PSA) liner (36). The peel force is then extrapolated to the likelihood of the film staying affixed to the topical surface. The peel test was not appropriate in the current study as a rigid film that could

be peeled off a surface was not always generated by the MDA formulations.

Probe tack testing, whereby a probe is driven into the topical formulation, held for a short period, and then removed to measure the force required to separate, is also a reliable method to assess tackiness (33). Probe methods are commonly employed to assess the tackiness of food coating preparations during drying as a method to determine how the systems change during solvent evaporation (37). In this study, a probe tack test was utilised to measure the adhesiveness of the MDA formulations after actuation, i.e. as they dried. In order to determine if the probe tack test could differentiate between tacky and non-tacky substances, three materials were measured: a solid, non-adhesive empty Transwell® plate, a solid adhesive piece of poly(vinyl alcohol) Sellotape which was adhered to the surface of the Transwell plate and the Transwell plate containing a non-adhesive liquid, PEG 400 (Fig. 4). Both liquid and solid test items were selected as it was anticipated that the films produced by the MDA formulations could take either form. The adhesive force of the probe with the non-adhesive empty Transwell container (the container that would hold the films) was 0.24±0.02 N. When the Transwell contained liquid PEG the adhesion was 0.12±0.01 N and when it held the Sellotape it was 2.82± 1.07 N. These measurements showed the range of adhesion with both solid and liquid materials. The slight apparent adhesion (~0.2 N) of the probe to the empty transwell plate was likely due to dry static friction between the probe and plate caused by forces such as van der Waals and capillary forces (38). The decrease in adhesive force when liquid PEG 400 was added to the Transwell plate was probably as a consequence of the PEG 400 lubricant effect which diminishes the static forces present, a phenomenon that has been demonstrated previously when PEG has been added to extruders (39). With this method of adhesiveness measurement, it was evident that differentiation between the two surfaces of different adhesion properties could be determined. In addition, measurements determined in the current study were in the same order of magnitude as probe studies

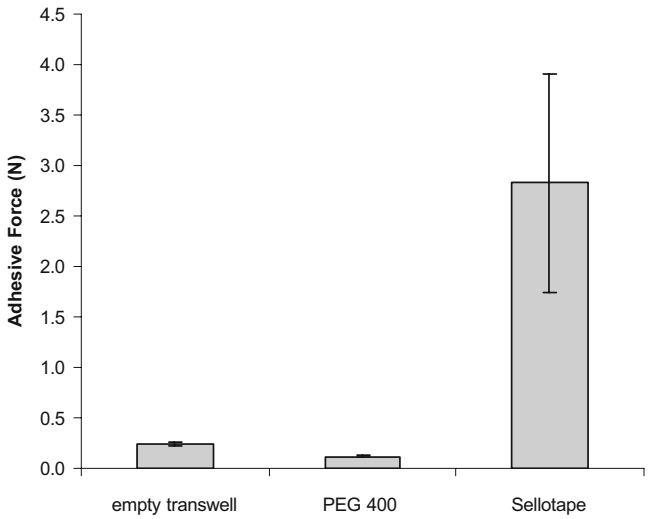

Fig. 4. The adhesive force of an empty transwell, a non-tacky liquid (polyethylene glycol (PEG) 400), and a very tacky surface (Sellotape) using a flat probe. Points represent a mean of n=4±one standard deviation.

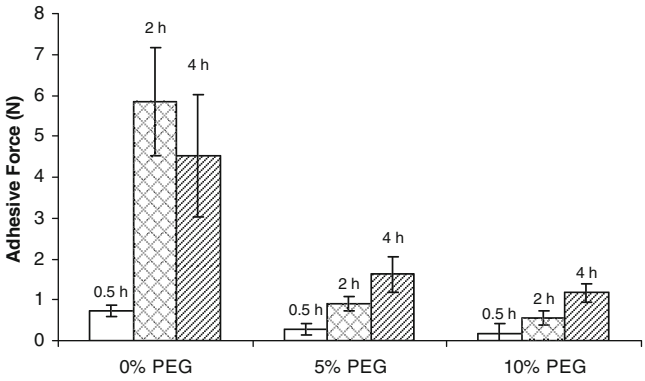

Fig. 5. Effect of poly(ethylene glycol) (PEG) 400 percentage film tackiness over 0.5 h (*white*), 2 h (*hatched*) and 4 h (*diagonal lines*). The metered dose aerosols were equivalent but contained 10% *w/w* PEG, 5% PEG or 0% PEG. Points represent a mean of n=4–7±one standard deviation.

previously reported with similar materials which been reported to lie in the range of 0.1 to 2 N (31, 40, 41).

