Rationalising polymer selection for supersaturated film forming systems produced by an aerosol spray for the transdermal delivery of methylphenidate

A. Edwards[1], S. Qi[2], F. Liu[1], M.B. Brown[1, 3] and W.J. McAuley[1*]

[1]Department of Pharmacy, Pharmacology and Postgraduate Medicine, University of Hertfordshire, College Lane, Hatfield, AL10 9AB, UK

[2]School of Pharmacy, University of East Anglia, Norwich, NR4 7TJ, UK

[3]MedPharm Ltd, Unit 3 Chancellor Court, 50 Occam Road, Surrey Research Park, Guildford, GU2 7AB, UK

Corresponding author: William McAuley, w.j.mcauley@herts.ac.uk

Abstract

Film forming systems offer a number of advantages for topical and transdermal drug delivery, in particular enabling production of a supersaturated state which can greatly improve drug absorption and bioavailability. However the suitability of individual film forming polymers to stabilise the supersaturated state and optimise delivery of drugs is not well understood. This study reports the use of differential scanning calorimetry (DSC) to measure the solubility of methylphenidate both as the free base and as the hydrochloride salt in two polymethacrylate copolymers, Eudragit RS (EuRS) and Eudragit E (EuE) and relates this to the ability of films formed using these polymers to deliver methylphenidate across a model membrane. EuRS provided greater methylphenidate delivery when the drug was formulated as the free base in comparison EuE because the lower solubility of the drug in EuRS provided a higher degree of drug saturation in the polymeric film. In contrast EuE provided greater delivery of methylphenidate hydrochloride as EuRS could not prevent its crystallisation from a supersaturated state. Methylphenidate flux across the membrane could be directly related to degree of saturation of the drug in the film formulation as estimated by the drug solubility in the individual polymers demonstrating the importance of drug solubility in the polymer included in film forming systems for topical/transdermal drug delivery. In addition DSC has been demonstrated to be a useful tool for determining the solubility of drugs in polymers used in film forming systems and the approaches outlined here are likely to be useful for predicting the suitability of polymers for particular drugs in film forming transdermal drug delivery systems.

Introduction

Film forming systems for topical or transdermal application contain drug and film forming excipients along with volatile solvent(s) in a formulation which typically presents as a solution or spray. On contacting the skin, the volatile solvent evaporates leaving the drug in a residual film of excipients on the skin surface. Film forming systems offer a number of advantages over more conventional formulation types; they can provide a unit dose, improve drug delivery, be applied easily to large application areas and their rapidly drying/absorbing nature can help to minimise transference losses of product onto clothes or other people. As such a number of topical film, forming pharmaceutical products have been successfully marketed [1].

Perhaps the key advantage of film forming systems over other topical/transdermal formulation types is their potential to improve drug absorption into and across the skin, potentially increasing the total amount of drug delivered and also improving bioavailability. Drug bioavailability from dosage forms applied to the skin is typically low, such that large amounts of drug are unabsorbed, remaining on the skin surface or being retained in the dosage form in the case of transdermal patches [2, 3]. Improving bioavailability so that more drug is transferred from the dosage form into the skin may improve therapeutic outcomes and decrease production costs as it reduces the quantity of drug required in a dosage form for a particular dose of drug to be delivered into the body. Developing film forming systems with improved bioavailability for drugs that are delivered transdermally and may be abused, such as opioids (e.g. fentanyl) or stimulants (e.g. methylphenidate), may help to assist in the development of products that are less attractive for drug abuse, as a result of a lower abusable drug content [4].

Early examples of improving drug delivery across skin by the use of a volatile solvent that evaporates from a formulation leaving the drug in residual solvent or film of material date back to the 1960s [5, 6]. The simplest design of these systems is a solution in which the volatile solvent (usually ethanol or isopropanol) is the main formulation ingredient and is a carrier for the rest of the formulation. The loss of solvent from the formulation increases the drug saturation in the residual phase of the formulation that remains on the skin surface. This increase in drug saturation or thermodynamic activity in the formulation produces an increased driving force for the delivery of drug across the skin which increases in a proportional manner with the degree of saturation (DS) of the drug in the residual formulation. If the degree of saturation of the drug in the formulation increases above the solubility limit of the drug (above 1DS), the system becomes supersaturated [7]. Supersaturated systems can provide proportional improvements in drug delivery in relation to the degree of saturation of the drug, however these systems are unstable and if the drug precipitates from the formulation, the potential drug delivery advantages are lost [8]. Selection of suitable formulation excipients, for example anti-nucleant polymers can delay drug crystallisation for a sufficient period of time allowing improved drug delivery to be achieved [9].

The dynamic nature of film forming systems makes fully understanding drug delivery from these formulations challenging. Not only does the degree of drug saturation in the film change as the volatile components evaporate, but permeation of any residual solvent or penetration enhancer into the stratum corneum will also affect the degree of drug saturation in the residual formulation. Moreover the individual capabilities of the chemical penetration enhancers along with their ability to work with the supersaturated system will also influence the overall drug permeation rate [10]. Therefore developing a thorough understanding of the drug delivery behaviour of these formulations has proven difficult. Much of the current

knowledge relating to the use of anti-nucleant polymers to provide stabilisation relates to systems where the supersaturated state was produced via the cosolvent method where the polymer concentration is relatively low, for example 1% w/w and has a negligible effect on the drug solubility in the formulation [11]. Previous work has been performed to understand permeation from film forming systems considering the degree of drug saturation in the solvents contained in the formulation alone [12, 13]. However with film forming systems a polymer is often a main component of the residual film formed on the skin surface and it may have a large effect on drug saturation in the residual formulation and consequent drug delivery. A clear understanding of the effects of polymers on drug delivery from film forming systems and the stabilisation of supersaturated films would provide key insights into helping improve the design of such formulations.

In this study methylphenidate which is available commercially in a transdermal patch formulation (Daytrana) has been formulated in film forming, metered dose aerosol spray formulations with two different polymethacrylate polymers, Eudragit® E (EuE) and Eudragit® RS (EuRS). Detailed physical characterisation of the interaction between methylphenidate and the polymers was performed with differential scanning calorimetry (DSC) and used to measure drug solubility in the polymers to guide interpretation of drug release from and stabilisation of supersaturated films.

Materials and Methods

Materials

Methylphenidate hydrochloride USP (MPH-HCl) was supplied by Macfarlan Smith (Edinburgh, UK). Dimethyl ether (DME) (99.9%) was obtained from Azkonoble (London, UK). Methanol (MeOH), acetonitrile (ACN), triethylamine (TEA), isopropyl alcohol (IPA), absolute ethanol (EtOH) (all HPLC grade), sodium hydroxide (NaOH) (99%), phosphoric

acid (85%), hydrochloric acid (37%), dichloromethane (DCM) (99%), propylene glycol (PG) (99%) and sodium chloride (NaCl) (99.5%) were all acquired from Fisher Scientific (Loughborough, UK).EuE and EuRS were donated by Evonik (Essen, Germany). Non-porous, non-reinforced silicone membrane of 0.13 cm thickness was purchased from Bioplexus (Ventura, USA).

Preparation of MPH-base

MPH-base was prepared by performing an acid-base extraction. In summary, accurately weighed MPH-HCl was dissolved in deionised water using a separation funnel. Sodium hydroxide (3 M) was added to the funnel to render the solution alkaline and it was shaken for 30 seconds. Dichloromethane (DCM) was added to the aqueous phase to extract the methylphenidate free base. The DCM and aqueous phase mixture was shaken for 1 minute and then left to stand for 2 minutes. The clear organic phase was aliquoted into a round bottom flask. The extraction process using DCM was repeated twice. The organic phase (the 3 extracts of DCM) was rotary evaporated before storing at 5^{o}C to induce crystallisation of MPH base. Differential scanning calorimetry (DSC) (TA Instruments Q200 DSC, New Castle, USA) and infrared spectroscopy (Perkin Elmer Frontier FTIR, Seer Green, UK) were used to confirm the production of MPH-base (data not shown).

Preparation of metered dose aerosol formulations

MPH-base or MPH-HCl was weighed into a Purgard® canister made of clear glass and safety coated in polypropylene. All formulations contained propylene glycol, either ethanol or isopropanol as volatile solvents and either EuE or EuRS as the film forming polymer, which were added to each canister as required. The formulations containing ethanol had 45.5.mg of 0.03M hydrochloric acid added to improve drug stability. The canisters were sealed with 50 µl metered Seaquest valves and DME was pressure-filled into the sealed glass canister using

a Pamasol Laboratory Plant Filling and Sealing Station (Willi Mader AG, Pfäffikon, Switzerland). The metered dose aerosol formulations (MDAs) were left to mix on a roller mixer for 24 hours at room temperature to allow dissolution of the components which was assessed visually. The composition of the formulations used in this study are provided in Table 1.

