Brief Report

Effect of drug-polymer binary mixtures on the *in-vitro* release of ibuprofen from transdermal drug-in-adhesive layers

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ABSTRACT: We report on the formation of eutectic mixtures of ibuprofen using two different polymers together with investigations on the *in-vitro* release of ibuprofen from drug-in-adhesive layers. Ibuprofen, literature melting point (m.p.) = 73.5-76.5°C, was tested together with Pluronic F127, literature m.p. = 54.4-60.5°C, and polyethylene glycol 1000 (PEG 1000), literature m.p. = 37-40.9°C, as second components in binary mixtures, incorporated into an acrylic adhesive, either as solid physical mixtures (PM) or molten mixtures (MM). Studies of how the type of mixture preparation (PM *versus* MM) and the ratio of components in binary mixtures affecting the *in-vitro* drug release of ibuprofen, compared with ibuprofen-adhesive layers without polymer addition were conducted. Ibuprofen release did not improve using the eutectic composition with Pluronic F127, possibly due to increased ibuprofen solubilisation in the adhesive and a subsequent decrease in the thermodynamic activity of the formulation. A significant increase in ibuprofen release ($P < 0.05$) was shown for compositions adjacent to the eutectic one, with ibuprofen: Pluronic F127 (40:60) and ibuprofen: PEG 1000 (20:80, 25:75, 30:70), from both PM- and MM-adhesive formulations, compared to the ibuprofen-adhesive formulations.

Keywords: Transdermal patches, Drug-in-adhesive, Ibuprofen, Eutectic mixture, Thermodynamic activity

1. Introduction

The advantages of transdermal drug delivery include avoidance of the gastrointestinal tract, sustained drug release and increased patient compliance. The barrier properties of the stratum corneum mean however that only certain drugs with specific physicochemical properties can be formulated into therapeutically effective passive transdermal patches. There are several strategies to further enhance the passive transdermal delivery of drugs including: the incorporation of chemical enhancers to the formulation, prodrug designs, attainment of maximum thermodynamic activity *via* ensuring saturated concentration of the drug in the formulation and a decrease of the melting point of the drug in the formulation (*1*).

The transdermal flux of a drug is proportional to the concentration of dissolved drug in the formulation; maximum flux being achieved at saturated drug concentrations. The tendency of the drug to crystallise on storage however eventually renders the formulation thermodynamically unstable with a subsequent decrease in drug flux (*2*). Several additives in monolayer transdermal (drug-in-adhesive) patches have been shown to decrease or prevent crystallisation of the drug (*3*). The melting point suppression strategy is based on the "ideal solution theory". This states that the lower the melting point of a drug, the greater the drug solubility in skin lipids (*4*). The formation of a eutectic binary mixture between the drug and an additional component is a well-known technique by which the melting point of the drug can be suppressed in the formulation. This has been previously examined as a potential method to enhance topical and transdermal drug delivery (*5,6*). There is however no published literature on the incorporation of eutectic mixtures into transdermal adhesive monolayers.

A eutectic binary mixture is a solid dispersion of two components at a specific ratio at which it possesses a lower melting point than either of the components and the other component ratios. At temperatures below this melting point the two components exist as an intimate microcrystalline mixture that melts uniformly at the melting temperature. At temperatures above the melting point the two components exist as a uniform melt that inhibit crystallisation of one another. Therefore a

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eutectic composition may confer stability to the drug against crystallisation.

In our study we used ibuprofen as the model drug and two hydrophilic polymers with low melting points, PEG 1000 and Pluronic F127 that would enable a considerable suppression of the melting point of the drug. Ibuprofen is a non steroidal anti-inflammatory drug (NSAID) with analgesic and anti-inflammatory properties. The main side effect of the oral administration of NSAIDS is irritation of the gastrointestinal wall lining, which can lead to the development of ulcers following long-term administration. For this reason ibuprofen and other NSAIDs have been studied extensively as candidates for systemic delivery *via* the transdermal route (*7*). PEGs are non-irritant nor toxic to healthy skin and do not readily penetrate it (*8*). Poloxamers have previously been used as a vehicle for the topical delivery of NSAIDs due to their low toxicity and irritation (*9*).

