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Generic patches containing fentanyl: In vitro equivalence and abuse deterrent evaluation according to EMA and FDA guidelines

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ABSTRACT

The aim of this work was to characterize in vitro and ex vivo the performances of Durogesic and of two bioequivalent generic products, by evaluating: (a) fentanyl release; (b) fentanyl permeation across porcine skin and (c) fentanyl ease of extraction. Additional characteristics studied are the effect of temperature and skin integrity, applied individually or combined, to check a possible synergism. The two generic patches resulted equivalent to the originator according to the new Guideline. Nevertheless, the same data reported in a different way, i.e. considering the total amount of drug permeated from the whole patch over the application time, highlight differences among the patches. The additional tests performed showed that skin integrity does not represent a barrier for fentanyl permeation across the skin, regardless of the type and complexity of the patch. The effect of temperature resulted critical for two out of three patches, probably due to the different composition and to the different structure. The combination of skin damage and elevated temperature did not produce a synergistic effect. Fentanyl extraction was different for the different products and variable according to the conditions used.

The results reported in the present work underline the influence of patch composition and complexity on fentanyl extraction, release and skin permeation, in particular in conditions that can be critical, such as elevated temperature. In particular, the effect of critical variables, such as skin integrity and temperature, should be addressed to in the development of a new or new generic patch and new discriminant tests should be developed.

1. Introduction

Transdermal delivery systems (TDDS) are single dose pharmaceutical forms to be applied to the skin for systemic absorption. The first TDDS appeared on the market in the early '80, the last was approved in US in 2012 (Watkinson et al., 2016). Despite several advantages of transdermal delivery, only 17 drugs are presently administered by this route, essentially because of the very specific drug physico-chemical properties required to cross the skin barrier. The size of TDDS market is small, if compared to other pharmaceutical sectors, but growing, principally driven by patent expiration and subsequent entry of generic companies. The most successful TDDS is without doubt Durogesic (Janssen), a transdermal patch containing fentanyl, a potent opioid, used for the management of cancer pain. The first Durogesic approved by FDA was characterized by a drug reservoir containing fentanyl dissolved in ethanol gel. The ease of extraction of the gel for recreational purposes and leakage problems that can expose the patient to potentially fatal overdose, determined a redesign of the patch towards a matrix type in 2009. Because of the commercial success of Durogesic, many generic companies started producing equivalents, once the patent expired in 2006 (Pastore et al., 2015). Durogesic is today probably the innovator TDDS with the higher number of generic versions: only in Italy at least 11 generic products are now registered (AIFA, 2017).

In Europe the registration of a generic patch is regulated by the Directive 2001/83/EC and two EMA Guidelines that have been revised in 2014 (EMA, 2014a, b). The Guidelines came into effect on June 2015 and aimed at filling the gaps of the previous documents, specifically concerning the requirements to support the registration of a new or new generic patch. In particular, the main novelties are: the recommendations on how to conduct an adhesion, skin irritation and sensitization study; the definition of "a parameter that puts patch size and in vivo release into relation", the patch area activity; the possibility to evaluate drug release also with tests alternative to Ph.Eur. dissolution test; the need for skin permeation studies. Presently, a generic patch, in addition to bioequivalence, comparable skin adhesion, tolerability and sensitization, must have the same or higher patch area activity, the same or lower amount of residual drug, similar drug release/dissolution and skin permeation profiles, compared to the reference product (EMA, 2014a, b). As regards the residual drug, this is a very sensitive issue in the case of patch that contains narcotics. In order to guarantee a

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clinically effective release rate over all the application period, patches usually contain an excess of drug. This means that at the end of the intended period of application, a residual of drug of about 50% of the stated amount remains in the patch and, in the case of narcotic drugs, this represents a risk.

Abuse and misuse of opioid products is a growing problem of public health. In April 2015, the FDA published a new guidance entitled "Abuse-deterrent opioids - Evaluation and labeling" with the aim of helping producers to develop abuse-deterrent formulations. The text contains, among others, some indications about the methodology to use for the in vitro evaluation of the ease of drug extraction.

Additional problems of fentanyl patches, linked to the active used, are the effect of temperature and skin integrity, parameters known to modify skin delivery of the drug from transdermal patches (Shahzad et al., 2015). In particular elevated temperature is known to increase skin penetration of fentanyl (Ashburn et al., 2003; Kim et al., 2015; Prodduturi et al., 2010): this topic has been recently addressed in an exploratory study for the development of an in vitro permeation test (Shin et al., 2017).

The aim of this work was to characterize in vitro and ex vivo the performances of Durogesic and of two bioequivalent generic products, already on the market in Italy before June 2015, Fentalgon (Zecca et al., 2015) by Italfarmaco and Matrifen (Lane, 2013) by Grunenthal. In particular, we evaluated, according to the Guideline: (a) fentanyl release from the patches; (b) fentanyl permeation across porcine skin and (c) fentanyl extraction from patches in different conditions. Additional characteristics, not included in the Guideline but very relevant for patient safety are the effect of temperature and skin integrity, parameters known to modify skin delivery of drug from transdermal patches. Heat and partial skin damage (produced by tape stripping) were applied individually or were combined, to check a possible synergistic effect.