High-performance liquid chromatography (HPLC)

Quantitative analysis of MPH was performed using HPLC with a Hewlett-Packard Series 1050 system and a Phenomenex, Kinetex™ 2.6 µm XB-C_{18} 100 Å LC Column 100 x 4.6 mm. An isocratic mobile phase of 12.5:12.5:75 ACN:MeOH:pH 3 phosphate buffer (10 mM buffer containing 8.48 g/L NaCl and 1.3ml/L TEA with phosphoric acid for pH adjustment) was used. The UV detection wavelength, flow rate and injection volume were 206 nm 0.6 ml/min and 10µl, respectively. The retention time of methylphenidate under these conditions was approximately 9 minutes. The HPLC methods were validated for linearity, precision and accuracy according to the current ICH guidelines [14, 15]. The calibration curve produced was linear over the concentration range 1-1000 µg/ml, with a coefficient of determination (r^2) of 0.9999. The limits of detection (LOD) and quantification (LOQ) were 8.80 and 26.60 µg/ml respectively. Intra- and inter-day precision (% RSD) for three standards representative of high, medium and low drug concentrations ranged from 0.12 to 0.22 % and 0.16 to 0.78% respectively. Accuracy of the same three concentrations ranged between 99.74 and 101.67%.

Solubility studies

The solubility of MPH-base and MPH-HCL in the receiver fluid used in the permeation studies (0.1 M pH 3 phosphate buffer) and solvents used in the formulations were determined at 32^{o}C. Saturated solutions were prepared by adding excess MPH into the solvents to form a

suspension and continuing to stir these for 24 hours in the presence of drug particles. The saturated suspensions were filtered (using 0.2 μm PTFE filters) to remove drug particles and the clear solutions were diluted in mobile phase prior to analysis using HPLC to quantify the drug concentration.

Drug transport studies

Measurement of MPH transport across silicone membrane was performed using Franz cells (Soham Scientific, UK). The cells were individually calibrated using deionised water to determine their volume and the diameter of the cell was measure using a calliper. Each Franz cell had an approximate receiver volume and surface area of 3 ml and 1 cm^2, respectively. Silicone membrane was cut to fit and mounted in each diffusion cell. The donor and receiver chambers were clamped together and sealed with Parafilm®. The receiver fluid, 0.1 M pH 3 phosphate buffer was added to the receiver compartment and any air bubbles trapped next to the membrane were removed. A magnetic flea was added to the receiver compartment and the Franz cell was placed on a submersible stirring plate places in water bath at 37°C. This provided a membrane temperature of 32°C which was confirmed with a probe K style thermometer (Fisher Scientific, UK). To examine drug transport from MDA produced drug containing films, 15 sprays of each formulation were applied to each Franz cell donor chamber. Glycerol was used as a solvent to determine the drug flux from a saturated solution of MPH-base. This was performed by adding 0.5 ml of a saturated suspension onto each Franz cell donor chamber to provide 'infinite' dose conditions over the testing period. Samples of 0.2 ml of receiver fluid were removed at 0, 0.5, 1, 2 and 3 hours and either 0.2 ml or the entire quantity of receiver fluid was removed at 4, 6, 8 and 24 hours in order to maintain sink conditions and the samples were placed in a HPLC vial prior to analysis. Following removal of each sample, the same volume of thermostatically equilibrated receiver

fluid was added to the receiver compartment. Statistical analyses of the permeation data was conducted using Graphpad Prism software (version 7.0 for Windows, La Jolla, USA). Data were checked for normality using the Shapiro-Wilks test prior to statistical comparison with one way analysis of variance (ANOVA). Post hoc comparison between groups was performed with either Tukey's or Dunnett's multiple comparisons test as appropriate. Statistical significance was accepted at the $p \leq 0.05$ level.

Differential scanning calorimetry (DSC)

A TA Instruments Q200 DSC (TA Instruments, New Castle, USA) was used to perform all thermal analysis. Cell constant and temperature calibrations were performed using n-octadecane, indium and caffeine for a range of heating rates including 0.2, 10 and 50 ^{o}C/minute. A nitrogen purge of 50 ml/min was used. For the melting enthalpy analysis of physical mixtures of MPH with EuRS or EuE, a heating rate of 0.2^{o}C/min was used. Physical mixtures were prepared by accurately weighing the required quantities of drug and polymer and by mixing/grinding in a pestle and mortar for 1 minute. Accurate quantities were then weighed into TA standard aluminium crimped DSC pans. Glass transition analysis was performed on solvent cast films that were prepared by dispensing a 38µl of drug and polymer solution into a pre-weighed standard aluminium DSC pan using a calibrated Gilson pipette. The samples were placed under vacuum for 24 hours to evaporate the volatile solvent and were then weighed twice over a one-hour period to ensure solvent evaporation was complete. Ethanol was used as the volatile solvent for MPH-HCl containing polymeric films and isopropyl alcohol was used for those containing MPH-base. All data analysis was performed using Universal Analysis 2000 from TA Instruments.

Determining the degree of saturation of MPH within film formulations

The degree of saturation of the drug within the film formulations was assessed using two different calculation methods. The first method [12, 16, 17] is described by Equation 1 where RS is the amount of residual solvent (propylene glycol) within the formulation and SS is the saturated solubility of MPH within the residual solvent. MPH saturated solubility within the residual solvent (PG) was assessed using HPLC.

$$\mathrm{DS} = \frac{\%\ \mathrm{MPH}}{(\%\ \mathrm{RS} \times \mathrm{SS})} \qquad \text{Equation 1}$$

The second method (Equation 2) involved the replacement of the saturated solubility values within the solvent with that of the drug in polymer (M), where P is the amount of polymer within the formulation.

$$\mathrm{DS} = \frac{\%\ \mathrm{MPH}}{(\%\ \mathrm{P} \times \mathrm{M})} \qquad \text{Equation 2}$$

The solubility of MPH-base in the polymers (EuE and EuRS) was determined from the melting enthalpy analysis of physical mixtures using DSC as described above.

Results

Drug transport across silicone membrane

The 24-hour drug transport data across silicone membrane of formulations 1.2% MPH-HCL EuE spray, 1.2% MPH-base EuE spray and the 1.2% MPH-base EuRS spray are shown in Figure 1a. Drug transport from the 1.2% MPH-HCL EuRS spray formulation across silicone membrane was not presented as the concentrations measured were below the limit of quantification at all time points. It was noted in contrast to the other formulations, the film formed by the 1.2% MPH-HCL EuRS formulation rapidly became cloudy following application to the silicone membrane, suggesting that crystallisation of the drug may have

occurred in the film which would be expected to reduce or prevent drug permeation [11]. The 1.2% MPH-HCL EuE spray and 1.2% MPH-base EuE spray, were initially designed to differ with regards to whether the salt or free base form of the drug was included in the formulation. However the solubility and stability of these different forms of the drug necessitated the use of different volatile solvents, with the 1.2% MPH-HCL EuE formulation containing 50% acidified ethanol and the 1.2% MPH-base EuE spray containing 30% IPA. Statistically the same drug transport was observed from these two formulations. In contrast, changing the polymer from EuE (1.2% MPH-base EuE) to EuRS (1.2% MPH-base EuRS) significantly increased drug transport from the films, indicating that the polymer included in the formulation has a considerable influence on drug transport. The saturated solubilities of MPH-HCL and MPH-base in the receiver fluid used were 152.8 and 7.0mg/ml respectively and in order to ensure sink conditions were maintained throughout the experiment, whereby the drug concentration in the receiver fluid did not exceed 10% of its saturated solubility, all of the receiver fluid was removed from the Franz cells where necessary and replaced with fresh receiver fluid. The drug transport profiles of the three formulations shown in Figure 1a are similar in that they initially show rapid drug transport that gradually decreases over time. The plot of this data against the square root of time is shown in Figure 1b where it can be seen that the data is linear over the initial time points which account for approximately 60% of MPH transport from the formulations. Such behaviour is consistent with the Higuchi model of drug release [18].The 1.2%, 3% and 6% MPH-base EuE formulations showed proportional increases in the drug transport with drug concentration (Figure 2a). In contrast the formulations containing different concentrations of MPH-base with EuRS (1.2%, 2%, 3%, 4 %, 4.5% and 5% MPH-base EuRS sprays), drug transport was observed to increase with increasing the drug concentration up to 4.5% drug loading (Figure 2b). Further increasing the MPH-base concentration to 5% significantly reduced drug transport compared

to that obtained with formulations containing either 4% or 4.5% drug loading. This coincided with a visual observation of the film produced by the 5% MPH-base formulation rapidly becoming cloudy, suggesting that the drug may have crystallised in the film. The formulations containing 3% or more MPH-base with EuRS, all showed some signs of cloudiness after 24 hours, which as mentioned suggests drug crystallisation within the film. In contrast, the formulations up to 6% of MPH-base with EuE all appeared visually clear throughout the 24-hour experiment.

The drug flux from a saturated solution of MPH-base in glycerol across silicone over 24 hours is shown in Figure 2c and was used as a standard to compare with the performance of the film forming formulations. The steady state drug flux from saturated solution of MPH-base in glycerol across the 24 hour period was 207 ± 54 $\mu g/cm^2/hr$ (Table 2). For all film forming formulations containing MPH-base, the drug flux between 1 and 4 hours were statistically greater than this value except 1.2% MPH-base EuE and 3% MPH-base EuE. Table 2 also provides the total drug transport after 24 hours of all MPH base formulations with EuE (Figure 2a) and EuRS (Figure 2b) after 24 hours. It is clear that both the polymer used and drug loading can have significant impacts on the efficiency of MPH transport from the film. For example formulations containing EuRS provided greater drug transport than those containing EuE and mostly there was an increase drug transport with increasing drug loading with the exception of the 5% MPH-base EuRS formulation for which drug transport was less than that of the 4.5% MPH-base EuRS formulation. The same data was used to calculate the percentage of the dose applied to the Franz cell that was transported across the silicone membrane. As expected significantly higher values were obtained for the EuRS containing formulations indicating that they are more efficient at delivering the drug across the membrane.

