# The use of optical differential scanning calorimetry to investigate ibuprofen miscibility in polymeric films for topical drug delivery

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## Abstract

Understanding drug miscibility in pharmaceutically relevant systems is essential for the development and optimisation of pharmaceutical dosage forms. This is particularly true for film forming systems which are designed to become supersaturated with drug, following application on the skin surface, whilst maintaining the physical stability of the drug for a suitable period to enhance drug delivery. For such formulations, chemical penetration enhancers as well as the drug are absorbed from the formulation into the skin, making understanding drug delivery from the films challenging. This study investigated the use of an optical differential scanning calorimetry (DSC) to understand drug miscibility in polymeric film forming systems and explain drug transport behaviour from film forming formulations, containing ibuprofen, a copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate (Eudragit® E, EuE), a copolymer based on ethyl acrylate, methyl methacrylate and methacrylic acid ester with quaternary ammonium groups (Eudragit® RS, EuRS) and a copolymer based on methacrylic acid and methyl methacrylate (Eudragit® S, EuS), with and without the chemical penetration enhancer propylene glycol, across a model membrane. The optical DSC enabled the rapid screening of not only drug-polymer miscibility, but also drug-vehicle miscibility, while considering both the melting-point depression and melting enthalpy of the drug due to the presence of the polymer/polymer-based vehicle, obtained via thermal analysis by structural characterisation (TASC) and DSC analysis, respectively. The results obtained enable the polymers studied to be ranked in the order of EuE > EuRS > EuS, with EuE being more miscible with ibuprofen, and the incorporation of a penetration enhancer in the film forming system formulation was found to increase ibuprofen solubility in EuE- and EuRS- based films. The drug-polymer/vehicle miscibility information obtained via optical DSC provided understanding of drug transport from film forming systems with the higher miscibility of ibuprofen with EuE reducing drug transport through decreasing drug saturation in the film. The higher drug transport from films containing EuRS and EuS could also be linked to drug miscibility with the polymer and showed dependence on ibuprofen loading in the formulation.

Overall optical DSC has been demonstrated to be a valuable tool for determining drug-vehicle miscibility for pharmaceutical product development.

Keywords

Drug-polymer miscibility, drug-vehicle miscibility, optical differential scanning calorimetry, thermal analysis by structural characterisation, preformulation screening, film forming systems.

## 1. Introduction

Polymers embedded with drugs are important constituents of a variety of pharmaceutical dosage forms, including amorphous solid dispersions for the oral delivery of poorly soluble drugs [1,2], film forming systems for topical drug delivery [3], transdermal patches [4] and drug-loaded coatings of biomedical devices [5]. Understanding drug-polymer miscibility is key to developing and optimising these systems, with differential scanning calorimetry (DSC) being the most widely used technique [6,7]. However, there are challenges with using DSC to study drug-polymer miscibility. The experimental work is time consuming and DSC is therefore not ideal for rapid investigations or polymer screening for formulation design. In addition, polymeric drug delivery systems often contain other excipients, such as plasticisers and penetration enhancers, and usually it is the behaviour of the drug in this mixed carrier that is most relevant to understanding the pharmaceutical properties of the formulation or device. Understanding drug miscibility in these pharmaceutically relevant systems using DSC is extremely challenging because of the effect of these excipients on thermal signals. For film forming systems for topical drug delivery, understanding drug miscibility in a realistic polymeric formulation is particularly relevant as these systems can be designed to become supersaturated on the skin surface following the evaporation of volatile solvent, improving drug delivery. For such systems, the polymeric film needs to enable the drug to become supersaturated whilst maintaining the physical stability of the drug for a suitable period of time to improve drug absorption. Moreover, the dynamic nature of these systems which form on the skin surface and from which chemical penetration enhancers as well as the drug are absorbed from the formulation into the skin, makes understanding drug delivery from these films challenging.

Recently, a thermal imaging-based method, thermal analysis by structural characterisation (TASC), has been found to show promise as a rapid screening tool for drug-polymer miscibility [8,9]. In particular the technique showed greater sensitivity in detection of drug-polymer interaction [10]. A further development of TASC is its

use in combination with DSC using a hybrid instrument, more specifically an optical DSC, which allows simultaneous sample analysis by TASC and DSC, providing a fuller characterisation of drug-polymer interaction. In this study, TASC with DSC was investigated as a tool to understand drug miscibility in polymeric film forming systems and explain drug transport behavior from these formulations. Ibuprofen in a film forming formulation containing three different commonly used polymethacrylate polymers, i.e., Eudragit® E (Poly[butyl methacrylate-co-(2-demethylaminoeethyl) methacrylate-co-methyl methacrylate] 1:2:1), Eudragit® RS (Poly[ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride] 1:2:0.1) and Eudragit® S (Poly[methacylic acid-co-methyl methacrylate] 1:2), with and without the chemical penetration enhancer propylene glycol, were characterised by TASC and DSC and this behavior was linked to drug transport from these formulations across a model membrane.

# 2. Material and methods

## 2.1. Materials

Ibuprofen (99.9%) was supplied by Sequoia Research Products Ltd (Pangbourne, UK). Eudragit® E (EuE), Eudragit® RS (EuRS) and Eudragit® S (EuS) were donated by Evonik (Essen, Germany). Absolute ethanol (EtOH) (HPLC grade), acetonitrile (ACN) (HPLC grade), formic acid (98-100%) and phosphate buffer saline tablets (pH 7.0) were all acquired from Fisher Scientific (Loughborough, UK). Propylene glycol (PG) (99%) was purchased from Sigma-Aldrich (Gillingham, UK). Non-porous, non-reinforced, 0.13 cm thick silicone membrane was purchased from Bioplexus (Ventura, USA).

## 2.2. TASC and DSC studies

TASC and DSC experiments were performed using a Linkam Optical DSC 450 attached to a Linkam imaging station, equipped with a 5X magnification lens (Linkam Scientific Instruments Ltd., Surrey, UK). The instrument was provided with a T96 controller, LINK software and TASC modules. It was calibrated with indium before use and liquid nitrogen was used for the controlled cooling of the sample stage post experimentation.

Film forming solutions were prepared containing EtOH and either EuE, EuRS and EuS with and without PG. These solutions were prepared by adding the excipients to a vial and stirring overnight at 35$^{o}$C, to form a clear solution. The composition of each film forming solution is shown in Table 1. Thirty microlitres of film forming solution was added to individually weighed TA Instruments standard aluminum DSC pans which were left for 24 hours at room temperature to allow the volatile solvent in the solution to evaporate and form a polymeric film in the DSC pan.

After 24 hours, the pans were visually inspected to verify that films had formed. The weight of the film formed ranged between 1 – 1.2 mg.

