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Transient drug supersaturation kinetics of beclomethasone dipropionate in rapidly drying films

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ABSTRACT

Supersaturation is an effective method to enhance the delivery of active compounds into the skin, however the long-term instability of the drug in these formulations that exceed thermodynamic unity prevents clinical use. The creation of supersaturation *in situ* by volatile solvent evaporation after application may overcome this. The aim of this study was to determine how altering the kinetics of transient supersaturation and recrystallisation would effect the rate of beclomethasone dipropionate (BDP) release from metered dose aerosols (MDA) that also consisted of hydrofluoroalkane 134a, ethanol (EtOH), and poly(vinyl pyrrolidone) (PVP) K90. An MDA containing 10% EtOH generated a sub-saturated concentration of BDP immediately after dose actuation and did not become supersaturated until 30 min post-actuation. Increasing the EtOH to 20% (w/w) and thus the BDP to 1.76% created supersaturation upon dose actuation but the drug recyrstallised within minutes of application. It was shown that the formulations with higher DS had accelerated rates of release despite rapid recrystallisation (444.9 ± 79.3 μg/(cm^2 h) for the fastest compared to 206.5 ± 23.0 μg/(cm^2 h) for the slowest). In highly volatile sprays maintaining BDP supersaturation for extended periods of time was less important than generating instantaneous, high levels of supersaturation to enhance drug release.

1. Introduction

The percutaneous delivery of drugs for the treatment of local diseases in the skin overcomes several issues associated with more traditional routes of administration (e.g., oral or intravenous) as it minimises systemic drug exposure and hence reduces the chance of side-effects. However, delivering adequate therapeutic concentrations of a drug into the skin can be problematic due to the relative impermeability of the outermost layer, the *stratum corneum* (SC) (Wickett and Visscher, 2006). To compound this problem the efficiency of topical delivery is often poor as a high percentage of the drug typically remains trapped in the vehicle when traditional formulations such as ointments and creams are used. For example, an extensive investigation into the release of hydrocortisone from several commercial creams revealed that only 5–10% of the dose applied was released from the formulation (Shah et al., 1989). As only a small proportion of the applied drug is typically available for delivery into the skin using conventional approaches novel administration strategies are required to improve this process (Barry, 1991).

Enhancing permeation into the skin via supersaturation of the drug in the application vehicle is a simple, cost-effective method that has previously been shown to improve the efficiency of topical drug release (Davis and Hadgraft, 1991; Pellett et al., 1994). Supersaturation is attained when a compound is solubilised at a concentration which is greater than the saturated equilibrium solubility (defined as a thermodynamic activity of one). The increase in drug concentration above equilibrium increases its thermodynamic activity, which according to the Higuchi equation, increases the rate at which the drug can permeate through a barrier, e.g., the skin (Eq. (1)):

$$J = \frac{\alpha DA}{\gamma L} \quad (1)$$

where J is the flux of the compound through the barrier, α is the thermodynamic activity of the compound in the donor solution, D is the diffusion coefficient of the compound, A is the effective cross-section area of the barrier, γ is the effective activity coefficient of the compound in the membrane, and L is the barrier thickness (Higuchi, 1960). According to Eq. (1) the drug thermodynamic activity and flux are directly proportional to one another and therefore a two-fold increase in thermodynamic activity would result in the compound flux being twice as fast, assuming all other parameters remain unchanged (Raghavan et al., 2000; Davis and

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Hadgraft, 1991). Therefore, theoretically, generating highly supersaturated topical formulations is an excellent method to improve percutaneous delivery.

Several studies have reported experimental data to support Higuchi's equation and revealed that an increased DS correlates to a faster flux through a membrane (Pellett et al., 1997; Iervolino et al., 2000, 2001; Raghavan et al., 2000). However, for this relationship to hold for a significant time period, the solution with a heightened DS must remain physically stable and minimal crystallisation of the drug should occur during the permeation process. Once initiated, precipitation of the drug quickly reverts the system to a saturated concentration (Hou and Siegel, 2006; Schwarb et al., 1999). In an attempt to circumvent this problem, anti-nucleant polymers have been added to supersaturated formulations to prevent crystal nucleation or growth and thus maintain the elevated thermodynamic activity (Lipp, 1998; Ma et al., 1996). The addition of anti-nucleant polymers can lengthen the time of supersaturated solution stability and also facilitate the generation of higher levels of supersaturation (Pellett et al., 1997; Raghavan et al., 2001a). For example, Megrab et al. (1995) found that the addition of poly(vinyl pyrrolidone) (PVP) to supersaturated solutions of oestradiol produced an 18-fold increase in drug saturated solubility, an effect that was hypothesised to be as a result of crystal growth inhibition by PVP (Megrab et al., 1995).

