International Journal of Pharmaceutics 488 (2015) 102–107

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Development and evaluation of a tampering resistant transdermal fentanyl patch

Bing Cai, Håkan Engqvist *, Susanne Bredenberg

Division for Applied Materials Science, Department of Engineering Sciences, The Ångström Laboratory, Uppsala University, Box 534, SE-751 21 Uppsala, Sweden

ARTICLE INFO

Article history:
Received 30 January 2015
Received in revised form 17 April 2015
Accepted 20 April 2015
Available online 22 April 2015

Keywords:
Transdermal patch
Tamper-resistance
Geopolymer
Fentanyl
Abuse
Drug delivery

ABSTRACT

With the increasing number of misuse and abuse of opioids, the resistance to tampering becomes an important attribute for transdermal opioid patches. In this study, drug-containing geopolymer granules were integrated into an adhesive matrix to improve the resistance of fast drug release against some common abuse techniques. Bench testing showed that fentanyl loaded geopolymer granules had better resistance to tampering compared to a commercial fentanyl patch. Moreover, in a pilot *in vivo* study on a few rats, the granules showed potential to give similar drug plasma concentrations as the commercial fentanyl patch. After integrating geopolymer granules into an adhesive matrix, the new patch showed a better resistance against the investigated tampering tests compared with the commercially available patch. In this study, we showed that incorporating drug loaded geopolymer granules into a patch adhesive has potential to improve the resistance of the fentanyl patch against tampering without compromising the drug release.

1. Introduction

The misuse and abuse of prescription opioid products have been medical concerns for many years. Fentanyl is one of the most abused opioids: a survey published in 2010 revealed that the number of emergency visits related to the non-medical use of the fentanyl has increased 105% during 2004–2008 in United States (Anonymous, 2010a). Although the transdermal fentanyl gained a lot of patient compliance for its non-invasive and around-the-clock treatment, the number of abuse cases on these patches increase significantly, causing dose dumping and thus serious side effects (Carson et al., 2010; Moon and Chun, 2011; Prosser et al., 2010; Woodall et al., 2008). Commonly, abusers override the controlled release mechanisms of the patches in order to obtain fast on-set euphoria by oral ingestion, injection and inhalation (Butler et al., 2011; Mastropietro and Omidian, 2013). To address the growing problem of the nonmedical use of fentanyl, there is a need for transdermal formulations that could reduce abuse potential and the risk of dose dumping (Howard and Reidenberg, 2004; Kugelmann and Bartholomaeus, 2006; Tavares et al., 2011).

Several tamper-resistant patches have been designed to solve this problem. Patent documents WO2004098568 A2, US7182955 B2 and US8790689 B2 describe transdermal dosage forms with a separated compartment containing antagonist/aversive agent (Hart et al., 2007; Howard and Reidenberg, 2004, 2005). The antagonists or aversive agents are not liberated if the patch is correctly used but will release along with the opioids if the patch formulation is tampered. US7511054 B2 illustrates a dosage form that contains opioid pro-drugs and a form of antagonist poorly absorbed through the skin (Stinchcomb et al., 2009). The antagonist would be minimally delivered transdermally but would take effect when the dosage form is tampered with. As the tamper-resistance of the product will never be absolute, researchers are endeavoring to find better formulations that will further reduce the abuse potential without compromising the efficacy of drug administration.

Geopolymers, a type of ceramic materials, are composed of three-dimensional networks of SiO_4 and AlO_4. Previous studies have suggested that geopolymers could be used as a drug carrier for controlled-release for oral formulation with better tamper-resistance than the compared commercial tablet (Cai et al., 2014; Jämstorp et al., 2010). For the geopolymer-based drug carrier, diffusion is the main rate-limiting step of drug release (Jämstorp et al., 2010, 2011). The physical properties of geopolymer, such as porosity and mechanical strength, could be adjusted by changing its composition and synthesis condition. Our previous study showed that these geopolymer-based formulations could maintain controlled drug release even after milled into fine

* Corresponding author. Tel.: +46 18 471 7130; fax: +46 18 471 3572.
E-mail address: hakan.engqvist@angstrom.uu.se (H. Engqvist).

http://dx.doi.org/10.1016/j.ijpharm.2015.04.061
0378-5173/

granules (Cai et al., 2014). Moreover, in comparison to the commercial tablet based on a polymer matrix, these formulations had better resistance against the extraction in heated water. In Cai et al. (2014), geopolymer showed its ability to increase the resistance of oral dosage forms against some common tampering methods and reduce the risk of dose dumping.

This study aims to evaluate geopolymer-integrated transdermal patch in its resistance to tampering. To our knowledge, this is the first attempt to integrate ceramics into the matrix of transdermal patches to reduce their abuse potential. The transdermal patch formulation that contains geopolymer granules in the matrix layer was expected to have better tamper-resistance against some common abuse methods without compromising the efficiency of drug delivery, as schematically illustrated in Fig. 1.

2. Materials and methods

2.1. Materials

Kaolin ($Al_2Si_2O_5(OH)_4$), fumed silica (SiO_2, 7 nm particle size), reagent grade sodium hydroxide (NaOH), monopotassium phosphate (KH_2PO_4), 37% fuming hydrochloric acid (HCl) and 99.5% ethanol were purchased from Sigma–Aldrich. Fentanyl base (MacFarlan and Smith, Edinburgh, UK) was donated by Orexo AB, Sweden. DuroTak® 87-4098 were obtained from National Starch Chemicals (Bridgewater, U.S.). A commercially available fentanyl patch, Durogesic® (Janssen-Cilag, Belgium) was used for comparison.