***Table 1.*** *Composition of film forming solutions used for the preparation of polymeric films in DSC pans.*

| Formula ID | EuE (% w/w) | EuRS (% w/w) | EuS (% w/w) | PG (% w/w) | EtOH (% w/w) |
|---|---|---|---|---|---|
| **EuE** | 5 | - | - | - | 95 |
| **EuRS** | - | 5 | - | - | 95 |
| **EuS** | - | - | 5 | - | 95 |
| **EuE/PG** | 5 | - | - | 2.5 | 92.5 |
| **EuRS/PG** | - | 5 | - | 2.5 | 92.5 |
| **EuS/PG** | - | - | 5 | 2.5 | 92.5 |

*Abbreviations: EuE, Eudragit® E; EuRS, Eudragit® RS; EuS, Eudragit® S; PG, propylene glycol; EtOH, ethanol.*

Approximately 3-5 µg ibuprofen particles were scattered on the films contained in the DSC pans, to provide a single, non-overlapping layer of ibuprofen particles on the film surface. Once loaded in the instrument, the samples were heated from 45°C to 80 °C, using a heating rate of 5 °C/min, and micrographs of the samples were collected during heating at a rate of 3 frames/°C. Each experiment was repeated three times and TASC analyses were performed on the central regions of six ibuprofen particles in each DSC run.

### 2.3. Quantitative analysis of ibuprofen

Ibuprofen was assayed using a Shimadzu Prominence high-performance liquid chromatography (HPLC) system (Shimadzu Corp., Kyoto, Japan) coupled with a Phenomenex® Kinetex EVO C18 100Å (250 mm x 4.6 mm x 5 µm) column. An isocratic mobile phase consisting of 50:50 ACN: pH 2.6 formic acid in water solution was used at a flow rate of 1.0 mL/min. The sample injection volume and UV detection wavelength were 20 µl and 225 nm, respectively. The retention time of ibuprofen was approximately 11 min. The HPLC method was validated for linearity, precision and accuracy according to current International Conference on Harmonization (ICH) guidelines [11,12]. The calibration curve produced was linear between the concentration range of 1-100 µg/mL, with a coefficient of determination ($r^2$) of 0.9998. The limits of detection (LOD) and quantification (LOQ) were 2.39 µg/mL and 7.26 µg/mL, respectively. Intra- and inter- day precision (%RSD) for three different standards, which were representative of low, medium and high drug concentrations, ranged from 0.55 - 1.21% and 0.35 - 0.79% respectively. Accuracy of the same three drug concentrations ranged between 99.16 - 101.42%.

## 2.4. Solubility studies

The solubility of ibuprofen in the receiver fluid used in the drug transport studies (30% EtOH in phosphate buffer solution) was determined at 37°C. A saturated solution was prepared by adding excess of ibuprofen into the 30% EtOH in phosphate buffer solution to form a suspension and stirring this continuously for 24 hours. The saturated suspension was filtered using a 0.22 µm PTFE filter to remove drug particles and the remaining clear solution was diluted in mobile phase prior to analysis using HPLC to quantify the drug concentration.

## 2.5. Drug transport studies

The formulations prepared for drug transport studies were similar to those used for the optical DSC studies, but also contained ibuprofen; their composition is shown in Table 2. To prepare the solutions, the ingredients were weighed, added to a vial, and left stirring overnight at 35 $^{o}$C to form a clear solution.

***Table 2.*** *List and composition of formulations used for the drug transport studies.*

| Formula ID | Ibuprofen (% w/w) | EuE (% w/w) | EuRS (% w/w) | EuS (% w/w) | PG (% w/w) | EtOH (% w/w) |
|---|---|---|---|---|---|---|
| **2.5% Ibuprofen-EuE** | 2.5 | 5 | - | - | 2.5 | 90 |
| **2.5% Ibuprofen-EuRS** | 2.5 | - | 5 | - | 2.5 | 90 |
| **2.5% Ibuprofen-EuS** | 2.5 | - | - | 5 | 2.5 | 90 |
| **5% Ibuprofen-EuE** | 5 | 5 | - | - | 2.5 | 87.5 |
| **5% Ibuprofen-EuRS** | 5 | - | 5 | - | 2.5 | 87.5 |
| **5% Ibuprofen-EuS** | 5 | - | - | 5 | 2.5 | 87.5 |

*Abbreviations: EuE, Eudragit® E; EuRS, Eudragit® RS; EuS, Eudragit® S; PG, propylene glycol; EtOH, ethanol.*

Drug transport from the film forming systems across silicone membrane was measured using Franz cells (Soham Scientific, UK). The Franz cells were individually calibrated and had an approximate receiver volume of 3 mL and receiver compartment diffusion area of 1 $cm^2$. Silicone membrane was cut to cover the receiver compartment diffusion area and sandwiched between the donor and receiver compartment of each Franz cell. The two compartments were then wrapped together with Parafilm® and clamped. The receiver compartment was filled with a solution of 30% EtOH in phosphate buffer solution and any air bubbles trapped next to the membrane were removed. A magnetic flea was added to the receiver compartment and the Franz cells were placed on a stirring plate in a water bath at 37 °C that provided a membrane temperature of 32 °C. The assembled Franz cells were placed in the water bath for 30 minutes to equilibrate after which 125 µl of a film forming formulation was

applied to the silicone membrane. A film formed on the membrane as the ethanol evaporated and left the formulation. Samples of 0.2 mL of receiver fluid were removed at 0, 1, 2, 3, 4, 5, 6, 7 and 8 hours, and placed in HPLC vials prior to analysis. An equal volume of thermostatically equilibrated receiver fluid was immediately added to the receiver compartment to replace the sampled volume. Six repetitions (n=6) of each experiment were performed.

### 2.6. Statistical analysis

Statistical analyses of the permeation data were conducted using SPSS26. The data were checked for normality using the Shapiro-Wilks test prior to statistical comparisons with one way analysis of variance (ANOVA). Post hoc comparisons between groups were performed using the Tukey's multiple comparison test. Statistical significance was accepted at the $p \leq 0.05$ level.