It has been shown previously that metered dose aerosol (MDA) formulations which utilise solvent evaporation to induce supersaturation improve the release of topical therapeutic agents (Jones et al., 2009). The aim of current study was to determine how altering the recrystallisation kinetics of these MDA systems would affect the release of a drug, in this case beclomethasone dipropionate (BDP). Attempts were made to alter supersaturation kinetics by increasing of the proportions of the volatile solvent, ethanol (EtOH) and drug in the propellant systems. It was anticipated that instantly supersaturated formulations and those that slowly became supersaturated could be produced and compared with regard to BDP solubility in the formulation, degree of saturation (DS), drug recrystallisation time and drug release profile through a synthetic membrane. It was hypothesised that studying the supersaturation kinetics of these formulations will ultimately allow the production of a highly efficient topical drug delivery system.

2. Materials and methods

2.1. Materials

BDP was purchased from Airfilco (UK) and was used as received. EtOH (99.7–100%, v/v) was purchased from BDH (UK). Acetonitrile (ACN) (high performance liquid chromatography, HPLC, grade) was from Fisher Scientific (UK). PVP K90 was purchased from Fluka (Switzerland). Solkane 1,1,1,2-tetrafluoroethane (HFA) 134a propellant was kindly donated by Solvay (Germany). Regenerated cellulose membrane (RCM) (12–14 kDa molecular weight cut-off) was purchased from Medicell International (UK).

2.2. Metered dose aerosol formulation

PVP K90 and BDP were weighed directly into a 10 ml Purgard® canister made of clear glass and safety coated in polypropylene (Adelphi Tubes, UK) at the desired weight/weight ratios. EtOH was 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., UK). This was left to stir overnight to allow the polymer to solvate. The HFA 134a was pressure-filled into the sealed glass canister using a MDA filler (Model # 2016, Pamasol Willi Mader AG, Switzerland) until the desired weight was obtained. The MDA was stirred for 24 h and solubility of the mixture assessed visually. Complete dissolution of all the components into a single phase was defined as a soluble system whereas the appearance of precipitate in the mixture was defined as an insoluble mixture.

2.3. Evaporation rate and degree of saturation calculation

Thirty actuations from an MDA were applied to a tared weighing boat on an analytical balance (type R160 P, Sartorius, Germany) and monitored for weight loss after application. Weight of the formulation (g) was plotted against time (min) using Excel (Microsoft, USA). The rate of solvent evaporation was calculated using a line of best fit over at least four time points, if appropriate. The study continued for 48 h to ensure the applied formulations were completely dry and no further weight loss occurred. The final weight of the film was compared to the weight at a set time point to calculate the weight of the remaining EtOH at that time, and this was used to determine the concentration of drug (%w/w), as described previously in Jones et al. (2009). By comparing this value with the saturated solubility of the drug in EtOH, a DS was obtained (Eq. (2)):

$$\frac{WD_{App}/(WF_t - WF_{Final})}{C_{SS}} = DS \quad (2)$$

where WD_{App} (mg) was the weight of the drug applied, WF_t (g) was the weight of the formulation at the time point t, and WF_{Final} (g) was the final weight of the formulation after 48 h. This gave a concentration (mg of drug/g of solvent) at time t, which was then divided by the saturated solubility concentration of the drug in the solvent, C_{SS} (mg/g). If the concentration at time t was greater than the saturated solubility, then the formulation was classified as supersaturated. The DS was plotted against time (min) using Excel 2003 (Microsoft, USA) to assess DS kinetics over the course of the experiment. Each film was examined visually using an Axioskop microscope (Carl Zeiss, Germany).

