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A glimpse in critical attributes to design cutaneous film forming systems based on ammonium methacrylate

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ABSTRACT

A film forming system based on Eudragit® RL (EuRL) was designed aiming to evidence the relevance of formulative variables on the following critical attributes: film forming rate, outward stickiness, Young modulus (*Y*) and *in vitro* drug skin permeation. Different solvent mixtures (acetone and isopropanol in the range from 10:90 to 40:60 v/v), polymer concentrations (10–30% w/w), and plasticizer types and concentrations (triacetin or tributyl citrate, up to 50% of EuRL) were evaluated. EuRL dissolved in 80/20 or 70/30 v/v isopropanol/acetone mixtures at the concentration of 20% and plasticized with tributyl citrate (20 or 30% with respect to polymer) gave films with negligible stickiness and *Y* lower than 3 MPa. This value should assure an intimate and prolonged contact with the skin since it was significantly lower than *Y* of human stratum corneum (55 MPa). The optimized formulations were able to sustain the skin permeation of ibubrofen, ketoprofen and flurbiprofen and evidenced the importance of each formulative variable. In particular, relatively slow solvent evaporation rate can determine an initial "burst" effect and can influence the drug permeation in the initial hours. Conversely, when the solvent evaporation rate is not discriminant, the thermodynamic activity remains the main parameter driving the skin permeation.

1. Introduction

The passive transport rate of a molecule through the skin is proportionally related to its degree of saturation in the applied vehicle [1]. Therefore, drug supersaturation in topical formulations can be induced to improve the penetration into stratum corneum. Systems that are transiently drug supersaturated, namely those systems which become supersaturated only after dose actuation, seem to be more promising as dosage forms compared to pre-formed drug supersaturated patches, since the latter need to maintain the supersaturated state during their entire shelf-life. Transient supersaturation entails the reduction of drug solubility in the vehicle that is applied on the skin surface and this is most commonly achieved through solvent evaporation [1]. The simplest approach to achieve this goal consists in the design of polymeric film forming systems (FFS) which comprises a film-forming polymer dissolved in a volatile and skin tolerated solvent. When they are applied and/or sprayed on the surface of the skin, the rapid solvent evaporation leads to the formation of a polymeric film *in situ* [2]. The potential advantages of these dosage forms reside not only in the possibility to overcome the issue related to the physical instability of a supersaturated system, but also in a possible enhancement effect related to the solvent skin penetration during the metamorphosis of the formulation [3,4]. The last claimed advantage of FFS is related to the cosmetic attributes of the film. Indeed, many patients complain about the high visibility of transdermal patches, which are considered cosmetically unattractive, while the formed film is supposed to be almost invisible.

Moving to the formulative requirements, a film-forming solution should exhibit some peculiar features related to both the applied dosage form (i.e. the polymeric solution itself) and the final film. Firstly, the novel dosage form should quickly dry on the skin and the minimum film forming temperature should be below the skin surface temperature (about 32 °C). Secondly, the mechanical properties of the formed film should overcome the tangential stress due to the body movements. Finally, the formed film is required to be non-sticky to avoid adhesion to the patient's clothes.

To satisfy these requirements, a broad range of polymers (e.g. acrylates, polyurethane-acrylates, cellulose derivatives, poly(vinyl pyrrolidones) and silicones) were tested [5,6]. Among them, the use

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of methyl methacrylate copolymers appears of particular interest [5,7–10], even if the literature reports contrasting results on Eudragit® RL (EuRL) when it was compared to another widely used film forming material, namely hydroxyethyl cellulose. As an example, the skin permeability of estradiol from EuRL based films resulted significantly lower than that obtained with the cellulose ether [11]. Nevertheless, the use of EuRL allowed to overcome the mechanical issues associated to films made of hydroxyethyl cellulose. Indeed, it was demonstrated that both tensile strength and percent elongation at break of the films were improved by mixing in appropriate ratio cellulose and EuRL [12]. However, a systematic study of the formulation variables, namely solvent composition, polymer concentration, nature and amount of plasticizers, on the FFS properties is still lacking.

The current work aimed to study the effect of formulation compositions on technological and biopharmaceutical properties of FFS based on EuRL solubilized in a mixture of acetone and isopropyl alcohol in different ratios. This volatile vehicle was selected since both solvents have a regulatory approval for topical use.

The effects of solvent systems as well as the addition of the plasticizer, namely triacetin or tributyl citrate, were preliminary evaluated on drying time, outward stickiness and mechanical properties. In particular, since a reference for the tensile properties of the formed film is not established, the elasticity of human stratum corneum was preliminary determined and used as reference.

The performances of the optimal formulations were further investigated studying the skin permeation of three different drugs, namely flurbiprofen, ibuprofen and ketoprofen.