# 3. Results and discussion

## 3.1. Drug-polymer miscibility

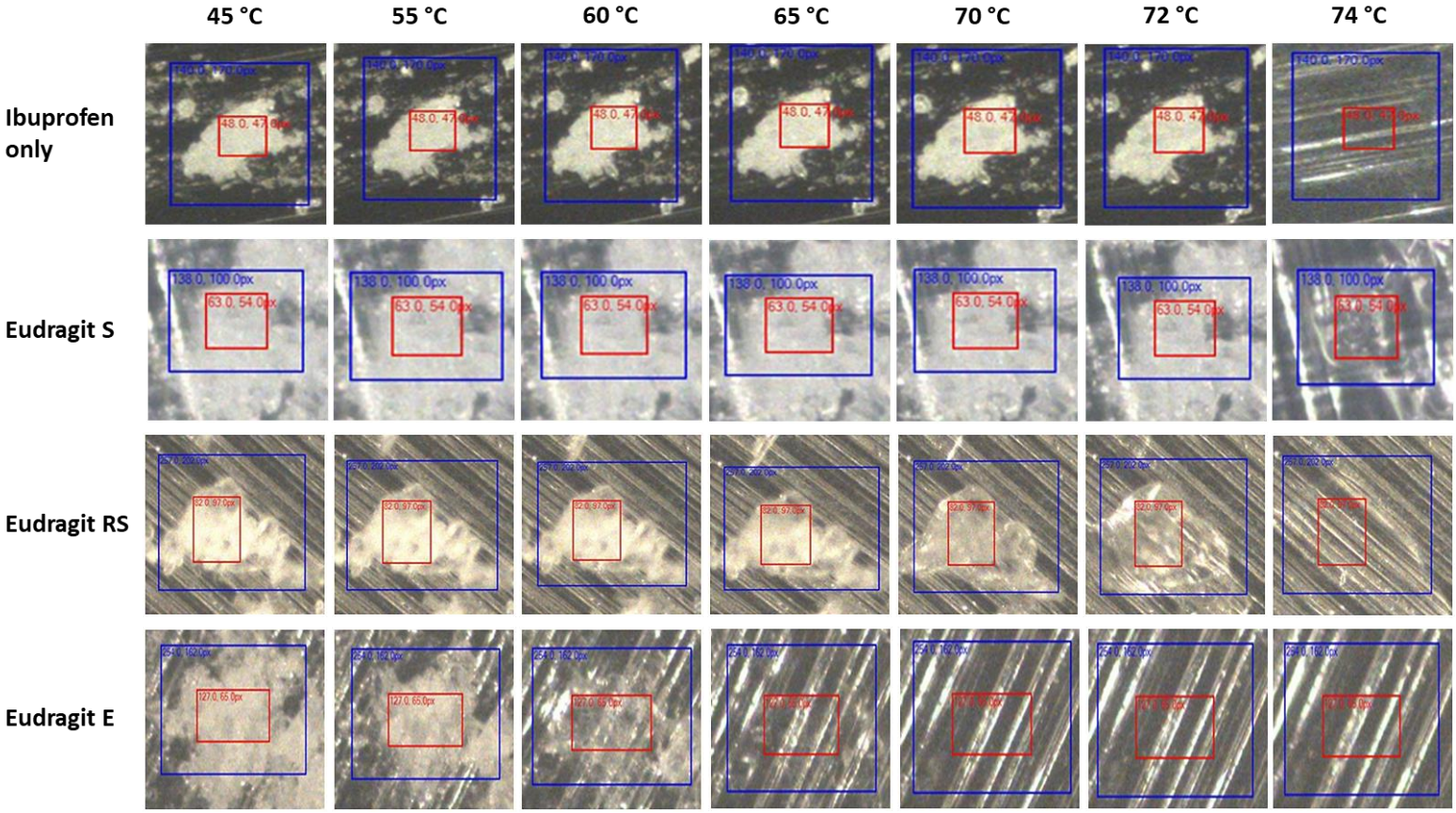


***Figure 1.*** *Micrographs obtained from optical DSC experiments showcasing structural changes to an ibuprofen particle alone and when placed on EuS-, EuE- or EuRS- based polymer films and heated.*

Figure 1 displays hot stage microscopy images showing changes to an ibuprofen particle when placed in a DSC pan or on a EuS-, EuRS- and EuE- based film in DSC pans at different temperatures during heating. It can be seen that when heated from 45$^{o}$C to 72$^{o}$C, there are no changes to the physical appearance of the ibuprofen alone particle, however increasing the temperature further to 74$^{o}$C leads to the sudden melting of the ibuprofen particle. This temperature is consistent with the ibuprofen melting temperature reported in literature [13,14]. The micrographs for the ibuprofen particle placed on a EuS-based film are comparable to that of ibuprofen alone, while the micrographs of the ibuprofen particles placed on the EuRS- and EuE- based films show visible changes in the physical features of the ibuprofen particle at temperatures lower than 74$^{o}$C, indicating that both polymers interact with ibuprofen. A slight change in the physical appearance of the ibuprofen particle on the EuRS-based film can be seen at 65$^{o}$C, and as the temperature is increased further to 70$^{o}$C the particle becomes translucent,

and at 72$^{o}$C the particle is transparent. In comparison, the ibuprofen particle on the EuE-based film becomes translucent at an earlier temperature of 55$^{o}$C, transparent by 60$^{o}$C and has dissolved once the temperature has reached 65$^{o}$C. This indicates that ibuprofen interacts more strongly with EuE compared to EuRS.

TASC is a microscopy analysis tool that scans the optical changes in successive microscopy images and converts it to a digital signal. In these experiments it describes changes in the physical features of drug particles when heated, which relate to their melting and thermal dissolution behaviour. A detailed working principle of the TASC methodology can be found in a previous study [15]. The micrographs collected during the optical DSC experiments were analysed using the TASC software. This involved selecting an ibuprofen particle in the micrograph as well as a larger area (the target area) over which the ibuprofen particle was present. The TASC software scanned the target area for any changes during heating. Once the scan was completed all differences obtained during the course of the scan, i.e., changes in the appearance of ibuprofen particles during heating, were converted into TASC values, which were normalized with respect to the image when it showed no further change. These TASC values were then plotted against temperature, to generate the profiles shown in Figure 2.

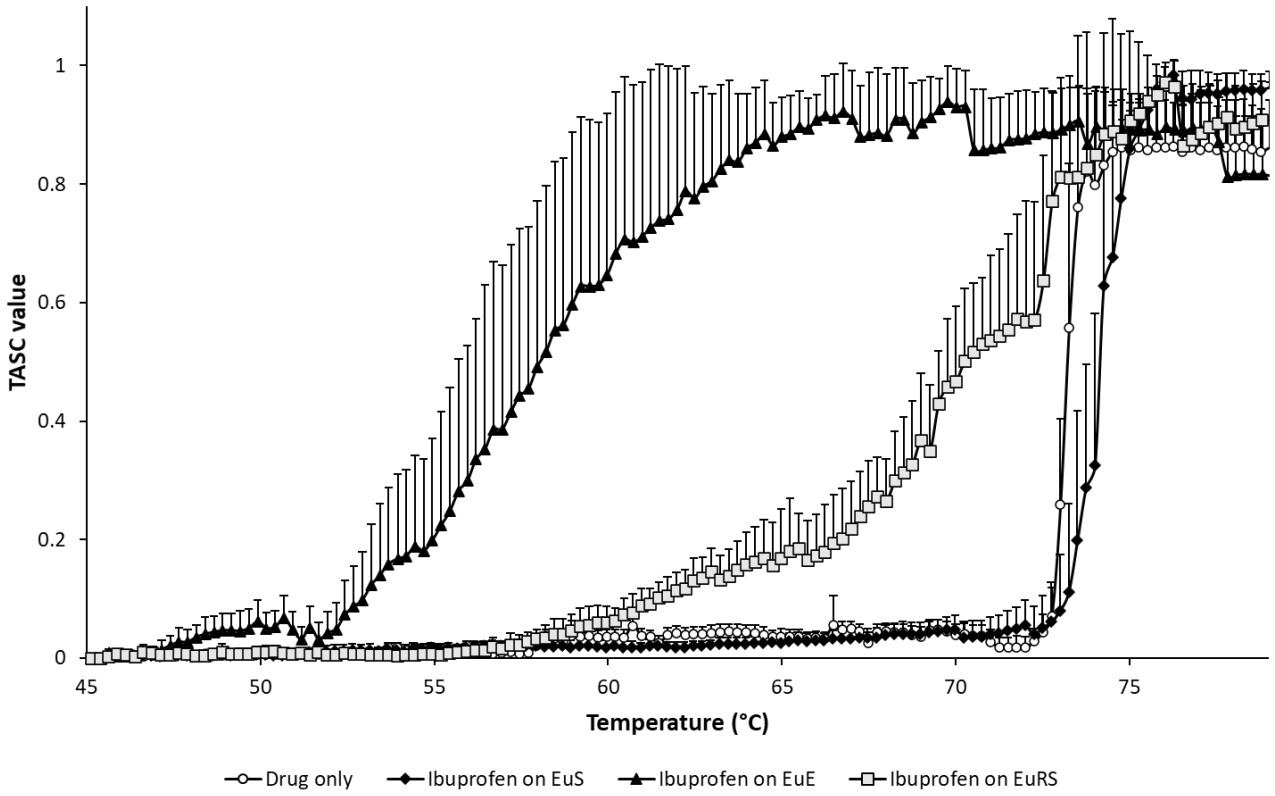


***Figure 2.*** *TASC analysis of ibuprofen samples placed on different polymeric films (mean value + SD displayed, n=6).*