2.4. Drug release studies

The release experiments were carried out in individually calibrated upright Franz cells (MedPharm Ltd., UK) with an average receiver volume of 10.8 cm^3 and an average surface area of 2.1 cm^2. The 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 previously sonicated receiver fluid of 70:30 ACN:DiH_2O (BDP was shown to be chemically stable in this solution over the time of the experiment; data not shown). The cells were checked for leaks by visual inspection and inversion and placed on a submergible stir plate in a pre-heated water bath set at 37 °C to obtain 32 °C at the membrane surface (Maddock and Coller, 1933). The cells were left to equilibrate for 1 h prior to the initiation of infinite dose studies. The MDA formulations (30 actuations) were applied to the apical surface of the membranes and release from the formulations was assessed by the removal of 1 ml samples from the receiver chamber of the Franz cell. These samples were placed into HPLC vials 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) using Excel 2003 (Microsoft, USA).

2.5. HPLC analysis

BDP was assayed using a HPLC system consisting of a 600E pump, a 996 PDA Detector, a 717 Plus Autosampler coupled with Millennium[32] Software, version 4.0 (Waters, USA). The mobile phase was 70:30 ACN:DiH_2O set at a flow 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. Peak retention times were ~3 min and calibration curves were constructed from integrated peak area from known concentrations of standards. This method 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, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996).

3. Results and discussion

Molecular size and lipophilicity are two of the most influential physicochemical parameters that determine the permeation rate of topically applied active agents into the skin. For example, compounds with an intermediate lipophilicity (e.g., log *P* from 1 to 3) demonstrate efficient partitioning into the skin, effective SC penetration and good accumulation in the underlying epidermis, which is the most common site of action for topically applied therapeutic agents (Potts and Guy, 1992; Yano et al., 1986). Highly hydrophobic compounds (e.g., log *P* > 3) show excellent partitioning but are typically retained within the SC. Despite only a very small proportion of the applied dose reaching the epidermis there is a clinical need to administer a wide range of hydrophobic agents with a log *P* > 3 topically and as a consequence drug delivery technologies that improve the efficiency of these agents are still required.

One approach that has recently been shown to improve the performance of corticosteroid drug release from topical formulations is administration using an MDA spray (Jones et al., 2009). This drug delivery technology formulates a saturated concentration of active ingredient (e.g., BDP) with a mixture of a film-forming antinucleant polymer (PVP K90), a propellant (HFA 134a) and a volatile organic co-solvent EtOH in order to transiently enhance the thermodynamic activity of the drug when applied to the skin. In such a formulation there is a complex relationship between the drug and the formulation excipients which control drug supersaturation and drug release kinetics. Through analysis of the formulation both pre- and post-administration this study attempted to examine the excipient interactions in order to better understand and thus optimise this novel means of topical drug delivery.

The behaviour of each component within the MDA canister was assessed by visual solubility experiments. The proportions of PVP K90, HFA 134a, and BDP were varied while the co-solvent EtOH remained constant at either 10 or 20% (Fig. 1). Only 1% (w/w) BDP was soluble in the MDA when 10% (w/w) EtOH was included in the formulation (Fig. 1a). Repeating this experiment with a 20% (w/w) EtOH increased the maximum amount of BDP that could be solubilised in the system to 2.2% (w/w) (Fig. 1b). This approximately proportional increase in BDP solubility demonstrated that EtOH was the main solubiliser of the drug in the HFA 134a propellant. However, increasing the amount of EtOH in the MDA had an even greater effect on the PVP K90 solubility compared to BDP. When 10% (w/w) EtOH was added to the MDA, the maximum amount of PVP K90 that could be solubilised was 2.8% (w/w), but when the EtOH content was increased to 20% (w/w), the amount of soluble PVP in the canister increased disproportionately to >17.9% (w/w). Theoretically it may be possible for greater amounts of PVP to be solubilised in the MDA, but the formulations with such large amounts of PVP became too viscous for application and therefore were not studied further.