Binary eutectic mixtures of ibuprofen with Pluronic F127 and PEG 1000 were formulated into drug-in-adhesive layers containing binary drug-polymer mixtures at several ratios, including the eutectic ratio. Hot stage microscopy (HSM) was used to study the melting properties of the solid dispersions and identify the eutectic composition. The HSM technique has been shown to be more efficient than differential scanning calorimetry in detecting the presence of drug crystals in solid dispersions and differences in the melting behaviour among samples, especially when a polymer with a low melting point is used as a drug carrier (*10,11*). The binary mixtures were prepared and incorporated in the adhesive layer according to two different methods; either as physical mixtures (PM) or as molten mixtures (MM) of the two components that would solidify after incorporation into the adhesive layer. The aim of our work was to study how the method of mixture preparation, as a PM or MM, and the ratio of components in the binary mixtures influence the *in-vitro* drug release of ibuprofen, compared with ibuprofen-adhesive layers without additive.

2. Materials and Methods

2.1. *Materials*

Ibuprofen was obtained from Knoll Pharmaceuticals (Nottingham, UK). DURO-TAK® 87-4287 was a gift from National Adhesives-Henkel (Slough, UK). Polyethylene glycol with an average molecular weight of 1000 Da (PEG 1000) was supplied by Sigma (St. Louis, USA). Pluronic F127 was supplied as Lutrol® F127 and was a gift from BASF AG (Ludwigshafen, Germany). The Scotchpak 9742 release liner was a gift from 3M Corporation (St. Paul, USA).

2.2. *Preparation of solid dispersions*

Solid dispersions of ibuprofen with either Pluronic F127 or PEG 1000 were prepared in ratios ranging from 90%: 10% to 10%:90% (w/w) according to the fusion method. Appropriate amounts of ibuprofen and polymer to give a 2 g mixture were accurately weighed in test tubes and were placed in a water bath (Techne Inc., Princeton, USA) with a VMR 1122S temperature control. The initial temperature of the water bath was 30°C, gradually increased to 75°C, at a rate of 3°C/min, while the drug-polymer mixtures were gently stirred with a glass rod. The molten mixtures were then allowed to solidify at 20°C for a week.

2.3. *Hot stage microscopy*

The melting temperature of the solid dispersions, ibuprofen, Pluronic F127 and PEG 1000 were recorded using a Vickers microscope attached to a Mettler FP5 hot stage temperature control and recorder. The temperature range was set from 25 to 80°C with a heating rate of 2°C/min. Each solid dispersion was tested in triplicate (n = 3). Two temperatures were recorded per sample, the first being the initial temperature when melting began (lower limit) and the second being the temperature that melting was complete (upper limit). Phase diagrams were then plotted and the eutectic compositions were identified.

2.4. *Preparation of the adhesive layers*

The following binary mixtures of ibuprofen:polymer were prepared as physical mixtures and solid dispersions: 60:40, 40:60, 30:70 with Pluronic F127, and 60:40, 30:70, 25:75, 20:80 with PEG 1000. A binary mixture that would contain 0.05 g of ibuprofen was accurately weighed and added to the required amount of liquid acrylic adhesive to produce dried circular adhesive layers with an ibuprofen concentration of 10% (w/w). Ibuprofen-adhesive layers without polymer were also prepared by mixing 0.05 g of either solid or molten ibuprofen with the acrylic adhesive to produce layers of 10% (w/w) ibuprofen concentration. All layers had a mean surface area of 4.5 ± 0.35 cm^2, with one side attached to a release liner. The layers were stored for a week at 20°C before dissolution testing.