The onset of ibuprofen alone melting is indicated by a sharp increase in TASC value, relating to the rapid change in the microscopy images at the melting point of the drug. As seen in Figure 2, the onset of melting of ibuprofen in the presence of EuS was similar to that of the pure ibuprofen. EuRS and EuE led to different levels of depression of the melting of ibuprofen, with EuE decreasing the melting point to a greater extent, which is consistent with the microscopy images in Figure 1. Figure 2 also shows that the physical structure of ibuprofen in the presence of EuRS changes more gradually during heating when compared to ibuprofen in the presence of EuE, as the TASC value for the latter increases more steeply as the temperature is increased. This provides a further indication that ibuprofen interacts more strongly with EuE in comparison to EuRS. The most widely used method for determining drug-polymer miscibility is measuring the onset of drug melting-point depression in the presence of polymers [16]. The TASC vs temperature curves were therefore analyzed manually using the direct extrapolation method (Figure 3) to obtain onset of melting-point depression of drug values. The depressed melting points of ibuprofen in the presence of EuS, EuRS and EuE are summarised in Table 3. It confirms that both the EuE- and EuRS- based polymers depress the onset of ibuprofen melting, and that the depression is greatest in the presence of EuE.

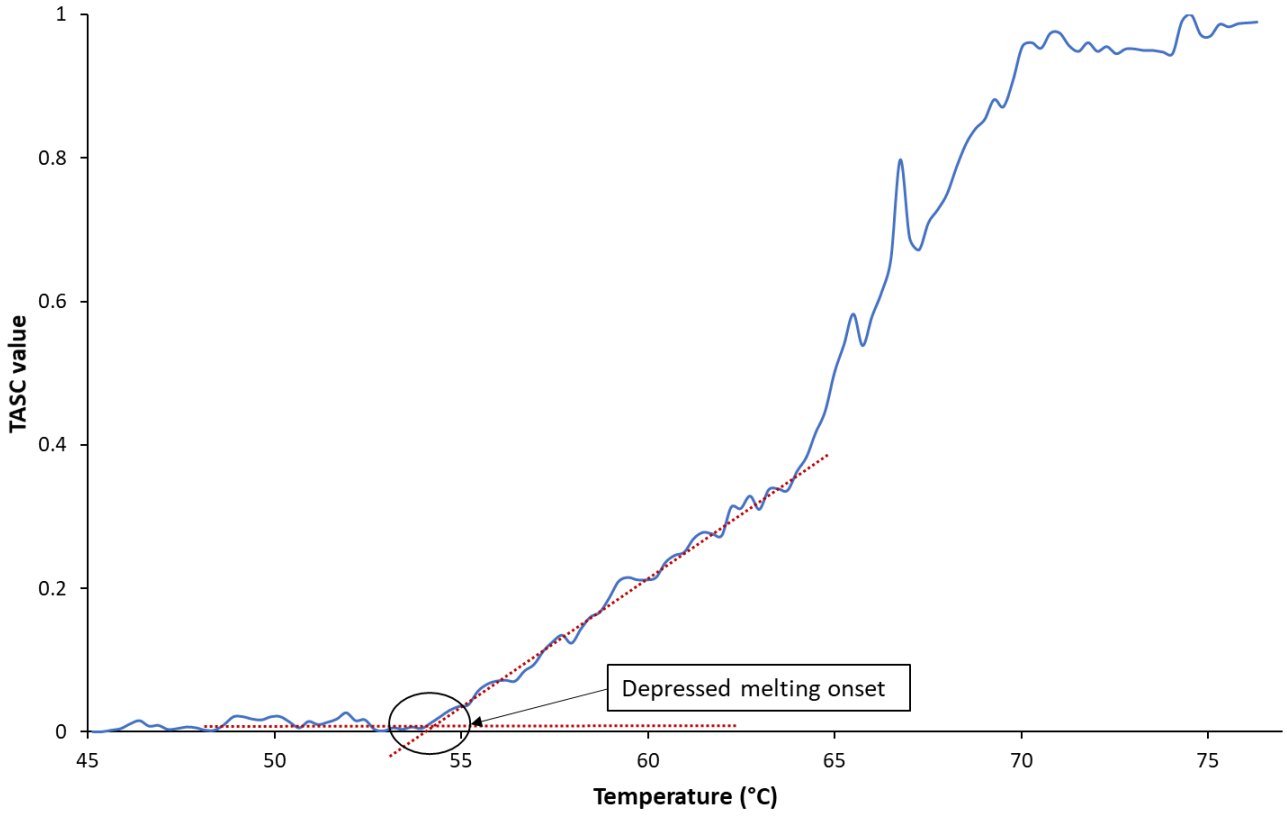


***Figure 3.*** *Demonstration of direct extrapolation method used to analyse TASC vs temperature curve to obtain onset of drug melting-point depression values.*

DSC data was generated simultaneously alongside the optical microscopy, providing further characterisation of the ibuprofen melting behaviour. The DSC curves obtained for pure ibuprofen and ibuprofen in the presence of EuS-, EuE- and EuRS- based films are shown in Figure 4 and the measured melting-point depression and melting enthalpy of the drug due to the presence of the polymer are reported in Table 3. The DSC results show that both EuE and EuRS depress the melting-point of ibuprofen, while EuS does not, and that all three polymers reduce the melting enthalpy of ibuprofen; however, the reduction in melting enthalpy is greater in the presence of EuE, followed by EuRS and then by EuS. The melting point depression and melting enthalpy reduction of a crystalline drug due to the polymer are both indicators of drug-polymer miscibility [3,8]. Based on the magnitude of depression of the onset of ibuprofen melting (obtained following TASC data analysis) and reduction of the melting enthalpy of ibuprofen, the polymers can be ranked in the order of EuE > EuRS > EuS, with EuE being more miscible with ibuprofen.