Three different BDP saturated 20% (w/w) EtOH MDAs formulated with equivalent amounts of drug and different amounts of PVP were chosen to study the effect of increased polymer concentration on the supersaturation and release kinetics (Table 1). These formula-

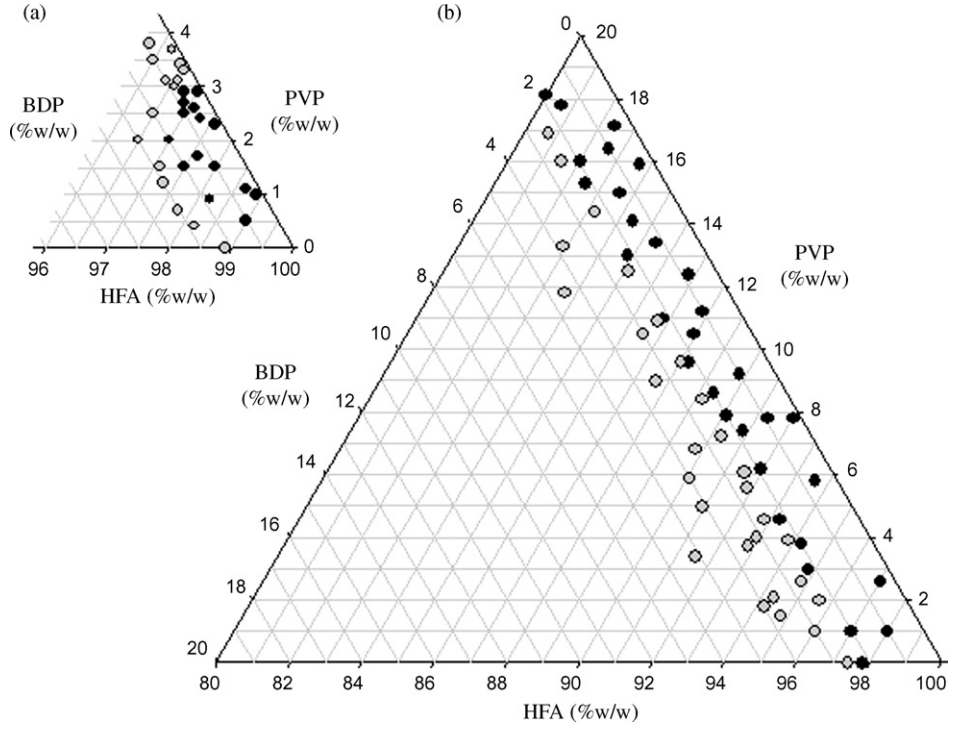

Fig. 1. Ternary phase plot depicting solubility of poly(vinyl pyrrolidone) K90 (PVP), hydrofluoroalkane 134a (HFA), and beclomethasone dipropionate (BDP) in either a 10% (w/w) ethanol (EtOH) (a) or 20% (w/w) EtOH mixture (b) (● soluble, ○ insoluble).

Table 1
Metered dose aerosol formulations employed in drug release studies.

Formulation name	20% EtOH *L* (%w/w)	20% EtOH *M* (%w/w)	20% EtOH *H* (%w/w)	10% EtOH (%w/w)
PVP K90	0.88	1.76	5.28	2.52
BDP	1.76	1.76	1.76	0.09
EtOH	20.0	20.0	20.0	10.0
HFA 134a	77.36	76.48	72.96	87.39
Ratio PVP:BDP	0.5:1	1:1	3:1	28:1

Three 20% (w/w) ethanol (EtOH) formulations were produced that contained different ratios of poly(vinyl pyrrolidone) K90 (PVP) to beclomethasone dipropionate (BDP), and these were compared to a formulation that contained only 10% (w/w) EtOH and thus a lower BDP concentration. All formulations contained hydrofluoroalkane 134a (HFA) as the propellant.

tions were designated low, medium, and high (*L*, *M*, *H*) in reference to the ratio of PVP to BDP, which ranged from 0.5:1 PVP K90:BDP to 3:1 PVP K90:BDP. To contrast the 20% (w/w) EtOH formulations which contained relatively high concentrations of BDP, a drug saturated MDA containing 10% (w/w) EtOH was also chosen for study as it contained a therapeutically relevant concentration of BDP at 0.1% (w/w).