At 0.5 h, the 0% PEG MDA generated a tackiness of 0.73±0.14 N (Fig. 5). At 2 and 4 h the tackiness values were both significantly higher at 5.84±1.31 N and 4.52±1.49 N ($p \leq 0.05$) respectively. This increase in tackiness of the PVP/EtOH film appeared to correlate with the both the evaporation data, which displays no further weight loss after 90 min, and also with the drug release profile that reveals no significant BDP release after 2 h. The goal of adding the PEG as a residual solvent to the MDA formulations was to prolong the film drying time and extend the time of drug release. Although it appeared that dose depletion was the ultimate determinant of drug release in the films containing PEG, the drug saturation was lower. Therefore, to achieve the same extent of drug release mobility must be retained in the films for a longer period of time. Unlike the PVP/EtOH film, the tackiness of PVP/EtOH/PEG films was significantly different at each time point measured. For example for the MDA containing 5% PEG at 0.5 h the tackiness was 0.28± 0.15 N, at 2 h it was 0.90±0.18 N, and at 4 h it was 1.62± 0.42 N ($p \leq 0.05$). As the adhesion force continued to increase over this time, it is assumed that the film was changing and the drug remained mobile within the film. The 10% PEG MDA exhibited an adhesion of 0.18±0.23 N at 0.5 h, 0.54± 0.17 N at 2 h, and 1.17±0.22 N at 4 h which were not significantly different to the equivalent time points for the 5% PEG MDA. These tackiness values were significantly different to the pure PEG system tested to validate the system and therefore it was predicted that a semi-solid film was formed even in the presence of PEG. However, it was apparent from the weight loss studies that no more EtOH is evaporating after 90 min and so this cannot be the reason for the increasing adhesion beyond this time point. As a consequence it appeared that the remaining components of the system (PVP K90, PEG 400, drug) were interacting in such a manner as to affect the temporal dynamics of the film.

Earlier studies have shown that miscibility in PVP–PEG systems is strongly affected by the molecular weight of PEG, and that PEG 400 mixed with PVP K90 is a completely miscible system (42). In these experiments, this was confirmed by the visual examination of the PEG MDA films

produced after actuation as they clearly formed a single phase and did not separate over extended periods of time. The proposed mechanism of interaction between the two molecules is that the terminal –OH groups of the PEG molecule forms hydrogen bonds to the carbonyl group on the repeating PVP monomer. When the PEG structures are short, as is the case with PEG 400, the hydrogen bonding allows intermolecular interactions with the longer PVP molecules. This gives rise to a mesh-like structure that has both a highly flexible and adhesive characteristics (43). Bairamov *et al.* (2002) found that inter-diffusion between PVP in PEG liquid systems would continue to take place over extended periods of time, and calculated that the final time for PVP and PEG to reach equilibrium under their experimental conditions would be up to 2 weeks (42). This explains why the physical characteristics of MDA films with PEG present continue to change over time despite the complete evaporation of EtOH. The PVP could be slowly diffusing through the PEG system, breaking and reforming –OH bonds as it becomes fully integrated (44). As the PEG was interfering with the film-forming abilities of the PVP, and acting as a liquid plasticizer, the dry, hard film seen with the 0% PEG MDA was unable to set. This theory may explain why the PEG MDAs have increasing adhesive force over time while the 0% PEG MDA gives a constant value after 2 h. This more liquid-like state allowed the continued release of BDP at a time period after the 0% PEG MDA had stopped.