Measurement of the solid state solubility of drug in film forming polymers

Measurement of the drug solubility and the degree of saturation in polymeric films that is representative of what is formed on the skin surface is not trivial, as the volatile and residual solvent levels in the film will change over time. However measuring the drug solubility in the polymer alone may provide useful insight into the drug transport data interpretation. One approach to measure the solubility of a drug in a polymer involves assessing the melting enthalpy of the crystalline drug (measured by DSC) when at different weight fractions with respect to the polymer [19]. When the drug is physically mixed with another substance such as an amorphous polymer that it can interact with, there is a decrease in the observed melting enthalpy as the physical mixture is heated through the drug melting temperature. This occurs because the drug dissolves in the glassy polymer as it melts, resulting in a reduction in the observed melting enthalpy. This reduction should be proportional to the weight fraction of the drug in a linear manner. When the weight fraction of drug is increased above the maximum solubility within the polymer, the linearity of the change in enthalpy changes as the drug no longer dissolves in the polymer. The drug fraction at this point can therefore provide a measurement of drug solubility in the polymer.

The melting enthalpy of the drug within physical mixtures of varied MPH-base content in EuE or EuRS was measured, with the DSC curves being shown in Figure 3. Two features can be clearly seen in Figure 3. Firstly, the DSC results of the physical mixtures containing EuE show more profound melting point depression of crystalline MPH-base in comparison to the physical mixes with EuRS. Secondly, the change of MPH-base melting enthalpy is greater in the presence of EuE then EuRS. Both of these are indications of a higher solubility of MPH-base in EuE than EuRS [20].

The measured enthalpy values for both EuE and EuRS physical mixes were plotted against the drug content and are shown in Figure 4. For the systems containing EuE, the increase in melting enthalpy with drug loading can be observed to occur in two linear stages with the first occurring between 25 and 40% drug loading, with the second from 40 to 70% drug loading (Figure 4). According to the methodology explained previously, the solubility of MPH-base in EuE can be estimated from the change in gradient of the plot which was determined using linear regression analysis to be 38% w/w. Similarly, two separate linear regions between 3 and 10% drug loading, and 10 and 65% drug loading can be observed in the data from the melting enthalpies of the physical mixes of MPH-base and EuRS (Figure 4). The drug solubility within the polymer was measured to be 12% w/w MPH-base in EuRS from the change in the linearity of the plot. This analysis confirmed and provided quantitative assessment of the earlier prediction of a higher solubility of MPH-base with EuE than EuRS made through melting point depression observations.

For comparative purposes, analysis of the glass transition temperatures (T_g) of solvent cast films containing different ratios of drug and polymer was performed. T_gs have been traditionally used to provide indication of phase separation in drug-polymer solid dispersions [21]. If the drug is molecularly dispersed in the polymer, a single T_g that changes with the proportion of drug and polymer and can be predicted by the Gordon-Taylor relationship is expected [22]. DSC data showing the T_gs of solvent cast films containing different proportions of MPH-base and EuRS are presented in Figure 5. With incorporation of MPH-base, the T_g of the cast films reduced. The change in T_g with drug content is plotted in Figure 4a. Initially, it can be seen that increasing the drug loading lowered the Tg of the film in a concentration dependent manner up to a drug loading of 12%. After this point the T_g of the

cast films remained relatively constant, indicating the saturation of drug being molecularly dissolved in the polymer film and therefore providing a measurement of the solubility of MPH-base in EuRS. This good agreement between the solubility values calculated by the separate glass transition and melting enthalpy methods supports the reliability of these methods for the measurement of solubility of drugs in polymeric films.

As MPH-HCl undergoes melt decomposition, it was not possible to determine the solubility of MPH-HCl within EuRS or EuE using the melting enthalpy methodology. Therefore the glass transition analysis method was used alone for determining the solubility of MPH-HCL within the polymers. In the absence of drug a T_g at approximately 46 ^oC was observed for the Eudragit EuE film. As the drug content was increased up to approximately 8% drug loading the T_g reduced to approximately 36 ^oC, with no further reduction being observed for the films tested containing higher concentrations of MPH-HCL. Linear regression analysis of this data allowed estimation the solubility of MPH-HCl with EuE to be 9% w/w (Figure 6). In contrast no change in the Tg of EuRS could be obtained when MPH-HCL was included in films formed with this polymer and visible signs drug crystallisation were observed even in films with low drug content.

Prediction of drug flux using degree of saturation measured drug solubility in polymer

Drug flux across membranes for topical formulations is typically directly proportional to the degree of saturation of the drug within the delivery vehicle, if the formulation constituents do not alter the properties of the membrane [23]. In an attempt to ascertain whether the drug solubility in the residual solvent or in the polymer had a greater effect in terms of determining the saturation of the drug in the film, the drug flux from the MPH-base formulations were plotted against the degree of drug saturation calculated using the drug solubility in the

residual solvent using Equation 1 (Figure 7) or in the polymer using Equation 2 (Figure 8). As seen in Figure 7, a linear correlation was observed between the average drug flux between 1 and 4 hours from the film forming formulations containing EuE and the degree of saturation calculated using the solubility of the drug in PG. A separate correlation with reduced linearity was observed for the formulations that contained EuRS. This reduced linearity for the data produced from formulations containing EuRS, was observed regardless of whether the data from the 5% MPH-base EuRS formulation (6.25 DS), which appeared to have drug crystallisation occurring rapidly following formation of the film, was included.

Figure 8a shows the correlation between the drug flux obtained from films between 1 and 4 hours following application of the formulations containing EuE and EuRS and the degree of drug saturation in the film calculated using the solubility of the drug in the polymer. The formulations containing both EuE and EuRS fitted upon the same line of best fit up until the EuRS formulation containing 5% MPH-base. The decrease in drug flux for the formulation containing 5% MPH-base, as discussed previously, is likely to be a result of significant crystallisation of the drug in the formed film. The drug transport data in Figures 1a, 2a & 2b showed that for all formulations containing MPH base that drug flux was high over the first four hours following application, but reduced between 6 and 24 hours. In order to determine whether a similar correlation existed for the drug flux data between 6 and 24 hours as for that between 1 and 4 hours, the average flux data between 6 and 24 hours for the MPH-base formulations was plotted against the degree of saturation of the drug in the films as calculated from the solubility of the drug in the polymer (Figure 8b). Although the magnitude of the drug flux was reduced between 6 and 24 hours a very similar correlation was observed to the drug flux data produced between 1 and 4 hours, with the drug flux from both EuE and EuRS

formulations following a linear correlation with respect to the degree of drug saturation in the formulation up to the 6.25DS produced by the 5% MPH-base EuRS formulation.

Discussion

The focus of this study was to develop approaches that would help identify selection of polymers for inclusion in film forming systems for topical and transdermal drug delivery. This would help rationalise the development process and provide understanding of how to optimise drug delivery from these formulations. The metered dose aerosol produced films used in this study exhibited drug transport data that was linear when plotted against the square root of time consistent with Fickian diffusion as described through the Higuchi model of drug release. This type of drug transport profile is expected for drug containing topical films, including supersaturated systems [24]. Knowledge of the extent of drug saturation in a formulation is a key for understanding drug delivery into and across the skin and is difficult to assess with film forming systems given their solid nature and that the degree of saturation changes with time in response to evaporation of solvents and the permeation of solvents and drug into the skin. One approach to try to understand the degree of saturation is to consider the solubility of the drug in the solvents alone and how the drug saturation in the formulation is expected to change with solvent evaporation [12]. It has been observed however that the polymer included in a film forming formulation can have a significant influence of the delivery of drugs from the films, with the authors typically postulating that the polymer will influence the degree of drug saturation in the film and therefore the ‘driving force’ of the drug from the formulation [25, 26]. Similar results were obtained in this study with the polymer included in the formulation being observed to have a substantial effect on drug transport from the formulation, with different polymers offering improved drug transport depending on whether the drug was in the free base or salt form. These data suggest strongly

that the polymer has a significant role in determining the degree of saturation of the drug in the formed film and the resultant flux as these large polymer molecules are unlikely to be able to modify drug transport by other means, for example through acting as a chemical penetration enhancer [27].

Therefore measuring drug-polymer solubility will be useful in designing and understanding the behaviour of these dosage forms. Assessment of drug solubility within polymeric matrices has been investigated at some length for the development of drug containing solid dispersions for oral drug delivery with DSC being commonly used as a supporting tool for measurement of drug polymer solubility and assistance of polymer selection [20]. Different methodologies using DSC to measure drug-polymer solubility were employed here. The melting enthalpy method is relatively simple and does not require the production of drug containing films, however this approach was not suitable for MPH-HCL which decomposes as it melts; instead glass transition analysis of solvent cast films was used. When MPH-base solubility was assessed using the glass transition method, good agreement was found between the solubility values supporting the use of either methodology to measure drug-polymer solubility.