2.5. *In-vitro drug release studies*

In-vitro drug release studies were conducted according to the B.P. Dissolution method for transdermal patches. The release of ibuprofen from each set of layers (n = 3) was tested for 5 h using a paddle dissolution apparatus (Copley instruments Ltd, Nottingham, UK) with 900 mL of citrophosphate buffer (pH 5.6) as the dissolution medium under sink conditions. The temperature of the

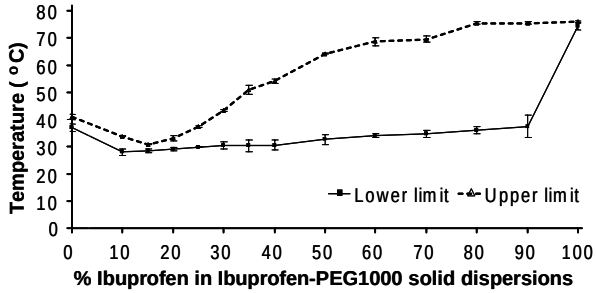

Figure 1. Phase diagram showing the melting behaviour of ibuprofen-PEG 1000 solid dispersions. Lower limit points show the mean temperature (n = 3) reading where melting of the sample started; upper limit points show the mean temperature (n = 3) reading where melting of the sample was complete. Error bars represent the standard deviation from each mean temperature reading.

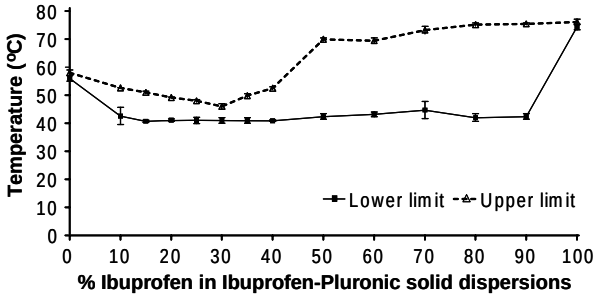

Figure 2. Phase diagram showing the melting behaviour of ibuprofen-Pluronic F127 solid dispersions. Lower limit points show the mean temperature (n = 3) reading where melting of the sample started; upper limit points show the mean temperature (n = 3) reading where melting of the sample was complete. Error bars represent the standard deviation from each mean temperature reading.

dissolution medium was maintained at 32 ± 0.5°C and the paddle stirring rate was set at 50 rpm. 10 mL samples of dissolution medium were withdrawn from each vessel every 10 min during the 1st hour and then every 30 min up to 5 h. The ibuprofen content of the samples was analysed using a CE272 Linear Readout Ultraviolet (UV) Spectrophotometer (CECIL instruments Ltd, Cambridge, UK) at a wavelength of 272 nm.

2.6. *Statistical analysis*

The % cumulative amount of ibuprofen released (n = 3) at 5 h was plotted against time. Statistical differences were determined using a Student *t*-test (two independent samples) with significance at $P < 0.05$.

3. Results and Discussion

The eutectic composition of ibuprofen with PEG 1000 was found at ibuprofen:PEG 1000 ratio of 15:85, with a melting point of 30.9°C (Figure 1). This temperature is lower than normal skin temperature (32°C), implying that ibuprofen will be in liquid form when applied onto the skin. Theoretically this would favour drug permeation into the stratum corneum (*4*). The eutectic composition of ibuprofen with Pluronic F127 was found at the ibuprofen:Pluronic F127 ratio of 30:70, with a melting point of 46°C (Figure 2).

The drug concentration in the adhesive layers (10%, w/w) was selected to be lower than the saturation solubility of ibuprofen in the adhesive polymer, in order to avoid suppression of drug release by drug crystallization and, thus, observe only the effect of binary mixtures on drug release. All layers prepared with the MM method were transparent in appearance with no drug crystals observed. The layers prepared with the PM method contained undissolved polymer dispersed in the adhesive layer. When the eutectic composition of ibuprofen with PEG 1000 (15:85) was incorporated into the adhesive as a molten mixture, it did not solidify on cooling but remained as liquid and leaked out of the borders of the adhesive layers on storage. For this reason it was not possible to carry out dissolution studies with the ibuprofen-PEG 1000 eutectic composition.