2. Experimental

2.1. Materials

Fentanyl standard (1 mg/ml in methanol) was obtained from Sigma-Aldrich Italia (Milano, I).

Durogesic (Janssen-Cilag SpA, Milano, I), Fentalgon (Italfarmaco, Milano, I) and Matrifen (Grunenthal Italia s.r.l., Milano, I), transdermal delivery systems containing fentanyl (50 μg/h) were purchased from a local pharmacy.

2.2. Release studies

The release of fentanyl from the selected patches was evaluated by clamping a disc of the patch (0.8 cm^2) between the two halves of a vertical diffusion cell (Disa, Milan, I, permeation area 0.6 cm^2). Receptor compartment was filled with NaCl 0.9% (w/v) containing NaN_3 0.002% (w/v) as preservative. At prefixed time intervals, samples (0.3 ml) were collected from the receiver solution and replaced with fresh solution. All the experiments were performed in a water bath thermostatted at either 37 ± 1 °C or 50 ± 1 °C, to produce patch temperatures of 32° and 40 C, respectively.

2.3. Skin permeation studies

Pig ears were obtained from a local slaughterhouse (Macello Annoni, Madonna dei Prati, I) immediately after the death of the animal. Full thickness skin was excised from the outer region of the ear and separated from the underlying cartilage with a surgical blade. Hairs were trimmed carefully with scissors. After the removal of subcutaneous fat, the skin was wrapped in aluminum foil and stored at −20 °C until use, that occurred within 2 months. The skin integrity was evaluated by measuring the basal trans-epidermal water loss (TEWL) (OECD, 2004).

Minimally compromised skin was produced by tape stripping technique, i.e. partial removal of the stratum corneum by the application of adhesive tape (Scotch™ 845, 3M, St. Paul, MN, USA) on skin surface. The number of strips used was the minimum able to double the basal value of TEWL (7–8 strips). Skin was stripped before the separation from the cartilage.

A circle of patch, with the same area of the diffusion cell (0.6 cm^2), was attached to the skin surface by applying a slight pressure. The skin with the patch was then mounted between the two halves of a vertical cell, with the stratum corneum facing the donor compartment, and the receptor compartment was filled with about 4 ml of NaCl 0.9% (w/v) containing 0.002% (w/v) of NaN_3 as preservative. Experiments had a duration of 72 h, corresponding to the intended period of application, and were conducted in thermostatted bath at 37 ± 1 °C (skin temperature 32 ± 1 °C) or at 50 ± 1 °C (skin temperature 40 ± 1 °C).

2.4. Fentanyl extraction form patches

Circular samples of the patches (0.6 cm^2) were extracted with 2 ml of different solvents. The solvents used were: water; ethanol 40% water solution; pH 2.6 phosphate buffer (7.8 g/l of NaH_2PO_4 adjusted to pH 2.6 with H_3PO_4) or isopropanol. Extraction was made under magnetic stirring (200 rpm) at room temperature in all cases, except in hot water (70 °C). After 2 h of contact, the patch was removed and solutions, opportunely diluted, were analyzed by HPLC. All experiments were conducted in triplicate.

2.5. Fentanyl analysis

The amount of fentanyl in samples was quantified by HPLC (PerkinElmer, Norwalk, CT, USA) using a Novapack C18 column (3.9 × 150 mm, Waters, Milford, MA, USA). The mobile phase was a mixture of 0.23% perchloric acid water solution and acetonitrile (60:40, v/v) pumped at 1 ml/min. UV detector was set at 206 nm. In these conditions, the retention time of fentanyl was about 3.5 min and the run time was 6 min. The detector response was linear up to 22.5 μg/ml with a limit of detection of 0.09 μg/ml. The method was validated according to USP 40.

2.6. Statistical analysis

All data are reported as mean value ± sd of 3–6 replicates. Statistical differences were evaluated by one-way analysis of variance (one-way ANOVA) with Dunnett post hoc (level of significance $p < 0.05$).

3. Results and discussion

The EMA Guidelines on the quality of transdermal patches came into effect on 17 June 2015 and aimed at filling the gaps of the previous document, in particular as regards the requirements to support the registration of a new, or new generic, patch. Presently, the generic patch, in addition to bioequivalence, comparable skin adhesion, tolerability and sensitization, must have the same or higher patch area activity, the same or lower amount of residual drug, similar drug release/dissolution and skin permeation, compared to the reference product (EMA, 2014a, b). These last four requirements were evaluated in this work for two generic patches, Fentalgon and Matrifen, in comparison to the innovator product, Durogesic. Both generics were on the market in Italy before June 2015.

The structure and the characteristics of the patches selected for this work (strength 50 μg/h), are summarized in Fig. 1 and Table 1. All three patches have a matrix design (Fig. 1). Durogesic patch, the innovator product, consists of three layers, top to bottom, an impermeable backing of polyethylene terephthalate/ethylvinyl acetate, an adhesive semisolid polyacrylic matrix in which the active is dissolved and