International Journal of Pharmaceutics 394 (2010) 68–74

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Inhibition of crystallization in drug-in-adhesive-type transdermal patches

Piyush Jain, Ajay K. Banga*

Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, 3001 Mercer University Drive, Mercer University, Atlanta, GA 30341-4155, United States

ARTICLE INFO

Article history:
Received 20 February 2010
Received in revised form 25 April 2010
Accepted 26 April 2010
Available online 9 May 2010

Keywords:
Captopril
Levonorgestrel
Enhancer
Transdermal
Crystallization
Irritation testing

ABSTRACT

In this study the ability of various additives to inhibit crystallization of two model drugs, captopril and levonorgestrel, in acrylate and silicone adhesives was investigated. Among the various additives tested, PVP was found to be the most effective in inhibiting the crystallization of both drugs. Incorporation of PVP in patches (PVP stabilized patches) allowed incorporation of both drugs in amounts higher than their respective saturation solubility in pure adhesives (saturated patches). Skin permeation profiles of the drugs from the patches across hairless rat skin were obtained using Franz diffusion cells. For the hydrophilic drug captopril the skin flux over the first 24 h was the same for the saturated and PVP stabilized patches, but after 24 h the PVP stabilized patches produced higher skin flux values. However this may be because the saturated patch was depleted of the drug after 24 h. It is not clear if PVP performs as a solubilizer or a crystallization inhibitor for hydrophilic drugs. For the lipophilic drug levonorgestrel, the skin flux profile from the saturated and PVP stabilized patches was the same, suggesting that PVP acts just as a drug solubilizer and does not produce supersaturation.

1. Introduction

Drug-in-adhesive-type patches have been gaining increasing popularity as effective transdermal delivery systems during the last two decades (Chien, 1991; Lipp and Muller-Fahrnow, 1999). The concentration gradient of the drug between the delivery system and the skin is one of the important factors controlling the rate of percutaneous drug absorption (Lipp, 1998). Keeping this in mind, transdermal matrix type patches containing high concentrations of drug are generally preferred and required (Hadgraft, 1999; Latsch et al., 2004). Crystallization of drug is, however, a serious problem faced in formulating such a patch design (Variankaval et al., 1999; Minghetti et al., 2007). It not only makes the patch lose its aesthetic appeal after crystallization, but also makes the patch unstable, reduces the amount of drug present in the patch and decreases the original flux shown by a particular patch formulation (Ma et al., 1996; Kim and Choi, 2002). The recent withdrawal of Neupro (Rotigotine patch) from the market is an example of the severe implications crystallization can have on a patch formulation (http://www.neupro.com/Home/Home.asp).

In this study, various additives were investigated for their ability to inhibit the crystallization of drugs in adhesives. We defined crystallization inhibition as the prevention of crystal formation in patches by additives, due to (a) prevention of crystal nucleation, (b) adsorption of the additives onto crystals and (c) formation of amorphous additive/drug co-precipitates. In the cases mentioned above, the patches will be supersaturated and the patches stabilized with the additives would produce higher skin flux values than the patches that do not contain any additives. We also propose another mechanism of crystallization inhibition by an additive which can be acting as a solubilizer of the drug. In this case, since the prevention of crystallization is due to the fact that the additive simply increased the solubility of the drug in the patch, the skin flux from the saturated patches and from the additive stabilized patches will be the same. To study how additives affect crystallization, levonorgestrel (LNG) and captopril (CPT) were chosen as model drugs. Levonorgestrel is a progestin used in conjunction with estradiol to treat postmenopausal symptoms such as hot flashes and development of osteoporosis (Loose and Stancel, 2006). It is marketed as a transdermal patch with estradiol under the name Climara Pro™. The patch is 22 cm^2 in area and delivers 0.015 mg of levonorgestrel per day. The patch uses copovidone to prevent drug crystallization but delivery rates of more than 0.04 mg/day require a patch size of more than 30 cm^2 (Harrison et al., 2007). Captopril, on the other hand, is a competitive inhibitor of angiotensin-converting enzyme and is widely used in the treatment of hypertensive disorders. It is administered orally in dosages of 25–50 mg, two to three times a day. Transdermal delivery of both drugs is limited, in part because both drugs are known to crystallize in adhesives (Park et al., 2001; Harrison et al., 2007), making it difficult to design patches which are stable over time.

This study is focused on finding the saturation solubility of each of the two drugs in an acrylate (Duro-Tak 2516) and a silicone (Blend of 70% Bio Psa-4301 and 30% Bio Psa-4101) adhesive. To increase the amount of drugs which can be incorporated

* Corresponding author. Tel.: +1 678 547 6243; fax: +1 678 547 6423.
E-mail address: banga_ak@mercer.edu (A.K. Banga).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.04.042

in the adhesive, additives were added to inhibit crystallization. The additives which were screened for crystallization inhibition were poloxamer (Lutrol F127), polyvinylpyrrolidone (PVP 360) and copovidone (Kollidon VA64). The additives were tested for their ability to inhibit crystallization by a novel method of mixing the drug and the additive in an organic solvent and looking for crystals under a microscope after the solvent is evaporated. PVP, which was found to be the most effective additive in inhibiting the crystallization on the slides, was then used in patch formulations to test for the minimum concentration needed to inhibit crystallization. After stabilization of the patches, the transdermal delivery of the drugs from these patches was then tested using a hairless rat skin (HRS) model mounted on a Franz type diffusion cell assembly. Hairless rat skin data has been shown to be correlated to human skin in the past and several transdermal studies have been done and reported using the HRS model (Van Ravenzwaay and Leibold, 2004; Paturi et al., 2010). HRS model was selected over other hairy rodent models (such as Sprague–Dawley rats) as it correlates to human skin better as compared to other models (Godin and Touitou, 2007).