% Cumulative ibuprofen release at 5 h was statistically higher ($P < 0.05$) for the ibuprofen:PEG 1000 ratios 30:70, 25:75 and 20:80 compared to the ibuprofen monolayer 100:0 and the 60:40 ratio, for both PM and MM (Figures 3 and 4). Similarly, the ibuprofen: Pluronic F127 composition with the significantly higher ibuprofen release ($P < 0.05$) for both MM and PM was the 40:60 ratio, which is adjacent to the eutectic composition (Figures 5 and 6).

The eutectic composition of ibuprofen with Pluronic F127 (30:70) showed lower drug release compared to the formulation containing ibuprofen alone (Figures 5 and 6). This could be attributed to the fact that the eutectic mixture increases the solubility of ibuprofen in the adhesive layer and so simultaneously decreases the thermodynamic activity of the formulation. This is in agreement with previous observations demonstrating that a decrease in the melting point of a compound *via* formation of a binary eutectic system can be used as an approach for increasing the drug solubility in the vehicle (*5*).

The agreement between MMs and PMs on the order of enhancing drug release using either PEG 1000 or Pluronic F127 is noteworthy indicating an interaction taking place. An interaction between the components of binary physical mixtures during mixing has been previously reported (*12*). In our case, the incorporation of the binary physical mixtures in the adhesive solution may have resulted in ibuprofen-polymer solid dispersion formation during drying of the monolayer.

In conclusion, our results showed that ibuprofen release was enhanced by binary mixtures adjacent to the eutectic composition that contain a higher proportion of ibuprofen than the eutectic. This enhanced ibuprofen release could be observed up to a certain ratio, after which any further increase in the amount of ibuprofen in the binary mixture showed no significant difference ($P > 0.05$) on drug release compared to the drug-adhesive alone. Our

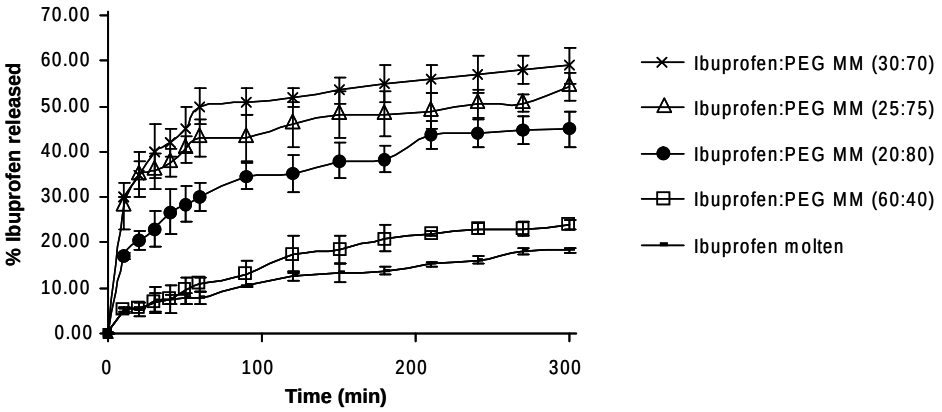

Figure 3. % Ibuprofen released from the adhesive layers containing MM of ibuprofen with PEG 1000. Error bars represent the standard deviation from the mean (n = 3).

