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Tuning the rheological properties of an ammonium methacrylate copolymer for the design of adhesives suitable for transdermal patches

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ABSTRACT

Eudragit® RL (EuRL) matrices have been proposed to release a drug to the skin. However, no information is available on both viscoelastic and adhesive properties of such compositions. This work focuses on the evaluation of both rheological and texture properties of EuRL differently plasticized with tributyl citrate (TBC) or triacetin (TRI) in order to design a pressure sensitive adhesive suitable for transdermal patch preparation. The patch adhesive properties (*i.e.* tack, peel adhesion and shear adhesion) as well as its *in vitro* biopharmaceutical performances were determined after loading ibuprofen, ketoprofen or flurbiprofen. The addition of 40–60% w/w TBC or 40–50% w/w TRI to EuRL permitted to obtain matrices with the desired adhesive properties. Moreover, the increase of plasticizer content and loading of the drug reduced the relaxation time (τ_R). Consequently, the shear adhesion values decreased and the *in vitro* drug release constants (k) increased. Indeed, the k values from patches containing TBC were lower than the corresponding with TRI because of the lower fluidity of such matrices. In conclusion, the 60/40 EuRL/TBC binary blend is suitable for the design of transdermal patches since the *in vitro* permeability of the three selected drugs appeared comparable to those described in literature for marketed products.

1. Introduction

Transdermal patches and medicated plasters are pharmaceutical preparations designed to provide a prolonged delivery of drugs to the skin to achieve a systemic or local effect, respectively. Usually, they are drug-in-adhesive systems, in which the drug is dispersed and/or dissolved in a pressure-sensitive adhesive (PSA) matrix. PSAs are defined as soft polymeric materials that display an instantaneous adhesion on almost any surface by simple contact under a light pressure and that can ideally be detached from the substrate without any residue (Tan and Pfister, 1999).

The efficiency of the therapeutic treatment by these dosage forms is related not only to their ability to release the drug through the skin, but also to their complete skin contact over the whole delivery surface for the entire treatment period. If the patch lifts or partially detaches, the effective contact area, and thus the drug absorption, is unpredictable and therapeutic failure can occur (Fauth et al., 2002).

The adhesion properties of a PSA strongly depend on their viscoelastic properties. Viscoelastic materials are needed in order to relax stresses, easily create a molecular contact, and dissipate energy upon debonding. Indeed, PSAs should be soft and relax stresses to favor the contact with the substrate (Creton and Leibler, 1996), but they should also be highly dissipative and lightly physically or chemically crosslinked to resist to the applied stress once the bond is formed. From a technological point of view, the PSA matrix is characterized by tack, peel adhesion and resistance to shear. Tack is the property that enables an adhesive to form a bond with the surface of another material upon brief contact and under light pressure; peel adhesion is the force required to peel away a patch from a surface; shear adhesion represents the resistance of the matrix to flow over long times and moderate loads (Cilurzo et al., 2012).

The literature reports the feasibility to design PSAs able to deliver several drugs made from a poly(ethylacrylate-*co*-methylmethacrylate-*co*-trimethylammonioethylmethacrylate chloride), traded with the name of Eudragit® RL PO (EuRL) (Cilurzo et al., 2014). However, no information is available about either the viscoelastic behavior or the

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adhesive properties of such compositions.

This study focuses on the evaluation of the viscoelastic and adhesive properties of PSAs made of EuRL differently plasticized in order to identify a matrix suitable to develop a patch and clarify the possible relationships between the main rheological descriptors and the adhesive properties of such patch and the drug release pattern. This kind of relationship is rarely investigated, although it could provide useful information to design both transdermal patches and medicated plasters in the attempt to optimize their performance.

To achieve this goal, several PSAs were designed by mixing EuRL in different ratios (40–60% w/w) with two plasticizers, namely triacetin (TRI) and tributyl citrate (TBC). The drug release properties of the optimal combinations were evaluated by adding three different drugs, namely ibuprofen, flurbiprofen and ketoprofen. PSAs were characterized in terms of rheological and tack properties. Probe tack tests were performed not only to evaluate the adhesive properties of the PSAs, but mainly to understand better the debonding mechanisms (Deplace et al., 2009; Nase et al., 2008). The patches were characterized by measuring shear and peel adhesion and cold flow, which refers to the dimensional change and/or deformation of the polymeric matrix of a patch beyond the boundaries (EMA, 2014). The drug release pattern was determined by both *in vitro* dissolution test and *in vitro* skin permeation using human epidermis as membrane.