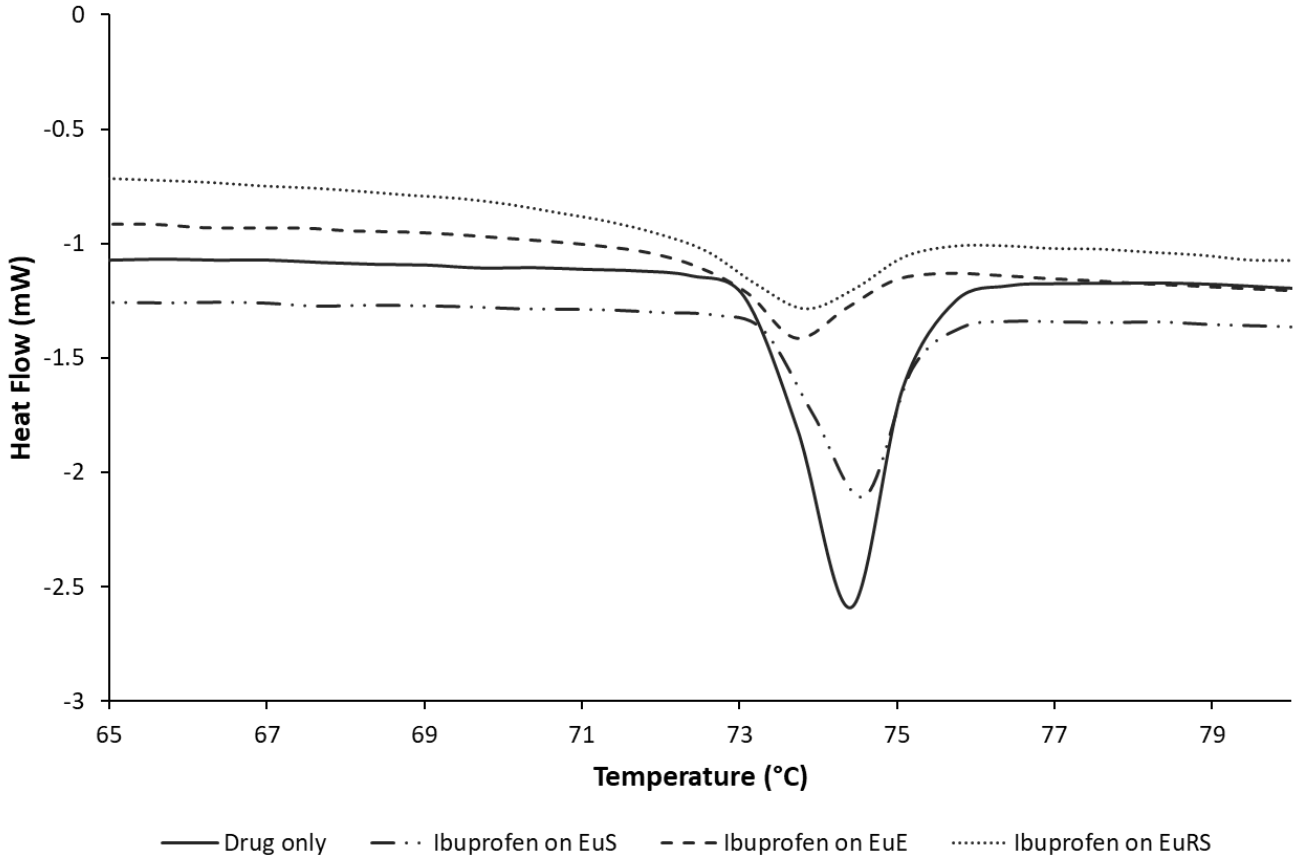


***Figure 4**. Representative DSC curves showing the melting transition of pure ibuprofen and of ibuprofen on top of EuE-, EuS- and EuRS- based films.*

***Table 3.*** *Melting-point depression temperatures following TASC data analysis (mean value ± SD displayed, n=6) and melting enthalpy (mean value ± SD displayed, n=3) and melting-point depression temperature (mean value ± SD displayed, n=3) following DSC data analysis of ibuprofen particles alone and ibuprofen particles on EuS-, EuE- and EuRS- based films. The direct extrapolation method was used for DSC data analysis.*

| | TASC melting-point depression temperature (°C) | DSC melting-point depression temperature (°C) | DSC melting enthalpy (J/mg) |
|---|---|---|---|
| **Ibuprofen on EuS** | 71.4 ± 3.7 | 73.2 ± 0.2 | 145.6 ± 3.2 |
| **Ibuprofen on EuE** | 51.3 ± 3.7 | 72.6 ± 0.1 | 52.5 ± 5.3 |
| **Ibuprofen on EuRS** | 57.9 ± 1.5 | 71.9 ± 0.1 | 78.9 ± 2.2 |
| **Ibuprofen alone** | 72.9 ± 0.3 | 73.1 ± 0.1 | 154.6 ± 1.3 |

These results agree with findings reported in the literature, following FT-IR, DSC and/or solubility studies, which indicate that EuE and EuRS strongly interact with ibuprofen [17,18], and that ibuprofen is more miscible in EuRS than EuS [19]. Hydrogen bonding between the ammonium groups in monomers of EuRS and EuE and the carboxylic acid group of ibuprofen is likely to explain ibuprofen miscibility in these polymers when compared to EuS [19]. The results obtained also confirms the interpretation of drug-polymer miscibility obtained via TASC elsewhere [8].

DSC is the most widely used method for gaining an understanding of drug-polymer miscibility and is a powerful tool characterising both the melting-point depression and melting enthalpy of the drug in the presence of a polymer. However, to optimally use the technique, careful consideration of experimental parameters such as the heating rate is required, which often needs to be slow, making the experimental work time consuming. TASC is an alternative method which can rapidly detect drug melting-point depression due to the presence of a polymer. While the technique is relatively novel, TASC method for melting-point depression detection and hence drug-polymer miscibility screening has been validated using IR imaging and long-term stability studies [8]. The use of the hybrid optical DSC allows the higher sensitivity and sample throughput of the TASC analysis to assess drug-polymer interaction with DSC data, providing confirmation of the interpretation of the optical analysis.

The results in this study show that measuring the onset of ibuprofen melting-point depression in the presence of polymers does not factor in the observance that an ibuprofen particle (placed on EuRS- or EuE- based polymers) becomes translucent and then transparent upon heating (Figure 1) and that the observance can be linked to drug dissolution through decreased drug melting enthalpy (obtained via DSC data analysis). The study therefore highlights that a hybrid optical DSC, not only confirms the interpretation of optical analysis but also enables a more complete understanding of drug miscibility in polymeric film forming systems. To add to this, unlike a DSC, the optical DSC drug-polymer sample does not require a high drug to polymer ratio, with previous studies having used polymer coated microscope slides as the solid substrate to sprinkle the drug particles on [8].

Such as set up is similar to the set up used in this study and is more representative of drug delivery systems such as films forming systems. However, when compared to the ibuprofen melting-point depression values obtained via TASC, the changes in the melting-point depression values obtained via DSC are small (Table 3). The optical DSC set up required approximately 0.001% of the amount of drug when compared to conventional DSC due to the high sensitivity of detection of the TASC experimentation [8]. A low ibuprofen mass may hinder drug-polymer interaction detection, and this may explain the small changes in ibuprofen melting-point depression values obtained by DSC; however, the ibuprofen melting enthalpy values, which also indicates drug-polymer interaction, showed obvious changes due to the presence of polymer. The results in this study therefore demonstrate that the drug melting-point depression values obtained via TASC can be supported by the drug melting enthalpy values obtained via DSC and that both bits of information are relevant and collectively enable the understanding drug miscibility in polymeric formulations.