2. Materials and methods

2.1. Materials

Eudragit® RL PO (poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride); molar proportions of the monomer units 1:2:0.2; weight average molar mass 32 kDa, EuRL) was kindly supplied by Rofarma Italia (Italy). Tributyl citrate (TBC) and triacetin (TRI) were provided by Morflex (USA) and Sigma Aldrich (Italy), respectively. Isopropanol and acetone were purchased by VWR International (Italy). Flurbiprofen (FP) and ketoprofen (KP) were purchased from Farmalabor (Italy) and *S*-ibuprofen (IB) from Francis (Italy).

All solvents were of analytical grade, unless specified.

2.2. Preparation of polymeric FFS

Film-forming systems (FFS) were prepared by adding 10, or 20, or 30 (%, w/w) EuRL to different mixtures of isopropanol and acetone (ratios: 90:10, 80:20, 70:30, 60:40%, v/v) with or without the selected plasticizer. Each solution was stirred overnight to ensure the complete swelling of the polymer in the solvent blend.

FP, or IB, or KP were dissolved in the FFS at a concentration of 4% w/w.

2.3. Characterization of the polymeric FFS

The preliminary screening of placebo compositions was carried out keeping in consideration the FFS drying time, the stickiness and cosmetic attributes of the formed film. Briefly, a small volume of the formulations was applied with a micropipette onto a plastic liner and the solvent was allowed to evaporate to form the film. The applied volume was fixed at 35 μL/2.5 cm^2 as this amount is small enough to be applied without flowing away from the application site. No-sticking films formed within 10 min and showing good cosmetic attributes were considered adequate for the aim of this work. The drying time was visually checked by evaluating the formation of a fingerprint on the film surface. This approach has been selected since the other method reported in literature, namely the use of a glass slide [5,6], did not permit to discriminate the formation of a dried, but sticky film.

The adhesive properties were preliminary evaluated by a thumb tack test [13] on the dry films according to the following score system: no adhesion, poor adhesion and good adhesion.

Afterwards, TBC or TRI were added to the most promising FFS in order to evaluate the effect of the plasticizers on the flexibility of films. To select the plasticizer concentration, the glass transition temperature (T_g) of films made by casting a polymeric mixture in isopropyl alcohol, containing the selected plasticizer in different ratios, was evaluated by differential scanning calorimetry (DSC) analysis (DSC1 Instrument, Mettler-Toledo, CH). Briefly, 20 mg (±0.01 mg) exactly weighted samples were sealed in aluminum pans and heated in inert atmosphere (70 mL min^{-1} of N_2). The reference was a pan containing aluminum oxide [10]. The equipment was calibrated with an indium sample. Films were scanned at 20 K/min from 20 to 80 °C in order to erase polymer thermal history, then cooled down to −50 °C at 20 K/min and re-heated up to 80 °C at 20 K/min. T_g was calculated as the inflection point in the second heating ramp.

2.4. Mechanical testing

Human stratum corneum isolation - The permeation studies were performed using the abdominal skin from female donors, who underwent cosmetic surgery and signed an informed consent for the use of the biological sample for research purposes [14]. After removing the subcutaneous fatty tissue, the skin was kept frozen until further use. For the stratum corneum isolation, skin sections were cut into squares of about 2.5 cm^2 and were immersed in water of 60 °C for 60 s according to an internal protocol [15]. Afterwards, the epidermis was carefully removed from the underlying tissue with the help of forceps and visually inspected for defects. Then, the epidermis samples were incubated for 24 h at 37 °C in a 0.1% w/v trypsin solution in pH 7.4 phosphate buffer [15]. After digestion, the underlying tissue of epidermis was scraped away and the remaining stratum corneum was washed in cold MilliQ® water. The stratum corneum samples were cut in 8 × 16 mm specimen, transferred into Petri dishes and left to equilibrate in a humidifier at 25 °C and 75% relative humidity using a saturated solution of sodium chloride, over a 12 h period.

Film preparation - Placebo films were prepared by a solvent casting technique by using a laboratory-coating unit Mathis LTE-S(M) (Mathis, CH), equipped with a blade coater. The coating thickness was set in order to obtain a dried film of about 50 μm. The FFS was spread on the release liner and dried at 32 ± 1 °C for 20 min. Film samples were cut in 7 × 20 mm specimen and stored at 25 °C until use.

Probe tack test - Probe tack test measures the force required to separate the test probe tip from the film sample by using a tensile testing machine equipped with a 50 N cell load transducer (Instron 5965, ITW Test and Measurement Italia S.r.l., Italy). The experiments were set according to an internal standard procedure [16]. Briefly, a flat stainless steel probe (diameter: 6 mm) was placed about 0.05 mm above the sample. Then, the probe was lowered onto the film surface and a constant force of 0.05 N was applied onto the sample for 5 s and, finally, the probe was removed at the debonding rate of 0.1 mm/s. The stress (σ) values for each experiment were calculated according to the following equation:

$$\sigma = F/A$$