2. Materials and methods

2.1. Materials

Poly(ethylacrylate-*co*-methylmethacrylate-*co*-trimethylammonioethylmethacrylate chloride), traded with the name of Eudragit® RL PO (EuRL), with molar ratio of 1:2:0.2 and molecular weight 32 kDa, was kindly donated by Rofarma Italia (Gaggiano, Italy). Tributyl citrate (Citroflex 4, TBC) was supplied by Morflex (Greensboro, USA) and triacetin (TRI), ethyl acetate (EtOAc) and isopropanol (iPrOH) were purchased from Sigma Aldrich (Milan, Italy). The release liner used for patch preparation was a siliconized polyester film from Saint Gobain kindly donated by Bouty (Cassina de Pecchi, Italy), while the backing layer was a polyester film with a thickness of 57 μm (Polifibra, Agrate Brianza, Italy). Three active ingredients were selected: *S*-ibuprofen (IB) was purchased from Dipharma Francis (Baranzate, Italy); ketoprofen (KP), and flurbiprofen (FP) from Farmalabor (Canosa di Puglia, Italy). All solvents were of analytical grade, unless specified.

2.2. Blend preparation

To obtain the EuRL organic dispersion, the powder was dispersed in the solvent, ethyl acetate or isopropanol, at the concentration of 40% w/w. The polymeric blends were prepared by adding the plasticizer (TBC or TRI) to the EuRL dispersions. The amount of TBC or TRI ranged between 40 and 60% with respect to EuRL weight. When the active ingredient (*i.e.* IB, KP or FP) was added to EuRL mixture, it was preliminarily dissolved in the plasticizer and, then, added to the polymeric dispersion. The drug content was 4% w/w calculated on EuRL weight.

The polymeric dispersion was mixed for 3 h at 60 °C with a magnetic stirrer of 100 rpm. One night of rest was necessary in order to reduce the air bubbles formed during the stirring and to favor the full swelling of the polymeric chains.

2.3. Rheological properties in the linear regime

The rheological characteristics were measured on a Discovery Hybrid Instrument HR-3 (TA Instruments, New Castle, USA). The frequency-dependence of the viscoelastic moduli G′ and G″ was characterized with a parallel plate geometry (diameter 20 mm), by using a crosshatched upper plate for the formulations containing the lower amount of plasticizer, and a sandblasted plate for the other formulations.

2.3.1. Sample preparation

In order to obtain equilibrated samples of about 1 mm thickness, a special sample holder was used. The device consisted of lower plate geometry, to which a ring was fixed through a Teflon tape; this particular device allowed to put 10–15 mL (depending on the plasticizer concentration) of solution and completely dry it (slowly drying in air for 48 h, and then 30 min of drying at 45 °C); the same sample holder was used to test the sample on the rheometer by simply removing the holding ring just before the analysis (after the 7 days required for matrices maturation).

2.3.2. Experimental setup

To evaluate the linear viscoelastic regime, a strain-sweep procedure at 1 Hz was performed; then, a frequency-sweep deformation (0.01–100 rad/s) was applied to the sample, and the resulting response in terms of stress was measured. Each sample was analyzed first at 25 °C, and then at 32 °C. The analyses were performed in triplicate to verify the reproducibility of the experimental conditions.

More details on the significance of this type of experiments are summarized in Appendix B.

2.4. ATR-FTIR spectroscopy

Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were recorded over the wavenumber region 4000–650 cm^{-1} with an ATR-FTIR spectrometer (Perkin Elmer, Waltham, USA), equipped with a diamond crystal. For each sample 256 scans were collected at a resolution of 2 cm^{-1}. Spectra were ATR corrected and smoothed and then analyzed by using Origin Pro (Origin Lab). The maximum absorbance of peaks in the 1650 and 1800 cm^{-1} region was assigned by second derivate.

2.5. Differential scanning calorimetry (DSC)

The glass transition temperature (T_g) of EuRL/plasticizer blends was evaluated by DSC (DSC1 Instrument, Mettler-Toledo, CH) according to the method previously described (Gennari et al., 2017).

2.6. Probe tack test

Probe tack experiments were performed on a custom-designed probe apparatus adapted on a MTS 810 hydraulic testing machine, allowing the simultaneous observation of the debonding process through a transparent glass substrate (Lakrout et al., 1999).

2.6.1. Sample preparation

In order to get films of thickness 180–200 μm on a glass slide 2.6 × 10 × 0.2 cm^3 previously cleaned and activated by a plasma technique, 2–3 mL (depending on their concentration) of each placebo formulation were deposited on each glass slide (using a perfectly levelled support plate). Each sample was dried slowly in air for 48 h and then for 30 min in an oven at 45 °C. The PSA thickness was measured by a white light scattering technique with an optical profilometer (Microsurf 3D, Fogale nanotech, Nimes, France). The resulting PSAs were stored in a container to prevent dust for the 7 days required for the matrices maturation at room temperature.

2.6.2. Experimental setup

The experiments were carried out as follows: a flat-ended probe was brought into contact with the adhesive layer at a constant probe velocity of 30 μm/s until a set compression force was reached, kept at a fixed position for a given time of 10 s, and subsequently removed at a constant crosshead speed which was varied between 1 and 1000 μm/s. Experiments were conducted at room (storage) temperature