A drug saturated MDA has previously been shown to enhance drug release by supersaturation. This process was driven by the evaporation of volatile solvents after dose actuation, which reduced the volume of liquid available to solubilise the drug and created a highly concentrated drug solution (Jones et al., 2009). To understand the impact of increasing the EtOH and PVP content on the evaporation profile, the weight loss of all four formulations was monitored after dose actuation (Fig. 2). Three gradients of weight loss were detected for all four MDA formulations: the first from approximately 0 to 1 min, the second from 5 to 30 min, and the third from 60 min to 4 h. These three regions in the MDA evaporation profile have previously been defined as HFA loss (first region) followed by EtOH loss (second region) and finally hardening of the film (no weight loss in the third region) (Jones et al., 2009; Stein and Myrdal, 2006). The volatile loss from the 10% (w/w) EtOH MDA in region one was significantly faster compared to the 20% (w/w) EtOH MDA at 197.3 ± 13.7 and 79.8 ± 7.9 mg/min, respectively ($p < 0.05$, linearity of $r^2 > 0.9$ for all). This may be explained by the vapour pressure depression effects of EtOH on HFA according to Raoult's law, as more EtOH is added to HFA the lower the vapour pressure became and therefore evaporation was slowed (van Wesenbeeck et al., 2008; Williams and Liu, 1998).

The second region of the weight loss profile was thought to be a reflection of EtOH evaporation. As expected, the MDA formulations containing less EtOH gave a shorter period of steady state evaporation in this region, e.g., 10% EtOH MDA produced weight loss for 15 min but the 20% EtOH for 45 min. The MDA EtOH evaporation for two of the three formulations containing 20% EtOH, the *L* and *M* (rates of 6.0 ± 0.1 and 5.9 ± 0.1 mg/min, respectively) was significantly faster ($p \leq 0.05$) compared to the 10% (w/w) EtOH MDA (5.2 ± 0.2 mg/min, linearity of $r^2 > 0.97$ for all formulations). The critical factor that appeared to influence the evaporation of EtOH was the ratio of EtOH to PVP. The *L* and *M* 20% (w/w) EtOH MDAs employed EtOH:PVP ratios of 22.7 and 11.4, respectively, which coincided with the fastest evaporation rates, whilst the 20% (w/w) EtOH H MDA and the 10% (w/w) EtOH MDA, formulated at EtOH:PVP ratios of 3.8 and 4.0, respectively, gave the slowest evaporation rates. As the MDAs with greater quantities of PVP gave slower rates of EtOH evaporation it was hypothesised that the viscosity of the films, which was probably controlled by the PVP K90 concentration, was the main determining factor of volatile solvent loss (Merkli et al., 1996; Nielsen and Olsen, 1995). In order to evaporate, the EtOH molecules must diffuse through the polymer solution to reach the surface of the film and escape. Increasing the viscosity of a solution via the addition of PVP will reduce the molecular diffusion and possibly lead to EtOH depletion at the air–liquid interface and thus a reduction in evaporation rate (Aronson et al., 2004).

Monitoring the evaporation of the MDAs enabled the levels of drug supersaturation in the films to be theoretically calculated over time (Fig. 3). The MDA formulation containing 10% (w/w) EtOH was sub-saturated at 0.1 DS immediately after dose actuation, while the 20% (w/w) EtOH formulations were instantly supersaturated at 1.4, 1.2, and 1.2 DS for *L*, *M*, and *H*, respectively. Drug crystals were observed in all the films generated by the 20% (w/w) EtOH MDAs and therefore the final DS for these formulations, which