2.2. Synthesis

The synthesis procedure of geopolymer drug carrier is described in detail in Jämstorp et al. (2010). The geopolymer precursor used in this study had the following composition: Si/Al 2.129, H_2O /Al_2O_3 14.95 and Na_2O/Al_2O_3 1.472 (in molar ratio). The cured geopolymer with 14.9 wt% of fentanyl was ground manually using a mortar and pestle and the residual particles were separated into two particle-size ranges: 315–710 μm and 50–100 μm, respectively, using Retsch® sieves (F. Kurt Retsch GmbH, Germany).

The geopolymer granules with particle size 50–100 μm were integrated into matrix layer to fabricate a transdermal patch intended to resistant against tampering. The drug containing geopolymer carriers with diameter between 50 and 100 μm or fentanyl base were dispersed in IPA (propan-2-ol) within 3 min before mixed with adhesive (DuroTak® 87-4098). The mixture was with the ratio of 1 g geopolymer or 149 mg of fentanyl base to 2.8 g of IPA and 9.98 g of adhesive. The vial contents were mixed *via* rotation for 3 min until the powder dispersion appeared homogenous. The mixture was immediately laminated on release liner at a 500 μm setting. The casted film was dried in steps: 15 min at room temperature, 5 min at 50 °C and then 5 min at 90 °C. The dried film was cooled and covered with a backing layer. The finished patches were stored in the ambient temperature with relative humidity <20% before testing. The drug concentration in the geopolymer-integrated patch (Patch A) was 0.314 mg/cm^2. A control patch (Patch B) that had the same adhesive matrix and backing layer as Patch A but contained fentanyl base without geopolymer carrier was used for comparison. The drug concentration in the control patch was 0.304 mg/cm^2. The drug concentration in Patches A and B were calculated based on patch area, thickness, fentanyl loading and an assumed adhesive layer density of 1. Patch C, a commercial fentanyl patch (Durogesic®), was used for comparison with Patches A and B in their tamper-resistance. The adhesive used in Patches A and B is DuroTak® 87-4098, which is an acrylates copolymer containing vinyl acetate similar to the adhesive used in Patch C, DuroTak® 87-4287.

2.3. Evaluation of the resistance to tampering and in vivo drug availability of the geopolymer granules and commercial patches

As a first step, a preliminary drug release study was performed in order to investigate the tamper resistance of geopolymer granules with the size range 315–710 μm. A single dose of Patch C (Durogesic® 12 mcg/h) was used as comparison to the geopolymer granules with the corresponding dose in terms of extractability in the selected media. The test was carried out in a USP dissolution apparatus II (Sotax AT7 Smart, Sotax AG, Switzerland) equipped with mini vessels and paddles. The measurements were performed using a paddle speed of 50 rpm at 37 °C in 200 mL of phosphate buffer at pH 6.8 ± 0.5 or in 200 mL of 50% v/v ethanol solution. The amount of fentanyl was analyzed using isocratic reversed-phase HPLC (Dionex Summit®, Dionex UK Ltd.) with a XTerra MS C_{18} column (2.1 mm ID × 50 mm, 3.5 μm, Waters Corp., Milford, MA, USA). A PDA detector was utilized at a wavelength of 210 nm. The mobile phase was a mixture of acetonitrile and the solvent with 0.1 v/v% TFA, 72 v/v% water and 28 v/v% acetonitrile. The mobile phase was degassed inline at a flow rate 0.25 mL/min.

As a second step, a pilot *in vivo* study on the plasma concentration response of one forth of Patch C (Durogesic® 12 mcg/h) and geopolymer granules (size range of 315–710 μm) with corresponding dose was investigated on male Sprague Dawley rats (Taconic, Denmark). The animals were housed in ventilated cabinet with 12 h lighting arrangement. A 5-week acclimatization period was allowed before the test commenced. The fur on the back of the rats was shaved and treated with depilatory agent the day before the experiment. The granules were attached to the skin on the back of the rats using a circular-shaped placebo elastic textile patch (Cederroth AB, Sweden) with 1.2 cm in diameter in order to hold the granules in place. Due to the size variance between rats, the applied dose was adjusted to around 1500 μg/kg for comparison. Blood samples were taken after 0.25, 0.5, 1, 2, 4, 6 and 24 h and stored at +4 °C for maximum 30 min until centrifugation at 6000 rpm for 5 min. Plasma was stored initially at –20 °C for 1–3 days and then at –80 °C for 4 days until analyzed. Before analysis, the plasma samples were thawed and mixed on a shaker. A 50 μL of plasma was transferred into a microwell plate and precipitated with 200 μL of acetonitile. Internal standard solution was added into the plate and the mixture was mixed on a shaker for 30 min. The plasma samples were then centrifuged at

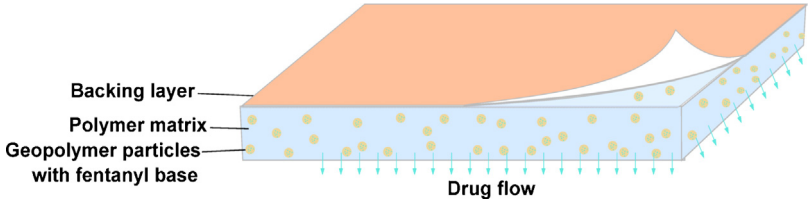

Fig. 1. Illustration of the geopolymer-integrated fentanyl transdermal patch.