2. Materials and methods

2.1. Materials

Levonorgestrel and captopril were obtained from Sigma–Aldrich (St. Louis, MO, USA). poloxamer (Lutrol F127) and copovidone (Kollidon VA64) were obtained as gift samples from BASF, The Chemical Company (NJ, USA). PVP (PVP 360) was obtained from Sigma–Aldrich (St. Louis, MO, USA). Duro-Tak 2516 was gifted by National Starch & Chemical (Kleve, Germany). BIO-PSA 7-4301 and BIO-PSA 7-4101 were gifted by Dow Corning Corporation (Midland, MI, USA). Backing membrane 9734 and Release liner 9744 were obtained as gift samples from 3 M Scotchpak (St. Paul, MN, USA). HPLC grade methanol, tetrahydrofuran, propylene glycol and phosphoric acid were supplied by Fisher Scientific (Pittsburgh, PA, USA). Hairless rats were obtained from Charles River (Wilmington, MA, USA).

2.2. Preparation of microscopic slides for different additives

The drugs and the additives were dissolved in a minimum amount of an organic solvent in different ratios and then placed on microscopic slides. The solvent was then allowed to evaporate by keeping the slides at room temperature for 72 h. The slides were monitored for appearance of drug crystals visually and microscopically (Leica MZ6). Images were taken using a DFC camera attached to the microscope.

2.3. Preparation of drug in adhesive transdermal patches

The drugs were dissolved in a minimum amount of organic solvent and added to the adhesives under constant stirring with a magnetic bar. The solution was stirred for 15 min to ensure complete mixing. The drug containing adhesive mix was then cast on a release liner using a Gardner film casting knife (BYK-AG-4300 series, Columbia, MD) followed by drying in an oven at 70 °C for 30 min. The additive, PVP, was mixed in a minimum amount of organic solvent and added to the drug-adhesive mix while stirring. Oleic acid was also added to the adhesive mix in specified concentrations while stirring. After drying in the oven, the backing membrane was placed on the cast layer with the help of a roller. The patches were then observed under a microscope over the entire area for the presence of crystals.

2.4. Quantification of drug in patches

The amount of captopril present per cm^2 of patch area was determined for both saturated and PVP stabilized patches. For this, 1 cm^2 of the respective patches was cut ($n = 3$), the release liner was removed and the contents of the patch were extracted using 10 ml of methanol. The resulting mixture was centrifuged and the supernatant was analyzed for captopril by HPLC.

2.5. Skin permeation experiments

Skin permeation experiments were carried out for both drugs from solutions and patch formulations using hairless rat skin. Hairless rats weighing 350–400 g were euthanized using CO_2 asphyxiation. Abdominal skin was removed and underlying fat was cleared. The skin was cut in appropriate sizes and mounted on the Franz diffusion assembly (Logan, Somerset, NJ, USA) with the dermis side facing the receptor compartment. For permeation studies from solutions, the donor compartment consisted of 300 μl of the respective donor solutions for each of the drugs. For the patch permeation studies, the release liner was removed and the patch was applied on the stratum corneum side of the skin. The effective diffusion area was 0.64 cm^2. The receptor compartment was filled with 5 ml of propylene glycol and water in ratio of 1:1 and maintained at 37 °C. The receptor medium was stirred at 600 rpm and gentamycin sulfate in concentration of 80 mg/l was added to it to avoid microbial growth (Chisty et al., 2002; Valiveti et al., 2004). Receptor solution (0.5 ml) was taken out for each sample time point and replaced with fresh receptor medium. The samples were analyzed using the respective HPLC methods. Sink conditions were ensured by the high saturation solubility of levonorgestrel (250 μg/ml) and captopril (>80 mg/ml) in the receptor medium.

2.6. In vitro drug release studies

The release studies were performed using a modified Franz diffusion cell assembly (Jain et al., 2003; Gupta et al., 2009). The backing membrane side of the patches was stuck on a parafilm membrane which was bigger than the actual size of the patch with the help of a water impermeable adhesive. The release liner was removed and the patch was mounted on the diffusion cell with the patch facing the receptor compartment. The receptor compartment was filled with propylene glycol and phosphate buffer (pH 7.4) in ratio of 1:1 and maintained at 37 °C. The receptor medium was continuously stirred at 600 rpm and 0.5 ml of receptor solution was taken for each sample time point which was immediately replaced with fresh receptor solution. The samples were analyzed using the respective HPLC methods.

2.7. Quantitative analysis by high performance liquid chromatography

2.7.1. Analysis of levonorgestrel

HPLC analysis of levonorgestrel was performed according to Matejicek and Kuban (2007) with modifications. The assay was done on Waters Alliance 2695 separations module (Milford, MA, USA). The amount of levonorgestrel permeated in the receptor compartment was determined by spiking 10 μl of the sample onto a C_{18} column (Zorbax Eclipse XDB, 3.0 mm × 150 mm, 5 μm particle size). Elution was performed with methanol/water (7:3 v/v). The flow rate was 1.0 ml/min and the detection wavelength employed was 243 nm.

2.7.2. Analysis of captopril

HPLC analysis of captopril was performed according to Huang et al. (2002) with modifications. The assay was done on Waters