### 3.2. Ibuprofen miscibility in polymeric films containing propylene glycol

The miscibility of ibuprofen with polymeric films consisting of EuE, EuRS or EuS along with the penetration enhancer PG was also investigated. The ratio between the polymer and the PG in the film was 2:1 w/w, which is consistent with what is typically used in film forming systems [3]. The TASC vs temperature curves obtained for ibuprofen in the presence of EuS-, EuE- and EuRS- based films containing PG are shown in Figure 5 and the measured melting-point depression of the drug due to the presence of the PG containing polymer films are reported in Table 4. The onset of melting of ibuprofen in the presence of the EuS film containing PG was similar to that of pure ibuprofen. EuRS- and EuE- based films containing PG led to different levels of depression of the melting point of ibuprofen, with EuE-based films depressing the melting-point to a greater extent.

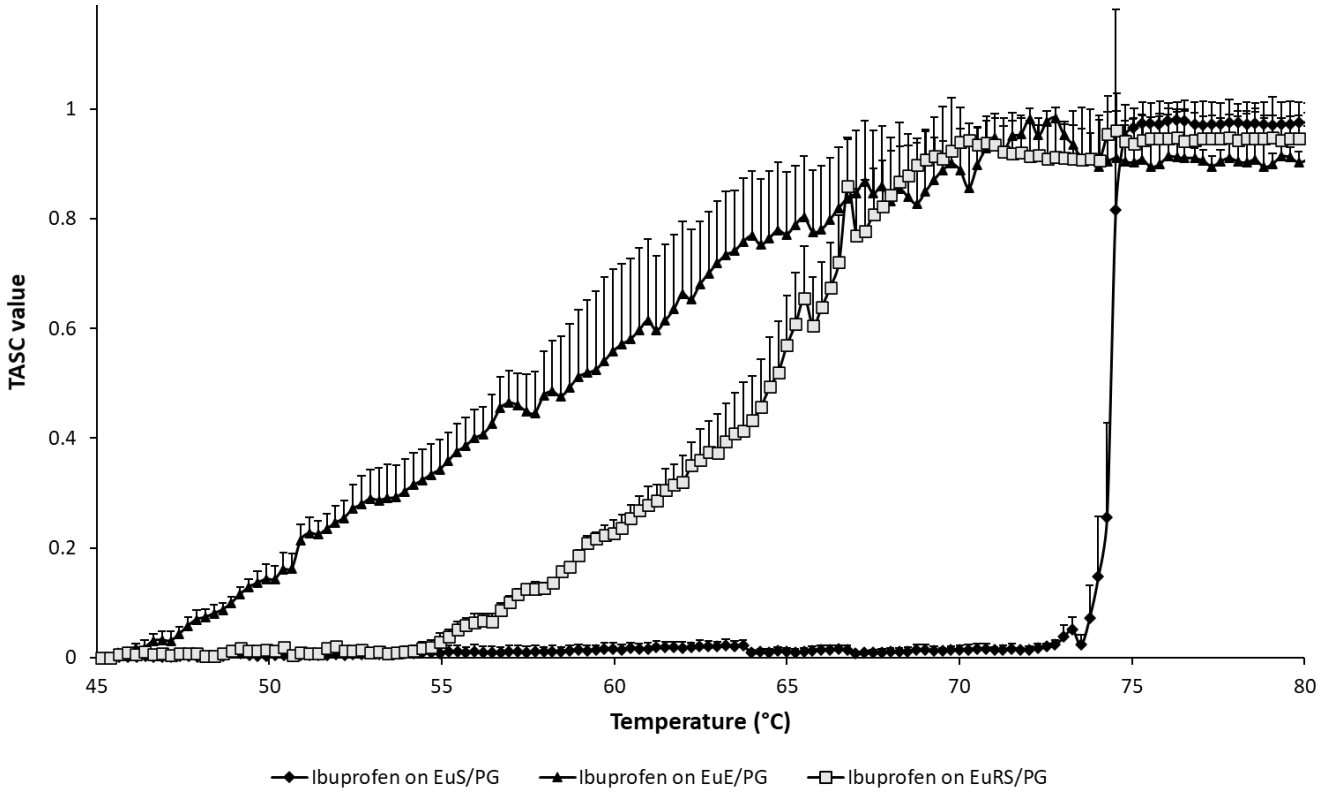


***Figure 5.*** *TASC analysis of ibuprofen samples placed on EuS-, EuE- or EuRS- based films containing PG (mean value + SD displayed, n=6).*

The DSC curves obtained during the experiment for ibuprofen in the presence of EuS-, EuE- and EuRS- based films containing PG are shown in Figure 6 and the measured melting-point depression and melting enthalpy of the drug due to the presence of the polymer containing PG are reported in Table 4. When observing the DSC curves obtained for ibuprofen in the presence of polymer films containing PG (Figure 6), it is evident that the melting transition of ibuprofen is less clear for the ibuprofen samples in contact with the EuE- and EuRS- based films. This supports the observation that it is difficult to analyse films containing other excipients such as chemical penetration enhancers by DSC. Whilst it was difficult to interpret the ibuprofen melting-point depression values obtained, which had small differences, it was possible to interpret the changes in the melting enthalpy of ibuprofen due to the presence of the polymer containing PG. The results show that the melting enthalpy of ibuprofen in the presence of the EuS film containing PG was similar to that of pure ibuprofen, while both the EuE- and EuRS- based films containing PG reduced the melting enthalpy of ibuprofen, with the reduction being greater in the presence of EuE. These results support the data obtained from the TASC experiments and indicate that ibuprofen is more miscible in the EuE-based film containing PG, and least soluble in EuS-based film containing PG.

This pattern of ibuprofen miscibility is similar to the pattern obtained when testing EuS-, EuE- and EuRS- based polymer films containing no PG. When comparing the melting-point depression values of ibuprofen (obtained via TASC) and the melting enthalpy of ibuprofen in the presence of the polymer films, with and without PG (Table 2 and 4), it can be seen that PG containing EuE and EuRS films display a greater magnitude of depression of the onset of ibuprofen melting and greater reduction of the melting enthalpy of ibuprofen, indicating that PG increases ibuprofen solubility in EuE and EuRS films. Ibuprofen has good solubility in PG [20], which likely explains why ibuprofen is more miscible in EuE and EuRS based polymeric films containing PG. In contrast, the presence of PG did not increase the miscibility of ibuprofen with the EuS-based film; the melting-point depression and melting enthalpy of ibuprofen was similar in the presence of EuS-based films with and without PG.