CONCLUSION

In this study the BDP release over time was assessed from three transiently supersaturated films. Adding PEG 400 to the MDA induced a slower drug release rate and also extended the time of drug dose depletion by 2 h. The drug release rate was controlled by the DS which was manipulated by changing the solubility of BDP in the residual ethanol/PEG co-solvent system. An increase in BDP solubility in the drying film lead to a slower increase in drug thermodynamic activity and hence reduction in the release rate. The adhesive force of the three formulations after application showed that PEG films continued to change during the course of the experiment while the non-PEG films were completely dry. All the films generated in this work had rapid drug release, hence dose depletion was ultimately controlled by the lack of drug remaining in the film. However, the increased mobility of the PEG films and slower supersaturation kinetics allowed a slower more sustained drug release. The ability to increase the release rate of a drug over a long period of time opens up the potential for development of a supersaturated MDA drug delivery system suitable for transdermal delivery. The next stage of testing these formulations is to measure the permeation through human skin or to otherwise determine the effect of supersaturation combined with these excipients (45, 46) on the stratum corneum as *in vitro–in vivo* correlations from experimental models should not be assumed.

REFERENCES

1. R. R. Wickett, and M. O. Visscher. Structure and function of the epidermal barrier. *Am. J. Infect. Control.* **34**:S98–S110 (2006). doi:10.1016/j.ajic.2006.05.295.
2. B. W. Barry. Modern methods of promoting drug absorption through the skin. *Mol. Aspects Med.* **12**:195–241 (1991). doi:10.1016/0098-2997(91)90002-4.
3. V. P. Shah, J. Elkins, S. Y. Lam, and J. P. Skelly. Determination of *in vitro* drug release from hydrocortisone creams. *Int. J. Pharm.* **53**:53–59 (1989). doi:10.1016/0378-5173(89)90361-X.
4. T. Higuchi. Physical chemical analysis of percutaneous absorption process from creams and ointments. *J. Soc. Cosmet. Chem.* **11**:85–97 (1960).
5. X. G. Ma, J. Taw, and C. M. Chiang. Control of drug crystallization in transdermal matrix system. *Int. J. Pharm.* **142**:115–119 (1996). doi:10.1016/0378-5173(96)04647-9.
6. R. Lipp, and A. Muller-Fahrnow. Use of X-ray crystallography for the characterization of single crystals grown in steroid containing transdermal drug delivery systems. *Eur. J. Pharm. Biopharm.* **47**:133–138 (1999). doi:10.1016/S0939-6411(98)00055-1.
7. X. Huang, H. Tanojo, J. Lenn, C. H. Deng, and L. Krochmal. A novel foam vehicle for delivery of topical corticosteroids. *J. Am. Acad. Dermatol.* **53**:S26–S38 (2005). doi:10.1016/j.jaad.2005.04.028.
8. Abram, A. Z. Mousse Composition. 09/719,662[6,730,288]. 2004. United States. Ref Type: Patent
9. D. Pabla, and H. Zia. A comparative permeation/release study of different testosterone gel formulations. *Drug Deliv.* **15**:389–396 (2007). doi:10.1080/10717540701203075.
10. Dudley, R. E., Kottayil, S. G., and Palatchi, O. Pharmaceutical composition and method for treating hypogonadism. [6,503,894]. 2003. Ref Type: Patent
11. C. Stone, A. J. Humberstone, K. Gard'ner, A. Evans, D. Shaw, and G. L. Ludbrook. Steady-state pharmacokinetics of fentanyl after administration of a novel non-occlusive transdermal system. *J. Clin. Oncol.* **23**:778S (2005).
12. Reed, B. L., Morgan, T. M., and Finnin, B. C. Dermal penetration enhancers and drug delivery systems involving the same. [6818226]. 2004. United States. Ref Type: Patent
13. Brown, M. B., and Jones, S. A. Topical formulations. [WO2007031753]. 2007. Ref Type: Patent
14. M. L. Leichtnam, H. Rolland, P. Wuthrich, and R. H. Guy. Formulation and evaluation of a testosterone transdermal spray. *J. Pharm. Sci.* **95**:1693–1702 (2006). doi:10.1002/jps.20641.
15. T. M. Morgan, R. A. Parr, B. L. Reed, and B. C. Finnin. Enhanced transdermal delivery of sex hormones in swine with a novel topical aerosol. *J. Pharm. Sci.* **87**:1219–1225 (1998). doi:10.1021/js980026c.
16. J. L. Bowen, and C. M. Heard. Film drying and complexation effects in the simultaneous skin permeation of ketoprofen and propylene glycol from simple gel formulations. *Int. J. Pharm.* **307**:251–257 (2006). doi:10.1016/j.ijpharm.2005.10.014.
17. S. J. Gallagher, and C. M. Heard. Solvent content and macroviscosity effects on the *in vitro* transcutaneous delivery and skin distribution of ketoprofen from simple gel formulations. *Skin Pharmacology and Physiology.* **18**:186–194 (2005). doi:10.1159/000085864.
18. S. Kondo, and I. Sugimoto. Enhancement of Transdermal Delivery by Superfluous Thermodynamic Potential.1. Thermodynamic Analysis of Nifedipine Transport Across the Lipoidal Barrier. *J. Pharmacobio-Dyn.* **10**:587–594 (1987).
19. M. F. Coldman, B. J. Poulsen, and T. Higuchi. Enhancement of percutaneous absorption by use of volatile—nonvolatile systems as vehicles. *J. Pharm. Sci.* **58**:1098–& (1969).
20. W. W. Hauck, V. P. Shah, S. W. Shaw, and C. T. Ueda. Reliability and reproducibility of vertical diffusion cells for determining release rates from semisolid dosage forms. *Pharm Res.* **24**:2018–2024 (2007). doi:10.1007/s11095-007-9329-x.
21. N. A. Megrab, A. C. Williams, and B. W. Barry. Estradiol permeation across human skin, silastic and snake skin membranes—the effects of ethanol–water cosolvent systems. *Int. J. Pharm.* **116**:101–112 (1995). doi:10.1016/0378-5173(94)00321-U.
22. W. G. Maddock, and F. A. Coller. The role of the extremities in the dissipation of heat. *Am. J. Physiol.* **106**:589–596 (1933).
23. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Q2(R1): Validation of Analytical Procedures: Text and Methodology. In 1996.