Using these methodologies marked differences in the solubility of MPH-base in EuRS and EuE were observed, with the drug solubility in EuE being considerably higher than EuRS. In addition the solubility of MPH-HCl is likely to be considerably higher in EuE than in EuRS, as no change in the Tg of EuRS could be obtained when MPH-HCL was included in the film and visible signs drug crystallisation were observed in the formed films even with low drug content. EuE (Poly[butyl methacrylate-co-[2- demethylaminoeethyl] methacrylate-co-methyl methacrylate] 1:2:1) is more hydrophilic than EuRS (Poly[ethyl acrylate-co-methyl

methacrylate-co-trimethylammonioethyl methacrylate chloride] 1:2:0.1), which may explain the improved solubility of methylphenidate, particularly MPH-HCL in EuE.

In this study, DSC has been used to measure drug polymer solubility to provide understanding of the delivery of methylphenidate from polymeric films assessed from transport studies across silicone membrane. Silicone membrane is commonly adopted as a surrogate model for skin for these sorts of studies investigating drug saturation on formulation performance [12, 28, 29]. Drug transport from the film forming systems has also been compared with that of saturated solution of MPH base in glycerol. If the solvents used in a formulation vehicle do not interact with the membrane to which they are applied, then drug transport rate from different formulations that are saturated with drug should be constant, allowing the DS of the film forming systems to be inferred [23]. Glycerol was chosen for this comparison because of the reasonable solubility of MPH base (16.8 mg/ml) within it. The solubility of MPH-base in propylene glycol or IPA, solvents used in the film forming formulations were very high, 309.4 mg/ml and >400 mg/ml respectively making it unsuitable to perform infinite dose, drug transport studies using these solvents. When comparing drug flux between 1 and 4 hours following application of the film forming systems with that of the saturated solution in glycerol, it would appear that most of the film forming systems are supersaturated. This is supported by the observation that several of the films developed small regions of crystallisation following application to the membrane by the end of 24 four testing period. The increased degree of supersaturation from formulations containing MPH-base and EuRS in comparison to those containing EuE relates to the lower solubility of the drug in EuRS. This agrees with previous literature that has suggested that polymers can increase drug solubility in a formulation which would be expected to decrease drug flux through reducing the DS of the drug in the vehicle [30, 31]. A related example from the literature examined the effect of polymethylmethacylates as crystallization inhibitors in

ibuprofen containing polydimethylsiloxane/silicate drug in adhesive patches, where inclusion of EuE instead of Eudragit RL (a Eudragit polymer with a similar structure EuRS, containing twice the quantity of the quaternary amine group), reduced drug flux from the formulation and could be ascribed to the higher solubility and thus lower saturation of the drug in the EuE [32].

The drug transport from the formulations showed similar profiles of relatively rapid transport up to 4 hours following dosing that then slowed over 6 – 24 hours. When the drug transport data for MPH base was considered in relation to its solubility in the residual solvent, propylene glycol, separate trends in the data were observable only within formulations containing the same polymer. In contrast when the drug transport data was considered in light of the solubility of the polymer a single trend was observed in the data across both polymers, up until crystallisation was observed occurring soon after application of the formulations with the highest degree of saturation. This trend was observable across the data of the two polymers regardless of whether the drug flux between 1and 4 hours or 6 and 24 hours and supports the consideration that drug solubility in the polymer is the key influence on drug saturation in the formed film.

As well as increasing drug flux from the formulation, supersaturated systems should be able to deliver a greater proportion of the drug included in the formulation. This is because as the drug content in the formulation decreases as the drug diffuses from the formulation following administration, a higher level of drug saturation in the formulation is maintained for longer compared to subsaturated systems, resulting in a greater proportion of the formulations drug content being delivered. When EuRS is used as the polymer equivalent drug delivery after 24 hours was obtained from the 1.2% MPH base in EuRS as with 3% MPH base in EuE, which correlates well with the lower solubility of MPH base in EuRS (12% w/w) compared to EuE

(38% w/w) providing two-three times more drug transport. This highlights the importance of the drug solubility in the polymer providing a high thermodynamic driving force of the drug within the film formulation. This has important applications as it may be able to help reduce manufacturing costs. In addition it may also be of benefit for transdermally administered drugs such as methylphenidate that can be abused through extracting the drug from the dosage form. This is the case as more efficient formulations will deliver a greater percentage of the applied dose thereby requiring a lower quantity of drug in the dosage form to achieve the same therapeutic benefit. This will reduce the potency of any extracts made from the product, something which will contribute to lowering the abuse potential of the dosage form [4].

As supersaturated systems are unstable and will eventually crystallise, polymers used in these formulations are often selected to act as anti-nucleants, delaying / retarding the crystallisation process until the drug has been delivered. The anti-nucleation effect is not well understood, and it is known that different polymers have different capabilities to stabilise supersaturated systems of different drugs. For example polyvinyl pyrollidone (PVP) was found to be superior to hydroxypropyl cellulose (HPC) in stabilising supersaturated systems of oestradiol, whereas PVP was not able to stabilise hydrocortisone acetate to the same level of supersaturation as HPC [9, 16]. The anti-nucleant polymers have been shown to delay crystal nucleation, slow drug crystal growth and alter crystal shape [33, 34]. Interactions between the polymer and the drug crystal face, often hydrogen bonding are considered to be important for the anti-nucleant action [33]. These anti-nucleant studies have been typically carried out in systems such as supersaturated cosolvent systems where the polymer concentration is low. In the polymeric films produced by film forming formulations, the polymer concentration is relatively high and the types of interactions such as hydrogen bonding that can contribute to an anti-nucleant action will also provide good drug solubility restricting the level of

supersaturation that can be achieved. This may explain why when DSC has been used previously to help aid selection of polymers as anti-nucleants for supersaturated film forming systems, it appeared not to be useful [35].

There may be other features of the films formed from the different polymers which may ultimately influence drug transport from them. For example they may exhibit different occlusive effects, which may alter the skin's barrier properties and affect drug delivery [36]. In addition uptake of water into polymeric films as a result of transepidermal water loss on skin or across silicone membrane mounted on Franz cells may alter interactions between the drug and the polymer within the film, something that would be expected to be related to the hygroscopicity of the polymer and may impact drug delivery [37]. Nonetheless the analysis presented here relating the delivery of MPH from the films to its solubility in the different polymers seems the most suitable explanation of the observed drug transport behaviour. This analysis also provides an explanation for the reduced transport of MPH-HCL from formulations containing EuRS, in comparison to those containing EuE. Although it is usually considered preferable for topical/transdermal drug delivery to have the drug in an unionised form in a formulation in order to show improved permeation across hydrophobic membranes such as the stratum corneum, in some cases the improved solubility of the ionised form may outweigh this and so it is appropriate to consider delivery of the salt form [38]. In this study MPH-HCl could not be delivered from formulations containing EuRS which is likely to be a result of the inability of this polymer to provide suitable anti-nucleant action allowing rapid drug crystallisation to occur which would prevent/reduce its transport across the silicone membrane [11]. In contrast delivery of MPH-HCl could be achieved when the more hydrophilic EuE was used, in which the drug was found to have a measurable level of solubility. Therefore polymer selection during formulation development for film forming systems should be based on a careful consideration of the solubility of the drug in polymers

used so that a sufficient anti-nucleation action can be obtained without preventing a high degree of drug saturation in the film from being achieved.

Acknowledgements

We would like to thank Medpharm Ltd for funding this work.

References

[1] W.J. McAuley, F. Caserta, Film forming and heated systems, in: R.F. Donnelly, R. Singh (Eds.) Novel delivery systems for transdermal and intradermal drug delivery, Wiley, Chichester, 2015, pp. 97-124.

[2] S. Wiedersberg, C.S. Leopold, R.H. Guy, Bioavailability and bioequivalence of topical glucocorticoids, Eur J Pharm Biopharm, 68 (2008) 453-466.

[3] K.A. Marquardt, R.S. Tharratt, N.A. Musallam, Fentanyl remaining in a transdermal system following 3 days of continuous use, Annals of Pharmacotherapy, 29 (1995) 969-971.

[4] N.P. Katz, D.C. Buse, S.H. Budman, S.W. Venuti, K.C. Fernandez, C. Benoit, R. Bianchi, D. Cooper, D.R. Jasinski, D.E. Smith, S.F. Butler, Development and preliminary experience with an ease of extractability rating system for prescription opioids, Drug Development and Industrial Pharmacy, 32 (2006) 727-746.

[5] M.F. Coldman, B.J. Poulsen, T. Higuchi, Enhancement of percutaneous absorption by the use of volatile : nonvolatile systems as vehicles, Journal of Pharmaceutical Sciences, 58 (1969) 1098-1102.

[6] R.J. Feldman, H.I. Maibach, Percutaneous penetration of 14C hydrocortisone in man. II. Effect of certain bases and pretreatments, Archives of Dermatology, 94 (1966) 649-651.