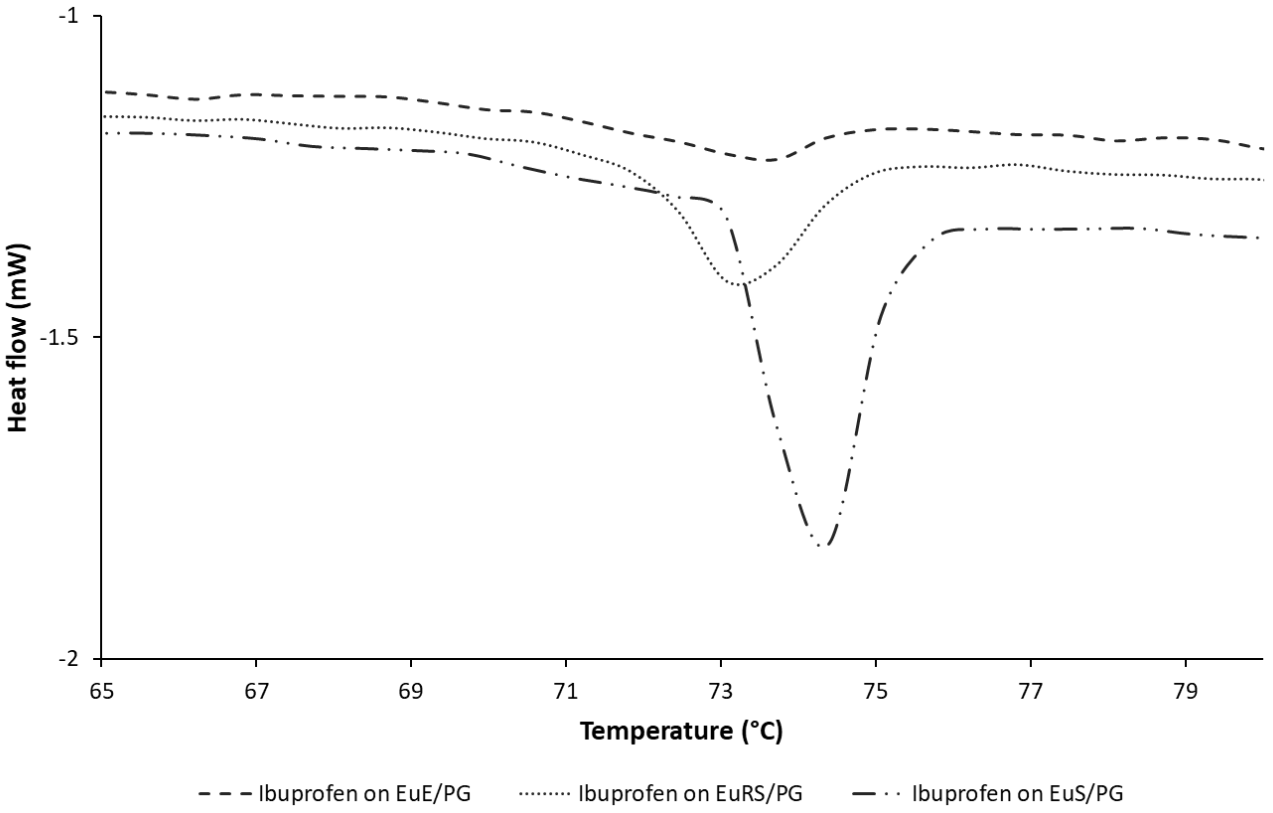


***Figure 6**. Representative DSC curves showing the melting transition of ibuprofen on top of EuE-, EuS- and EuRS-based films containing PG.*

***Table 4**. Melting-point depression temperature following TASC data analysis (mean value ± SD displayed, n=6) and melting enthalpy (mean value ± SD displayed, n=3) and melting-point depression temperature (mean value ± SD displayed, n=3) following DSC data analysis of ibuprofen particles alone and ibuprofen particles on EuS-, EuE- and EuRS- based films containing PG. The direct extrapolation method was used for DSC data analysis.*

| | TASC Melting Point Depression temperature (°C) | DSC Melting point depression temperature (°C) | DSC Melting Enthalpy (J/mg) |
|---|---|---|---|
| **Ibuprofen on EuS/PG** | 73.5 ± 0.7 | 73.2 ± 0.1 | 148.8 ± 6.7 |
| **Ibuprofen on EuE/PG** | 46.3 ± 0.7 | 71.3 ± 0.1 | 18.2 ± 4.1 |
| **Ibuprofen on EuRS/PG** | 54.4 ± 0.6 | 71.5 ± 0.2 | 51.0 ± 3.4 |
| **Ibuprofen** | 72.9 ± 0.3 | 73.1 ± 0.1 | 154.6 ± 1.3 |

Polymeric drug delivery systems, including film forming systems, often contain other excipients such as plasticisers and penetration enhancers and the result of this study suggests that incorporating an excipient that has good miscibility with a drug in a pharmaceutical formulation, does not necessarily increase the miscibility of the drug in the formulation containing other excipients, possibly due to the different ways the multiple components in the formulation interact. In this study, an optical DSC was used to investigate drug miscibility as the polymeric films used in the experiments can be produced using other excipients in addition to the polymer, presenting an opportunity to investigate ibuprofen miscibility in a pharmaceutically relevant film forming systems using TASC in combination with DSC. The results demonstrate that an optical DSC can be used to determine drug miscibility in a mixed carrier, while considering both the melting-point depression and melting enthalpy of the drug due to the presence of the mixed carrier (obtained via TASC and DSC analysis respectively), both of which are relevant for understanding of drug miscibility in polymeric film forming systems. Such a method can be used to rapidly screen drug-vehicle miscibility during the pre-formulation phase of not only film forming systems, but other polymeric drug delivery systems such as amorphous solid dispersions for the oral delivery of poorly soluble drugs and drug-loaded coatings of biomedical devices. This study gives an insight into the behaviour of ibuprofen in a mixed carrier containing PG and either EuE, EuS, or EuRS, and this was used to further increase current understanding of drug release from film forming systems.

### 3.3. Drug transport across silicone membrane

Film forming systems are typically used to deliver drug via the topical or transdermal route, and therefore drug transport studies were carried out using silicone membrane, a common surrogate model for skin [21,22]. The saturated solubility of ibuprofen in the receiver fluid used was 5.5 ± 0.028 mg/mL and sink conditions were maintained throughout the drug transport studies. The 8-h drug transport data across silicone membrane from formulations containing 2.5% w/w ibuprofen, EtOH, PG and the polymers EuE, EuRS or EuS are shown in Figures 7a. The drug transport profiles of all three formulations are similar in that they initially show rapid drug transport

that gradually decreases over time. It can be seen that the polymer included in the formulation has a considerable influence on drug transport from the formulation, with EuS enabling significantly more drug release from the formulation when compared to EuRS and EuE, and with EuRS enabling significantly more drug release from the formulation when compared to EuE. In order to assess drug delivery from formulations with a higher drug-load, the drug concentration in the formulations was increased to 5% w/w and the experiments repeated. The 8-h drug transport data across silicone membrane from formulations containing 5% w/w ibuprofen, EtOH, PG and the polymers EuE, EuRS or EuS are shown in Figure 7b. The drug transport profiles of all three formulations (Figure 7b) were similar to that obtained in Figure 7a, in that they too initially showed rapid drug transport that gradually decreased over time. However, the EuS formulations containing 2.5% w/w ibuprofen had a superior drug transport profile when compared to EuRS (Figure 7a), whereas the drug transport profiles for EuRS- and EuS- based formulations containing 5.0% w/w ibuprofen were similar (Figure 7b), with both still enabling significantly more drug release from the formulation compared to EuE. It can also be seen that doubling the drug concentration in the formulations from 2.5 to 5% w/w approximately doubled the total amount of drug released from the formulations.