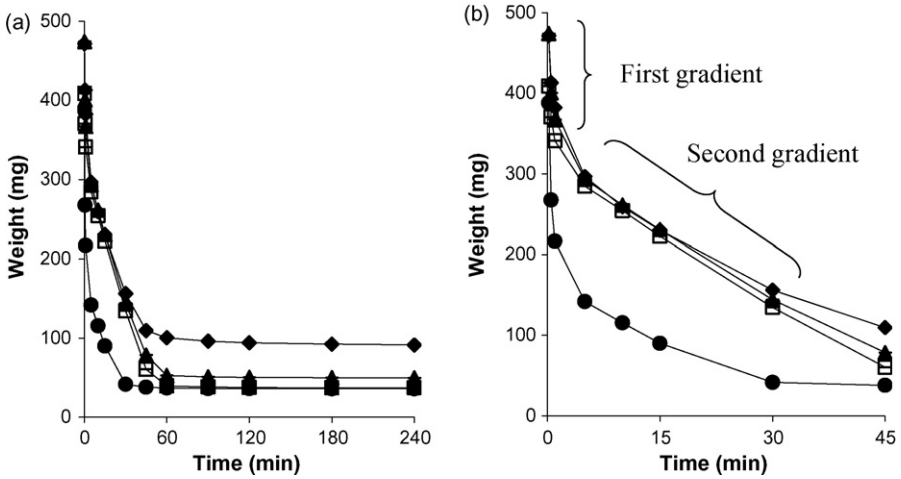

Fig. 2. A comparison of weight loss due to solvent evaporation from metered dose aerosol (MDA) formulations containing different weight ratios of polyvinyl pyrrolidone (PVP) to beclomethasone dipropionate (BDP) in 20% (w/w) ethanol (EtOH) MDAs: 0.5:1 PVP:BDP (square), 1:1 PVP:BDP (triangle), 3:1 PVP:BDP (diamond) compared against a 10% (w/w) EtOH 28:1 PVP:BDP MDA (circle) whereby where (b) is an expansion to show the two rate gradients over 45 min of the full data set (a). Points represent mean of $n = 3 \pm$ one standard deviation (error bars within symbols).

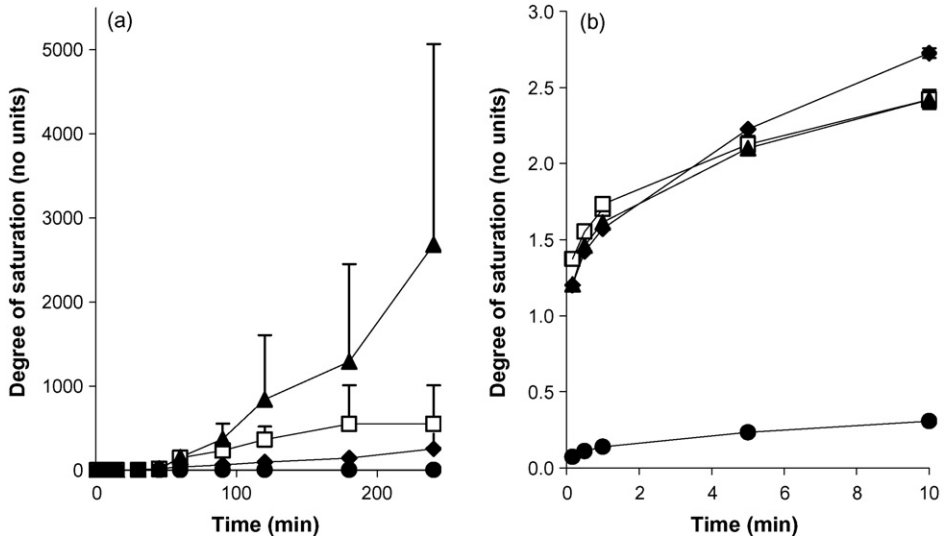

Fig. 3. Theoretical degrees of saturation drug (DS) after dose delivery from metered dose aerosol (MDA) formulations containing different weight ratios of poly(vinyl pyrrolidone) (PVP) K90 to beclomethasone dipropionate (BDP) in 20% (w/w) ethanol (EtOH) MDAs: 0.5:1 PVP:BDP (square), 1:1 PVP:BDP (triangle), 3:1 PVP:BDP (diamond) with the 10% (w/w) EtOH MDA (circle) where (b) is an expansion to show the differences over first 10 min of the full data set (a). Dashed lines indicate theoretical DS due to observations of drug crystals in the film. Points represent mean of $n = 3 \pm$ one standard deviation.

ranged from 257.5 ± 178.3 to 2685.3 ± 2382.5, was thought not to be accurate. The DS calculated immediately prior to the appearance of crystals for the MDAs containing 20% EtOH was 1.7 ± 0.0, 2.1 ± 0.0 and 3.3 ± 0.0 for the *L*, *M*, and *H* MDAs, respectively. The difference in supersaturation kinetics between the 10 and 20% EtOH containing MDAs was primarily due to the disparate drug loads in the formulations, the 10% (w/w) EtOH contained 0.09% (w/w) BDP and the 20% (w/w) EtOH contained 1.76% (w/w) BDP (Table 1).