[7] A.F. Davis, J. Hadgraft, Effect of supersaturation on membrane transport: 1. Hydrocortisone acetate, International Journal of Pharmaceutics, 76 (1991) 1-8.

[8] M.A. Pellett, S. Castellano, J. Hadgraft, A.F. Davis, The penetration of supersaturated solutions of piroxicam across silicone membranes and human skin in vitro, J Control Release, 46 (1997) 205-214.

[9] S.L. Raghavan, B. Kiepfer, A.F. Davis, S.G. Kazarian, J. Hadgraft, Membrane transport of hydrocortisone acetate from supersaturated solutions; the role of polymers, International Journal of Pharmaceutics, 221 (2001) 95-105.

[10] P. Santos, A.C. Watkinson, J. Hadgraft, M.E. Lane, Influence of penetration enhancer on drug permeation from volatile formulations, International Journal of Pharmaceutics, 439 (2012) 260-268.

[11] S.L. Raghavan, A. Trividic, A.F. Davis, J. Hadgraft, Crystallization of hydrocortisone acetate: influence of polymers, International Journal of Pharmaceutics, 212 (2001) 213-221.

[12] S.A. Jones, M.L. Reid, M.B. Brown, Determining degree of saturation after application of transiently supersaturated metered dose aerosols for topical delivery of corticosteroids, Journal of Pharmaceutical Sciences, 98 (2009) 543-554.

[13] M.L. Reid, S.A. Jones, M.B. Brown, Transient drug supersaturation kinetics of beclomethasone dipropionate in rapidly drying films, International Journal of Pharmaceutics, 371 (2009) 114-119.

[14] Q2A, Text on validation of analytical procedures: definitions and terminology, in: Proceedings of the International Conference on Harmonization (ICH), US FDA Federal Register, 1995.

[15] Q2B, Validation of analytical procedures: methodology, in: Proceedings of the International Conference on Harmonization (ICH) US FDA Federal Register, 1997.

[16] N.A. Megrab, A.C. Williams, B.W. Barry, Estradiol Permeation through Human Skin and Silastic Membrane - Effects of Propylene-Glycol and Supersaturation, J Control Release, 36 (1995) 277-294.

[17] S.L. Raghavan, A. Trividic, A.F. Davis, J. Hadgraft, Effect of cellulose polymers on supersaturation and in vitro membrane transport of hydrocortisone acetate, International Journal of Pharmaceutics, 193 (2000) 231-237.

[18] T. Higuchi, Physical chemical analysis of percutaneous absorption process from creams and ointments, J. Soc. Cosmet. Chem, 11 (1961) 85–97.

[19] S. Qi, P. Belton, K. Nollenberger, N. Clayden, M. Reading, D.Q.M. Craig, Characterisation and Prediction of Phase Separation in Hot-Melt Extruded Solid Dispersions: A Thermal, Microscopic and NMR Relaxometry Study, Pharm Res-Dordr, 27 (2010) 1869-1883.

[20] P.J. Marsac, S.L. Shamblin, L.S. Taylor, Theoretical and practical approaches for prediction of drug-polymer miscibility and solubility, Pharm Res, 23 (2006) 2417-2426.

[21] Q. Lu, G. Zografi, Phase behavior of binary and ternary amorphous mixtures containing indomethacin, citric acid, and PVP, Pharm Res, 15 (1998) 1202-1206.

[22] M. Gordon, J. Taylor, Ideal copolymers and the second-order transitions of synthetic rubbers. i. non-crystalline copolymers, Journal of Applied Chemistry, 2 (1952) 493-500.

[23] J.N. Twist, J.L. Zatz, Influence of solvents on paraben permeation through idealized skin model membranes, Journal of the Society of Cosmetic Chemists of Japan, 37 (1986) 429-444.

[24] Y.N. Kalia, R.H. Guy, Modeling transdermal drug release, Adv Drug Deliv Rev, 48 (2001) 159-172.

[25] K. Frederiksen, R.H. Guy, K. Petersson, Formulation considerations in the design of topical, polymeric film-forming systems for sustained drug delivery to the skin, Eur J Pharm Biopharm, 91 (2015) 9-15.

[26] I. Zurdo Schroeder, P. Franke, U.F. Schaefer, C.M. Lehr, Delivery of ethinylestradiol from film forming polymeric solutions across human epidermis in vitro and in vivo in pigs, J Control Release, 118 (2007) 196-203.

[27] A.C. Williams, B.W. Barry, Penetration enhancers, Advanced Drug Delivery Reviews, 56 (2004) 603-618.

[28] P. Santos, A.C. Watkinson, J. Hadgraft, M.E. Lane, Enhanced permeation of fentanyl from supersaturated solutions in a model membrane, Int J Pharm, 407 (2011) 72-77.

[29] K. Moser, K. Kriwet, C. Froehlich, A. Naik, Y.N. Kalia, R.H. Guy, Permeation enhancement of a highly lipophilic drug using supersaturated systems, J Pharm Sci, 90 (2001) 607-616.

[30] S. Raghavan, B. Kiepfer, A. Davis, S. Kazarian, J. Hadgraft, Membrane transport of hydrocortisone acetate from supersaturated solutions; the role of polymers, International Journal of Pharmaceutics, 221 (2001) 95-105.

[31] N. Rodríguez-hornedo, D. Murphy, Significance of controlling crystallization mechanisms and kinetics in pharmaceutical systems, Journal of Pharmaceutical Sciences, 88 (1999) 651-660.

[32] F. Cilurzo, P. Minghetti, A. Casiraghi, L. Tosi, S. Pagani, L. Montanari, Polymethacrylates as crystallization inhibitors in monolayer transdermal patches containing ibuprofen, Eur J Pharm Biopharm, 60 (2005) 61-66.

[33] M. Iervolino, B. Cappello, S.L. Raghavan, J. Hadgraft, Penetration enhancement of ibuprofen from supersaturated solutions through human skin, International Journal of Pharmaceutics, 212 (2001) 131-141.

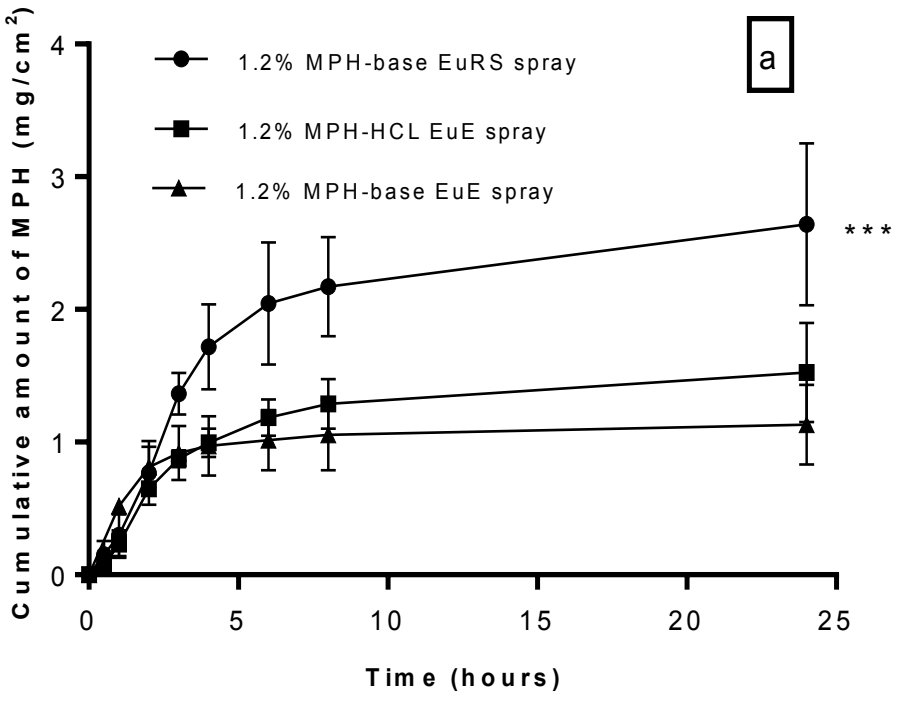
[34] L. Lindfors, S. Forssen, J. Westergren, U. Olsson, Nucleation and crystal growth in supersaturated solutions of a model drug, Journal of Colloid and Interface Science, 325 (2008) 404-413.

[35] M.L. Leichtnam, H. Rolland, P. Wuthrich, R.H. Guy, Impact of antinucleants on transdermal delivery of testosterone from a spray, J Pharm Sci, 96 (2007) 84-92.

[36] H. Zhai, H.I. Maibach, Effects of Occlusion: Percutaneous Absorption, in: R.L. Bronaugh, H.I. Maibach (Eds.) Percutaneous absorption: Drugs-Cosmetics-Mechanisms-Methodology, Taylor & Francis, Boca Raton, 2005, pp. 235-245.

[37] Y.C. Ng, Z. Yang, W.J. McAuley, S. Qi, Stabilisation of amorphous drugs under high humidity using pharmaceutical thin films, Eur J Pharm Biopharm, 84 (2013) 555-565.