Increasing the drug concentration in a formulation, may increase the degree of saturation of the drug within the delivery vehicle, which can in turn improve drug delivery from the vehicle. If the degree of saturation of the drug in the formulation increases beyond the solubility limit of the drug, the formulation becomes supersaturated, providing proportional improvements in drug delivery in relation to drug saturation in formulation. This is lost however if the formulation is unstable and if the drug precipitates from the formulation [23]. The results obtained confirm that the polymeric films could stabilize the drug at the higher concentration of 5% w/v, providing improved delivery. However, the improvement appears to be greater from the EuRS-based formulation when compared to the EuS-based formulation at 5% drug loading, suggesting that the EuS film is at the limit of drug saturation it can stabilize and that some drug may have precipitated from the EuS-based formulation. It is accepted that drug crystallisation can be delayed for a sufficient period, by selecting suitable formulation excipients such as anti-nucleant polymers [24]. Interactions between the drug and polymer are considered to be important for the anti-nucleant action of polymers [25], and the anti-nucleant action of polymers may be assessed by examining drug solubility in the polymer; with a polymer with good miscibility with a drug, considered as an effective anti-nucleant for the drug. Ibuprofen was found to be more miscible in EuRS than EuS from the TASC and DSC data. EuRS is therefore likely to be superior to EuS in preventing ibuprofen crystallisation at high drug levels whilst providing lower drug saturation at the lower ibuprofen concentration (2.5%) with commensurately lower drug transport at this concentration when compared to EuS.

Ibuprofen was also found to be considerably more miscible in EuE when compared to EuS and EuRS from the TASC and DSC data. The EuE-based formulation was therefore less saturated with drug compared to the EuS- and EuRS- based formulations. From Figures 7a and 7b it can be seen that drug release from the formulation containing EuE was lower than the formulations containing EuS and EuRS. These results associating lower drug transport across a membrane from vehicles in which a drug is more soluble in a vehicle, is consistent with previous literature [24,26]. The findings are also in agreement with two related studies; one of which suggested that EuE reduced ibuprofen release rate from polydimethylsiloxane/silicate drug in adhesive patches when compared to Eudragit® RL (a polymer with a similar structure EuRS, but with double the number of the quaternary amine group), due to the stronger association between ibuprofen and EuE than ibuprofen and Eudragit® RL [27], while the other suggested that EuRS provided greater methylphenidate delivery in comparison EuE because the lower solubility of the drug in EuRS provided a higher degree of drug saturation in the polymeric film [3].

The results here highlight how drug solubility in the vehicle can impact drug release from the formulation. They indicate that for film forming systems, a polymer with a 'good' miscibility with the drug is likely to be preferable to stabilize molecular dispersions at the higher saturation levels that provide improved drug transport across membranes such as skin, however if the drug-polymer miscibility is too high, drug saturation in the film and consequent permeation across the membrane will be lowered. This indicates that when developing or optimising film forming systems, excipient selection should be based on the solubility of the drug in the vehicle so that a balance can be achieved between obtaining a high degree of drug saturation in the film and sufficient anti-nucleation action. Given that polymeric drug delivery systems often contain other excipients, such as plasticisers and penetration enhancers, and that these excipients collectively affect the pharmaceutical properties of a formulation, this study emphasizes the relevance of understanding drug miscibility in the formulation vehicle.

To the authors' knowledge, this study is the first to explore drug-vehicle miscibility using an optical DSC to increase current understanding of drug release from film forming systems. As demonstrated in this study, an optical DSC can be used to identify polymers/vehicles with limited interaction with drug, likely to provide stability of the saturated/supersaturated state of the drug in the formulation and therefore optimal drug delivery and therapeutic outcomes. This is important as the drug bioavailability from formulations applied to the skin is typically low with large amounts of drug retained in the dosage form. An optical DSC can also rapidly screen drug-vehicle miscibility during the pre-formulation phase of pharmaceutical product development which in turn can reduce time and therefore their manufacturing costs.

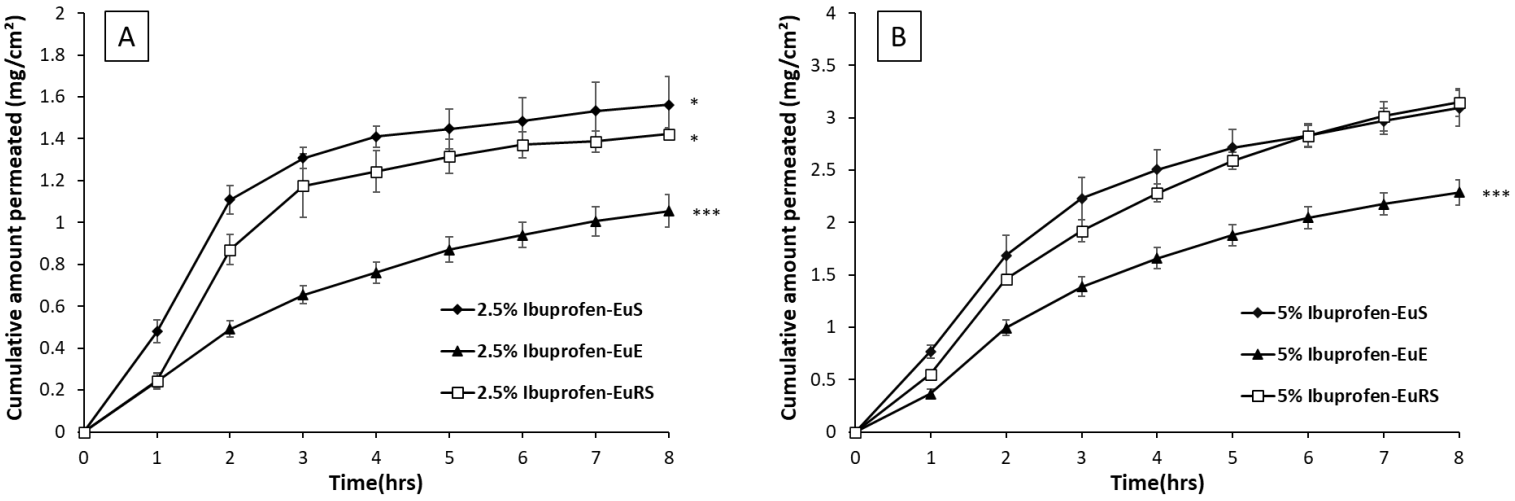


***Figure 7.*** *Cumulative amount of ibuprofen permeated across silicone membrane for formulations containing: A) 2.5% ibuprofen, 2.5% propylene glycol and 5% polymer, B) 5% ibuprofen, 2.5% propylene glycol and 5% polymer. *Indicates statistical difference ($p \leq 0.05$) between 2.5% Ibuprofen-EuS and 2.5% Ibuprofen-EuRS. *** Indicates statistical difference ($p \leq 0.001$) between 2.5% Ibuprofen-EuE and the other formulations, or 5% Ibuprofen-EuE and the other formulations.*

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## Declarations of interest

None.

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