24. S. A. Jones, M. L. Reid, and M. B. Brown. Determining degree of saturation after application of transiently supersaturated metered dose aerosols for topical delivery of corticosteroids. *J. Pharm. Sci.* (in press): (2008).
25. M. L. Reid, M. B. Brown, and S. A. Jones. An investigation into solvent–membrane interactions when screening topical corticosteroid release from organic vehicles using regenerated cellulose membranes, *J Pharm Pharmacol.* (in press): (2008).
26. R. O. Williams III, and J. Liu. Influence of formulation additives on the vapor pressure of hydrofluoroalkane propellants. *Int. J. Pharm.* **166**:99–103 (1998). doi:10.1016/S0378-5173(98)00031-3.
27. R. M. Balabin, R. Z. Syunyaev, and S. A. Karpov. Molar enthalpy of vaporization of ethanol–gasoline mixtures and their colloid state. *Fuel.* **86**:323–327 (2007). doi:10.1016/j.fuel.2006.08.008.
28. R. Rowe, P. Sheskey, P. Weller. *Handbook Of Pharmaceutical Excipients*. UK , Pharmaceutical Press, London, 2003.
29. F. Heymes, P. M. Demoustier, F. Charbit, J. L. Fanlo, and P. Moulin. Recovery of toluene from high temperature boiling absorbents by pervaporation. *J. Membr. Sci.* **284**:145–154 (2006). doi:10.1016/j.memsci.2006.07.029.
30. I. Zurdo Schroeder, P. Franke, U. F. Schaefer, and C. M. Lehr. Development and characterization of film forming polymeric solutions for skin drug delivery. *Eur. J. Pharm. Biopharm.* **65**:111–121 (2007). doi:10.1016/j.ejpb.2006.07.015.
31. P. A. McCarron, R. F. Donnelly, A. Zawislak, and A. D. Woolfson. Design and evaluation of a water-soluble bioadhesive patch formulation for cutaneous delivery of 5-aminolevulinic acid to superficial neoplastic lesions. *Eur. J. Pharm. Sci.* **27**:268–279 (2006). doi:10.1016/j.ejps.2005.10.009.
32. S. Benamer, M. Mahlous, A. Boukrif, B. Mansouri, and S. L. Youcef. Synthesis and characterisation of hydrogels based on poly(vinyl pyrrolidone). *Nucl. Instrum. Methods Phys. Res., B Beam Interact. Mater. Atoms.* **248**:284–290 (2006). doi:10.1016/j.nimb.2006.04.072.
33. S. Venkatraman, and R. Gale. Skin adhesives and skin adhesion 1. Transdermal drug delivery systems. *Biomaterials.* **19**:1119–1136 (1998). doi:10.1016/S0142-9612(98)00020-9.
34. A. D. Woolfson, D. F. McCafferty, and G. P. Moss. Development and characterisation of a moisture-activated bioadhesive drug delivery system for percutaneous local anaesthesia. *Int. J. Pharm.* **169**:83–94 (1998). doi:10.1016/S0378-5173(98)00109-4.
35. M. M. Feldstein, V. G. Kulichikhin, S. V. Kotomin, T. A. Borodulina, M. B. Novikov, A. Roos, and C. Creton. Rheology of poly(N-vinyl pyrrolidone)–poly(ethylene glycol) adhesive blends under shear flow. *J. Appl. Polym. Sci.* **100**:522–537 (2006). doi:10.1002/app.23290.