[38] J. Hadgraft, J.d. Plessis, C. Goosen, The selection of non-steroidal anti-inflammatory agents for dermal delivery, International Journal of Pharmaceutics, 207 (2000) 31-37.


a
1.2% MPH-base EuRS spray
1.2% MPH-HCL EuE spray
1.2% MPH-base EuE spray
***
Cumulative amount of MPH (mg/cm²)
Time (hours)
0
1
2
3
4
0
5
10
15
20
25

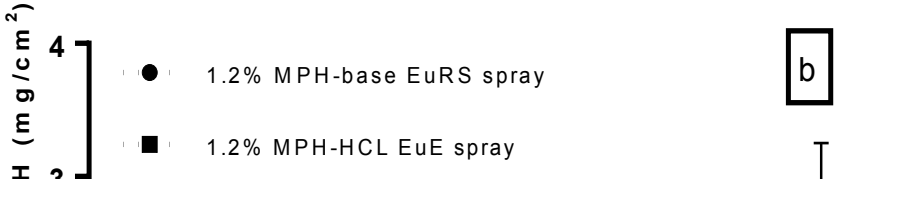
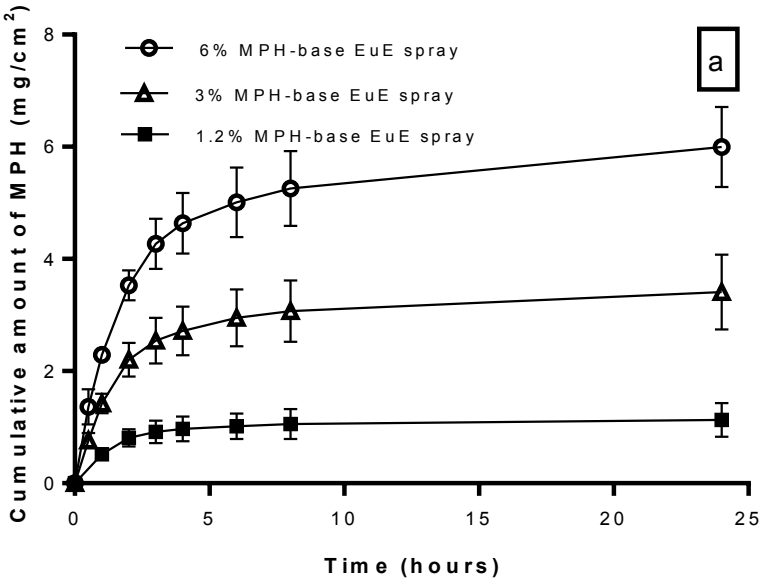

b
1.2% MPH-base EuRS spray
1.2% MPH-HCL EuE spray
H (mg/cm²)
4
3

Figure 1. The cumulative amount of MPH transport across silicone membrane (a) for formulations 1.2% MPH-HCL EuE (■),1.2% MPH-base EuE (▲),1.2% MPH-base EuRS (●),(n=5-6±SD), *** indicates statistical difference compared to 1.2% MPH-base EuE spray, $p<0.001$; (b) The cumulative amount of MPH transport across silicone membrane (a) for the same formulations, 1.2% MPH-HCL EuE (■),1.2% MPH-base EuE (▲),1.2% MPH-base EuRS (●) plotted against the square root of time. The solid lines show linear lines of best fit for each of the data sets for up to 60% of drug transport from the formulations.


6% MPH-base EuE spray
3% MPH-base EuE spray
1.2% MPH-base EuE spray
a
Cumulative amount of MPH (mg/cm2)
Time (hours)
0
2
4
6
8
0
5
10
15
20
25

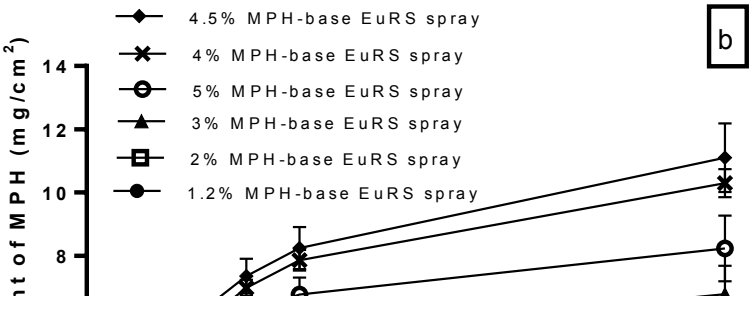

4.5% MPH-base EuRS spray
4% MPH-base EuRS spray
5% MPH-base EuRS spray
3% MPH-base EuRS spray
2% MPH-base EuRS spray
1.2% MPH-base EuRS spray
b
8
10
12
14

Figure 2. The cumulative amount of MPH transport across silicone membrane (a) for formulations 1.2% MPH-base EuE (■) 3% MPH-base EuE (Δ), 6% MPH-base EuE (○); (b) for formulations 1.2% MPH-base EuRS (●), 2% MPH-base EuRS (□), 3% MPH-base EuRS (▲), 4% MPH-base EuRS (×), 4.5% MPH-base EuRS (♦) and 5 % MPH-base EuRS (○) (n=5-6 ± SD) *** indicates statistical difference compared to 4.5% MPH-base EuRS spray, $p<0.001$; and (c) from a saturated solution of MPH-base in glycerol (n=6±SD).

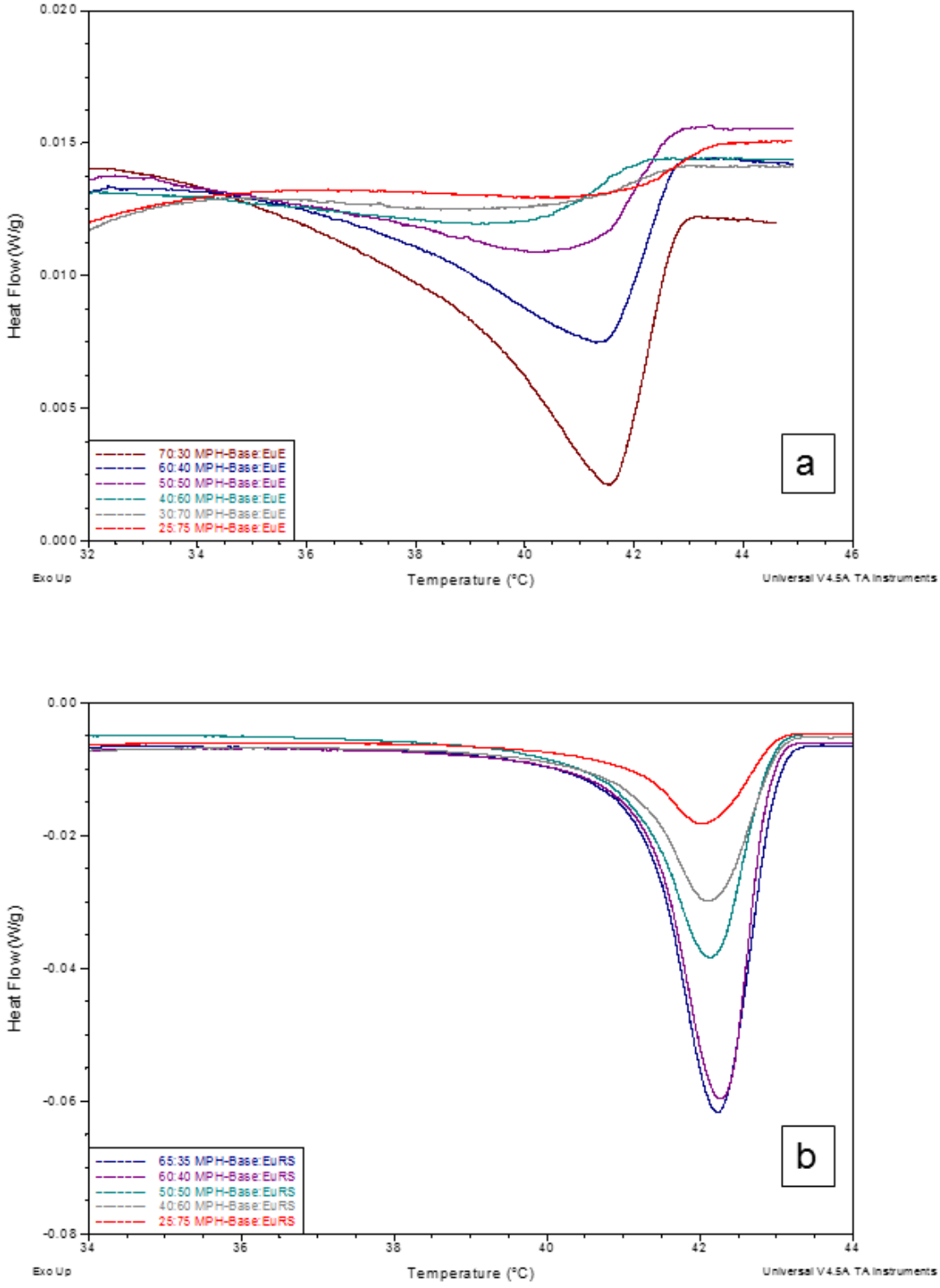


Figure 3. Representative DSC curves showing the MPH-base melting transition for physical mixtures of varying proportions of MPH-base with (a) EuE and (b) EuRS.