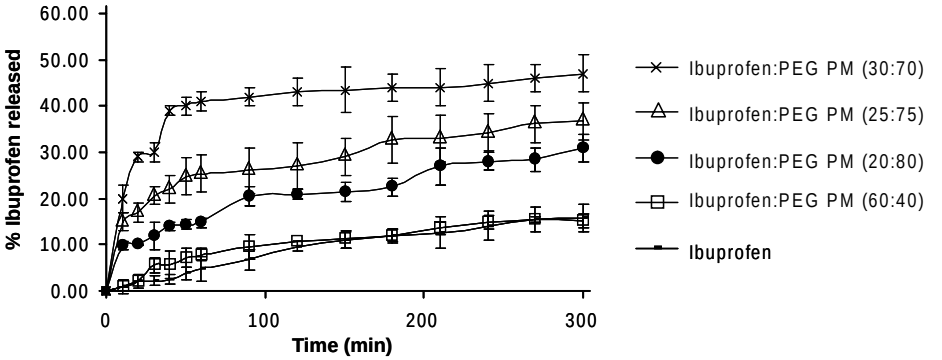

Figure 4. Ibuprofen released from the adhesive layers containing PM of ibuprofen with PEG 1000. Error bars represent the standard deviation from the mean (n = 3).

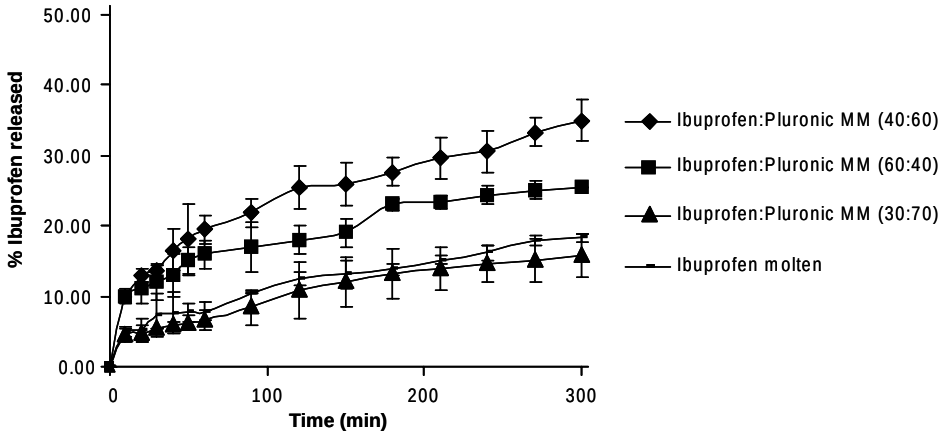

Figure 5. % Ibuprofen released from the adhesive layers containing MM of ibuprofen with Pluronic F127. Error bars represent the standard deviation from the mean (n = 3).

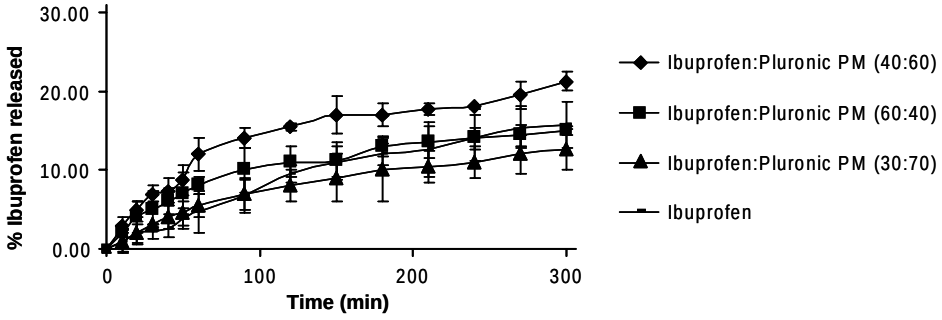

Figure 6. % Ibuprofen released from the adhesive layers containing PM of ibuprofen with Pluronic F127. Error bars represent the standard deviation from the mean (n = 3).

results also support the hypothesis that incorporation of an additional component as a eutectic mixture with the drug in the adhesive monolayer will increase the solubility of the drug in the adhesive, with a subsequent decrease in thermodynamic activity for the given ibuprofen concentration in the monolayer. This may indicate that using the eutectic composition, higher ibuprofen concentrations can be accommodated in the transdermal monolayer without compromising the stability of the formulation, considering the inherent stability of eutectic mixtures against crystallization.

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