36. R. D. Toddywala, K. Ulman, P. Walters, and Y. W. Chien. Effect of physicochemical properties of adhesive on the release, skin permeation and adhesiveness of adhesive-type transdermal drug delivery systems (a-TDD) containing silicone-based pressure-sensitive adhesives. *Int. J. Pharm.* **76**:77–89 (1991). doi:10.1016/0378-5173(91)90346-P.
37. S. R. L. Werner, J. R. Jones, and A. H. J. Paterson. Stickiness during drying of amorphous skin-forming solutions using a probe tack test. *J. Food Eng.* **81**:647–656 (2007). doi:10.1016/j.jfoodeng.2006.12.008.
38. S. J. Timpe, and K. Komvopoulos. The effect of adhesion on the static friction properties of sidewall contact interfaces of microelectromechanical devices. *Journal of Microelectromechanical Systems.* **15**:1612–1621 (2006). doi:10.1109/JMEMS.2006.885855.
39. M. J. Xie, X. L. Liu, and H. L. Li. Influence of poly(ethylene glycol)-containing additives on extrusion of ultrahigh molecular weight polyethylene/polypropylene blend. *J. Appl. Polym. Sci.* **100**:1282–1288 (2006). doi:10.1002/app.23510.
40. B. Kim, S. Kim, H. Do, S. Kim, and H. Kim. Probe tack of tackified acrylic emulsion PSAs. *Int. J. Adhes. Adhes.* **27**:102–107 (2007). doi:10.1016/j.ijadhadh.2006.02.002.
41. D. Lim, H. Do, and H. Kim. PSA performances and viscoelastic properties of SIS-based PSA blends with H-DCPD tackifiers. *J. Appl. Polym. Sci.* **102**:2839–2846 (2006). doi:10.1002/app.24571.
42. D. E. Bairamov, A. E. Chalykh, M. M. Feldstein, and R. A. Siegel. Impact of molecular weight on miscibility and interdiffusion between poly(N-vinyl pyrrolidone) and poly(ethylene glycol). *Macromol. Chem. Phys.* **203**:2674–2685 (2002). doi:10.1002/macp.200290050.
43. R. S. Vartapetian, E. V. Khozina, J. Karger, D. Geschke, F. Rittig, M. M. Feldstein, A. E. Chalykh, and E. V. Khozina. Self-diffusion in poly(N-vinyl pyrrolidone)—poly(ethylene glycol) systems. *Colloid Polym. Sci.* **279**:532–538 (2001). doi:10.1007/s003960000447.
44. M. M. Feldstein, A. Roos, C. Chevallier, C. Creton, and E. E. Dormidontova. Relation of glass transition temperature to the hydrogen bonding degree and energy in poly(N-vinyl pyrrolidone) blends with hydroxyl-containing plasticizers: 3. Analysis of two glass transition temperatures featured for PVP solutions in liquid poly(ethylene glycol). *Polymer.* **44**:1819–1834 (2003). doi:10.1016/S0032-3861(03)00046-6.
45. F. P. Schwarb, G. Imanidis, E. W. Smith, J. M. Haigh, and C. Surber. Effect of concentration and degree of saturation of topical fluocinonide formulations on *in vitro* membrane transport and *in vivo* availability on human skin. *Pharm. Res.* **16**:909–915 (1999). doi:10.1023/A:1018890422825.
46. Y. Y. Wang, C. T. Hong, W. T. Chiu, and H. Y. Fang. *In vitro* and *in vivo* evaluations of topically applied capsaicin and nonivamide from hydrogels. *Int. J. Pharm.* **224**:89–104 (2001). doi:10.1016/S0378-5173(01)00755-4.