An optical microscope was used to estimate the point at which the BDP within the 20% (w/w) EtOH formulations began to recrystallise (Fig. 4). Crystals were detected at 3.4 ± 0.1 min for the *L* formulation, at 6.1 ± 0.8 min for the *M* formulation, and 15.3 ± 2.7 min for the *H* formulation. Increasing the amount of PVP in the MDAs from 0.88% (w/w) to 5.28% (w/w) resulted in a 4.5-fold increase in the time it took crystals to appear in the films. The 10% (w/w) EtOH MDA, which had the highest ratio of PVP:BDP at 28:1 was monitored for up to 48 h after dose actuation but no crystals were detected. PVP K90 has previously been shown capable of retarding the growth of crystals and assisting the maintenance of supersaturation (Schwarb et al., 1999; Megrab et al., 1995; Raghavan et al., 2001a). Anti-nucleant polymers such as PVP are thought to prevent crystallisation through an increase in solution viscosity (an effect also shown by the evaporation studies in this work) which slows molecular diffusion and prevents seed nucleation (Raghavan et al., 2001b). However, a chemical interaction between PVP and the drug caused by the adsorption and the orientation of the polymer at the solid/liquid interface of the crystal as it forms makes the antinucleant capability of a polymer more efficient (Megrab et al., 1995; Sekikawa et al., 1978).

Although crystals were observed in the films generated by the MDAs during the time course of the release experiments, the BDP in the films did not necessarily return to saturated drug concentrations immediately. The quantity of drug remaining in solution is dependant upon the rate at which the drug recrystallises and thus the potential for enhanced drug release could still exist. As it was technically challenging to measure the drug solubility of these dynamic formulations, the effects of the potentially different recrystallisation kinetics was determined practically by assessing BDP release using a RCM (Fig. 5). The release of BDP from the 20% EtOH *L* and *M* MDAs was the highest of the assessed formulations and statistically similar at every data point ($p > 0.05$). The hypo-

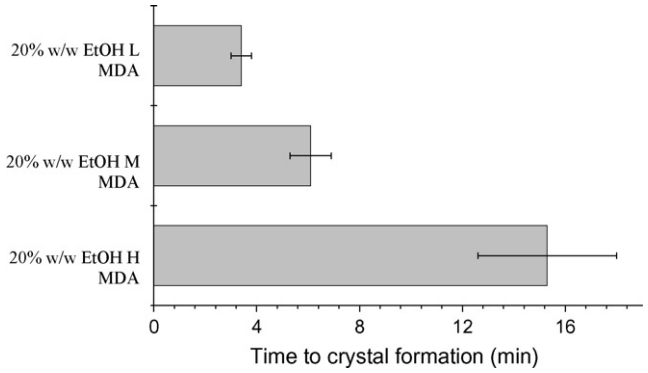

Fig. 4. Time for beclomethasone crystals to be detected by microscopic examination after 30 actuations of metered dose aerosols (MDA) containing different ratios of poly(vinyl pyrrolidone) (PVP) K90 in 20% (w/w) ethanol (EtOH): 0.5:1 PVP:BDP (*L*), 1:1 PVP:BDP (*M*), 3:1 PVP:BDP (*H*). No crystals were detected in the 10% (w/w) EtOH 28:1 PVP:BDP MDA, therefore this data was not shown. Points represent mean of $n = 3 \pm$ one standard deviation.