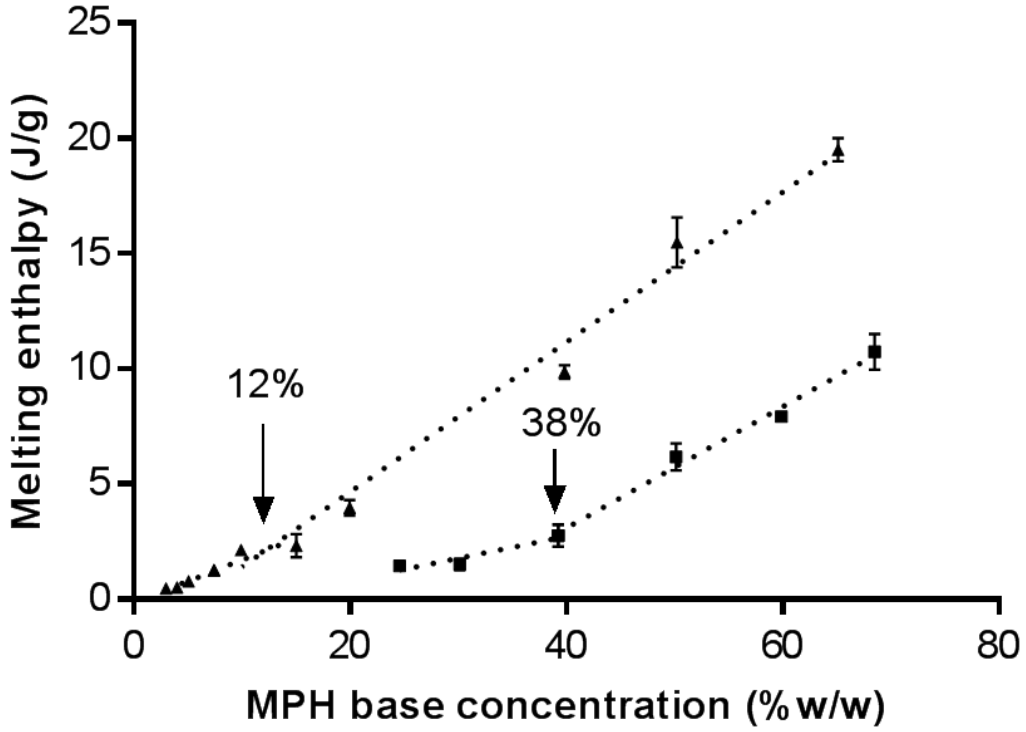
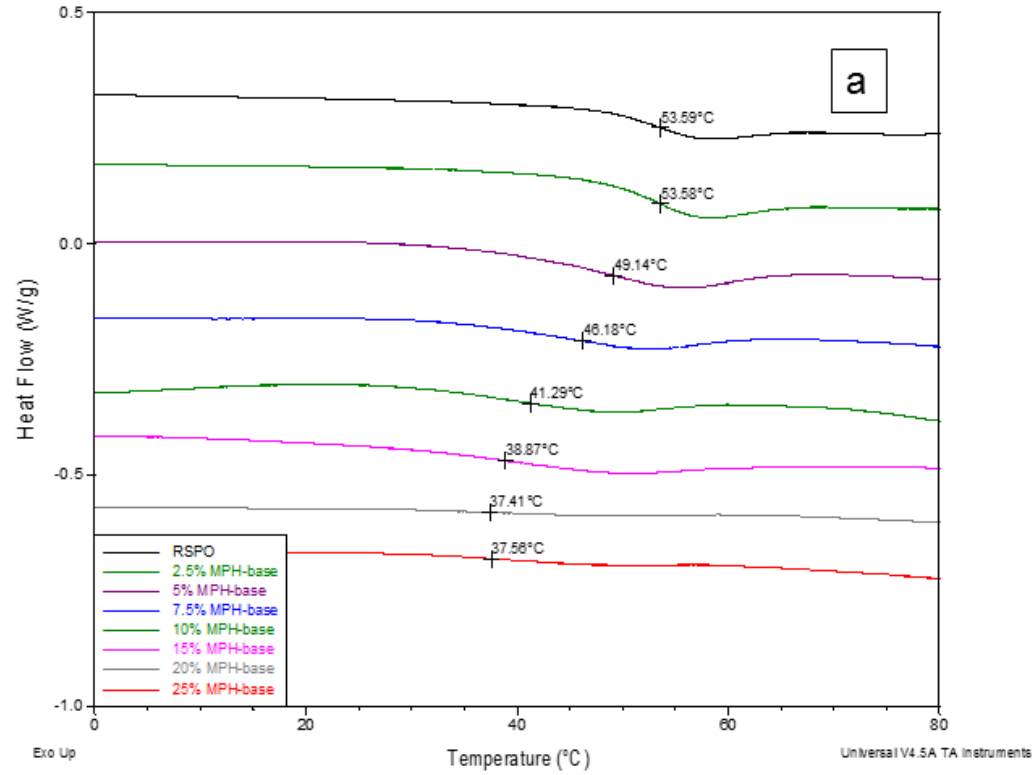


Figure 4. The melting enthalpy curve for physical mixtures of varying proportions of MPH-base with EuE (■)and EuRS (▲) (n=3, error bars represent the range)



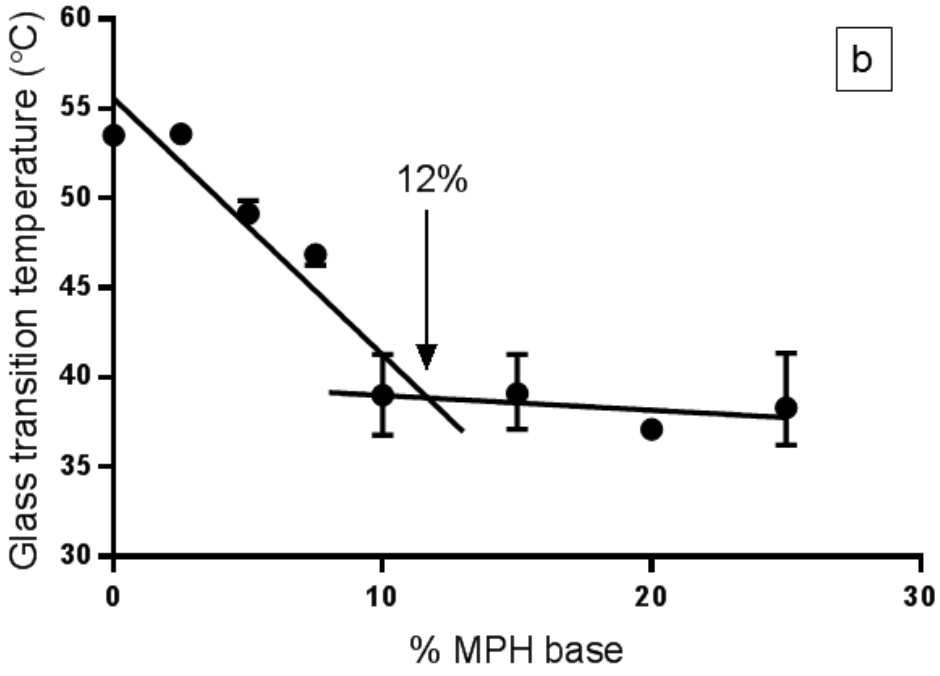


Figure 5. (a) Representative DSC curves for solvent cast film solid dispersions of varying proportions of MPH-base with EuRS and (b) the glass transition temperatures for these films plotted against drug loading (n=3, error bars represent the range)

