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

Kwong Yat Ho, Michael Ord, Kalliopi Dodou*

Department of Pharmacy Health & Well-being, University of Sunderland, UK.

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.

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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 (Technne 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, 25:75, 20:80 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 cm², 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
and leaked out of the borders of the adhesive layers it did not solidify on cooling but remained as liquid incorporated into the adhesive as a molten mixture, composition of ibuprofen with PEG 1000 (15:85) was dispersed in the adhesive layer. When the eutectic with the PM method contained undissolved polymer with no drug crystals observed. The layers prepared with the MM method were transparent in appearance binary mixtures on drug release. All layers prepared crystallization and, thus, observe only the effect of order to avoid suppression of drug release by drug solubility of ibuprofen in the adhesive polymer, in w/w) was selected to be lower than the saturation found at the ibuprofen:Pluronic F127 ratio of 30:70, composition of ibuprofen with Pluronic F127 was found at the ibuprofen:PEG 1000 ratio of 15:85, with a melting point of 30.9°C (Figure 1). This temperature was found at 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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References


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