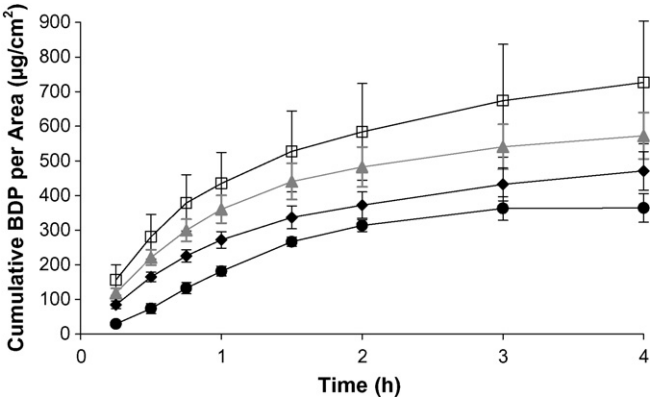

Fig. 5. A comparison of beclomethasone dipropionate (BDP) release profiles from metered dose aerosol (MDA) formulations containing different weight ratios of poly(vinyl pyrrolidone) (PVP) K90 to BDP in a 20% (w/w) ethanol MDA (*L*): 0.5:1 PVP:BDP (square), (*M*) 1:1 PVP:BDP (triangle), (*H*) 3:1 PVP:BDP (diamond) with the 10% (w/w) EtOH MDA (circle). Data points represent mean of $n = 5 \pm$ one standard deviation.

thetical DS for these two formulations did not correlate with the release profiles (Fig. 3a), as the extremely high DS did not result in a proportionate response in rate of BDP release. Despite an initially slower release rate, the total amount of BDP released by the 20% (w/w) EtOH *H* MDA was significantly equivalent at 1.0 ± 0.2 mg ($p > 0.05$) compared to the other two 20% (w/w) EtOH formulations at 1.5 ± 0.6 mg for the *L* MDA and 1.2 ± 0.3 mg for the *M* MDA ($p > 0.05$). Again a depressed release profile from the 20% (w/w) EtOH *H* MDA compared to the *L* and *M* formulations did not correlate well to the drug supersaturation achieved by this formulation. The trend in BDP release across the 20% EtOH MDAs could be attributed to the increased viscosity caused by the higher concentration of PVP K90 (Ruiz Martinez et al., 2007; Barreiro-Iglesias et al., 2001). Raghavan et al. (2000) saw a similar effect when studying supersaturated gels, in which an increase in formulation viscosity as a result of increase polymer concentration decreased diffusion of the drug to the membrane interface despite the ability of the polymers to inhibit crystal nucleation and thus retain increased thermodynamic activity (Raghavan et al., 2000).

Although the rate of release is the most commonly employed indices used to compare infinite dosing study results, in this work there was no steady state drug release seen up to 4 h and so the release rate could not be accurately assessed. The lack of steady state was a consequence of the films drying rapidly after dose actuation which inevitably increased viscosity and reduced drug mobility, a effect that has been previously observed (Reid et al., 2008). However, the 20% (w/w) EtOH MDAs did have a faster release profile and as all other variables in the formulations were controlled this was assumed to be indicative of a higher thermodynamic activity compared to the 10% (w/w) EtOH MDA according to the Higuchi equation, thus giving some validity to the DS determination used in this work (Higuchi, 1960). Using an abbreviated steady state over 45 min for the sake of a comparison only, the rates were 444.9 ± 79.3 μg/(cm^2 h) for the *L* MDA, 362.7 ± 43.3 μg/(cm^2 h) for the *M* MDA, and 282.1 ± 27.2 μg/(cm^2 h) for the *H* MDA. Again, the *L* and *M* formulations were statistically similar ($p > 0.05$) while both were greater than the *H* MDA ($p \leq 0.05$ for both). All three of the 20% EtOH formulations were faster up to the 45 min time point compared to the 10% EtOH MDA at 206.5 ± 23.0 μg/(cm^2 h) ($p \leq 0.05$).

4. Conclusion

Two types of quick-drying films, developed to enhance of topical drug delivery, were compared containing different levels of EtOH in order to investigate the effects of varying the supersaturation kinetics on BDP release from MDAs. Using only 10% EtOH and a relatively low drug load produced a film with a sub-saturated concentration of drug immediately after dose actuation which did not become supersaturated until nearly 30 min post-dose actuation. Including 20% EtOH and a relatively high drug load in the MDA produced supersaturation immediately upon dose actuation, but the BDP recyrstallised within minutes of film formation. It was shown that the formulations with higher drug loads and instant supersaturation had accelerated rates of drug release despite rapid recrystallisation. Attempts to reduce the recrystallisation of the instantly supersaturated films using greater quantities of antinucleant polymer simply retarded release by increasing film viscosity. In a fast drying system, attempting to maintain supersaturation for extended periods of time was not a successful drug delivery enhancement strategy and as such for a drug that requires rapid application effective instantaneous supersaturation was the key to enhancement of the drug release.

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