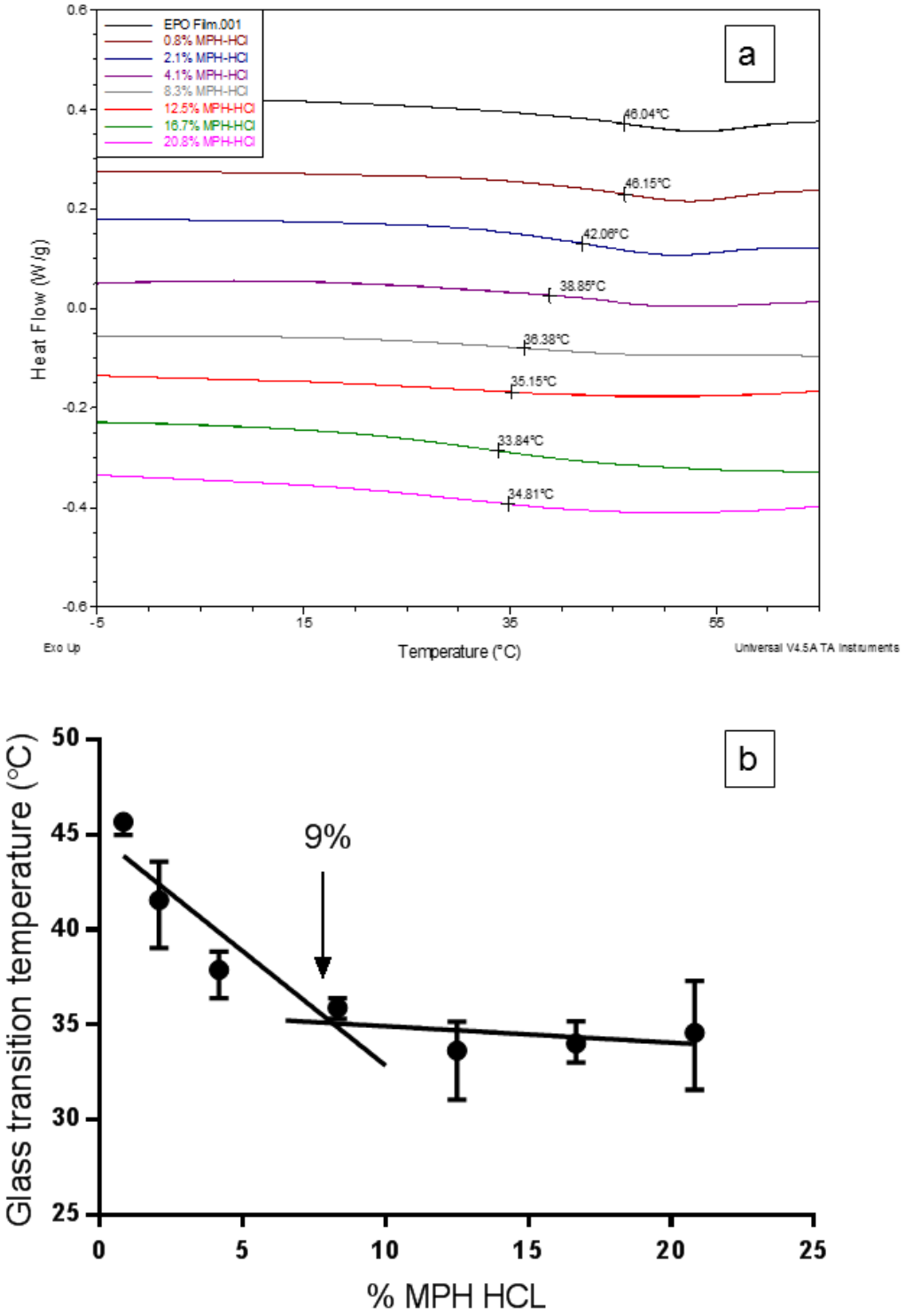


Figure 6. (a) Representative DSC curves for solvent cast film solid dispersions of varying proportions of MPH-HCl with EuE and (b) the glass transition temperatures for these films plotted against drug loading (n=3, error bars represent the range)

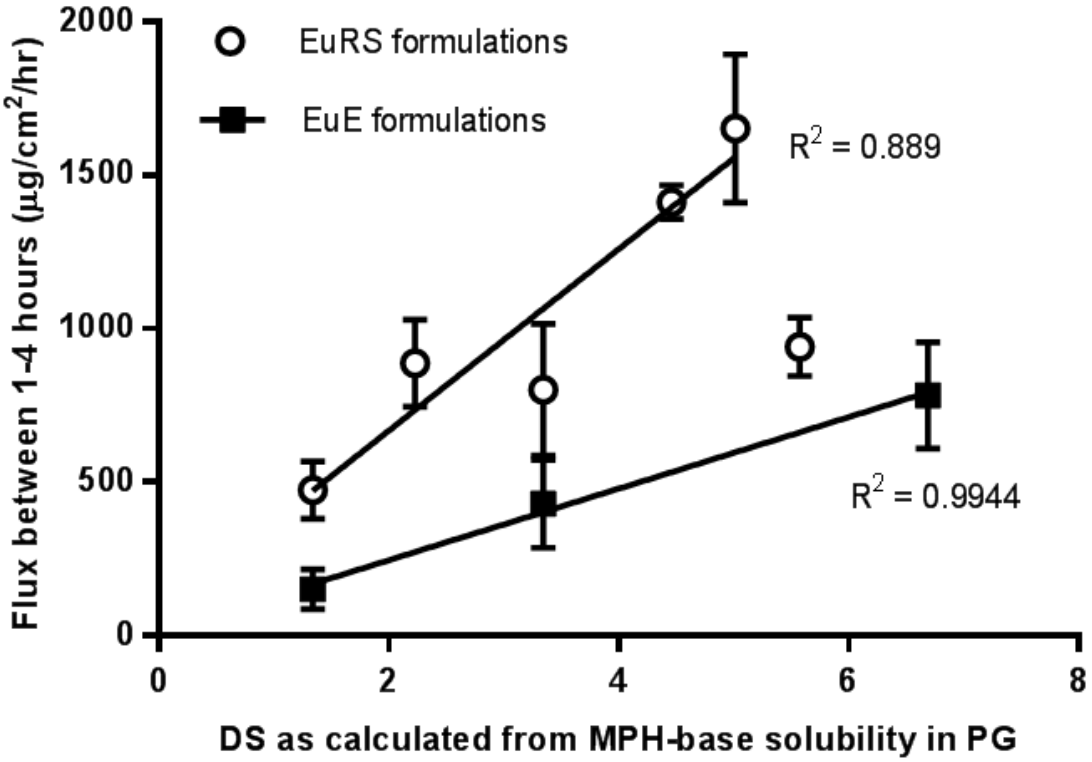


Figure 7. MPH flux between 1 and 4 hours plotted against the degree of saturation as calculated from the MPH-base saturated solubility within PG for MedSpray formulations containing varied quantities MPH-base containing 3% PG, 30% IPA, DME and either 6% EuE (■) or 6% EuRS (○) (n=5-6 ± SD)

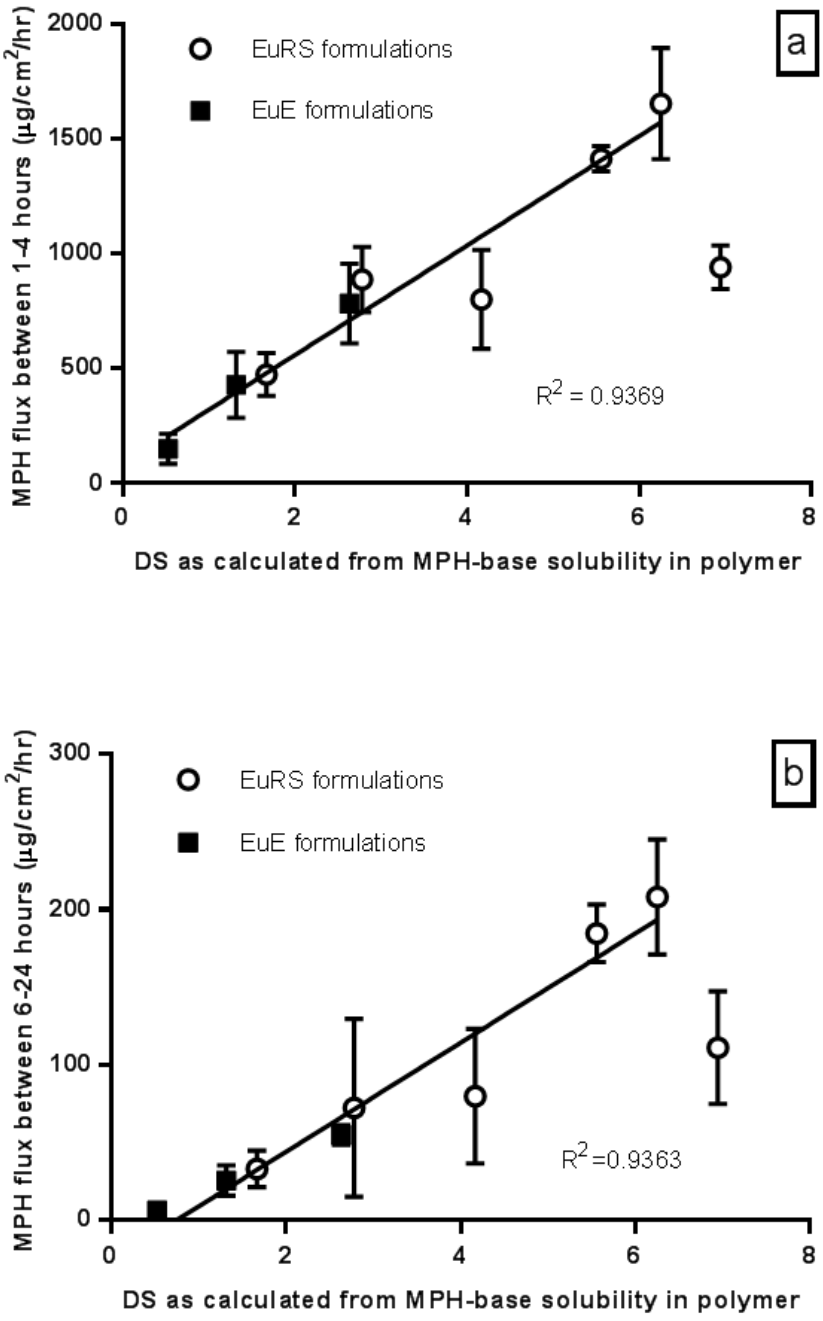


Figure 8. MPH flux between (a) 1 and 4 hours and (b) 6 and 24 hours plotted against the degree of saturation as calculated from the MPH-base solubility within EuRS (○) or EuE (■) for formulations of varied MPH-base content containing 3% PG, 6% EuRS or EuE, 30% IPA and DME (n=5-6 ± SD).