Development of a Polymeric Patch Impregnated with Naproxen as a Model of Transdermal Sustained Release System

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ABSTRACT: This paper describes the preparation and characterization of transdermal patches impregnated with naproxen. A mixture of ethylene vinyl acetate and Eudragit® E100 (80:20, w/w) is used as a polymeric matrix to obtain a thin membrane to be impregnated. Drug impregnation is carried out under pressurized CO_2 as a processing medium according to a two-step procedure. The patch is first soaked at 1000 psi and 22°C for 2 h, and then foamed as a result of the rapid release of CO_2 pressure in order to increase the porosity of the surface. Subsequently, the naproxen solution is placed in contact with the membrane and then soaked in CO_2 at 450 psi and 37°C for 2.5 h to enhance the mass transfer of drug into the polymer matrix. The characterization of the resulting samples by liquid chromatography, microscopy, and calorimetry provides information on naproxen content and distribution. Patches synthesized in this way are loaded with about 1% naproxen. The drug release and diffusion process through a membrane have been studied chromatographically using a Franz diffusion cell. Results have shown that a sustained delivery for more than 24 h is obtained. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:992–1000, 2011

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INTRODUCTION

An important pharmaceutical research field is focused on the development of new pharmaceutical forms with improved bioavailability and stable dosage by using clean technologies.[1–4] Processes carried out under dense (pressurized) or supercritical carbon dioxide result in an attractive alternative to those involving traditional solvents, especially to overcome the problems associated with toxicity and residual impurities.[5] Recent technological applications of pressurized and supercritical fluids comprise extraction of natural products; removal of contaminants,[6,7] protein, and peptide fractionation[8]; and preparative supercritical fluid chromatography.[9,10] However, apart from such type of industrial applications, the potentiality of CO_2 as a processing medium in pharmaceutical particle engineering cannot be underestimated[11,12] and following three main working topics are being investigated: (a) the preparation of active compound powders with improved or modified therapeutic action, (b) the production of polymers to be used as a matrix for drug impregnation, and (c) the preparation of drug delivery systems with enhanced bioavailability or sustained release characteristics. Hence, multiple pharmaceutical applications have been reported including the preparation of patches, sponges,[13] and catheters[14] with potential use in tissue engineering and drug delivery.

Advantages gained from the use of supercritical or dense CO_2 include the excellent uniformity in the distribution of the solute into the matrix, the reduction of process steps, and the simplicity of solvent removal. As nonporous polymeric matrices exposed to these fluids swell, the solute penetration through the matrix is thus enhanced. In addition, the drug entrapment can be carried out in a quick and easy one-step procedure. As an example, Kazarian and Martirosyan[15] described the impregnation of ibuprofen in polyvinylpyrrolidone (PVP), resulting in the

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formation of a molecular dispersion of drug into the matrix.

Although a wide variety of polymers have been used in the past 40 years as drug carriers, recent trends rely on water-soluble matrices such as PVP or its copolymer with vinylacetate (PVP-VA 64).[16] Other polymers such as cellulose derivatives [e.g., ethylcellulose (EC), methylcellulose][17,18] ethylene vinyl acetate (EVA),[19,20] and pH-dependent polymers such as Eudragit® E100 (Evonik Degussa, Essen, Germany), (polymethacrylate copolymer)[18] are being increasingly used.

This study is focused on the preparation and characterization of a transdermal patch as a model system of sustained released using pressurized CO_2 as a processing medium. Naproxen is the drug chosen here for this development. Naproxen is a member of the 2-arylpropionic acid family of nonsteroidal anti-inflammatory drugs commonly used for the reduction of mild-to-moderate pain, fever, inflammation, and stiffness.[21] The US Food and Drug Administration approved the use of naproxen sodium as an over the counter drug in 1994. Analytical techniques, including differential scanning calorimetry (DSC), confocal fluorescence microscopy, and high-performance liquid chromatography (HPLC), have been utilized for a more rigorous characterization of naproxen samples.

MATERIALS AND METHODS

Materials

Sodium hydrogenphosphate, sodium dihydrogenphosphate, formic acid, rhodamine (5,6-carboxytetramethylrhodamine), and naproxen (99%) were purchased from Sigma–Aldrich (St. Louis, Missouri). Methanol and methylene chloride (HPLC grade, Merck, Darmstadt, Germany) were used as solvents. Carbon dioxide (CO_2, 99.99 mol% purity) was supplied by Praxair (Columbus, Ohio). Polymers used were EC 20 cps from Keyser & Mackay (Brussels, Belgium), PVP-VA 64 (molecular weight = 45,000–70,000 g mol^{-1}) from BASF (Ludwigshafen, Germany), Eudragit® E100 (acrylic polymer, molecular weight = 150,000 g mol^{-1}) from Evonik Degussa (Essen, Germany), and EVA (70 wt% of vinyl acetate) from Sigma. Ultrapure water (Millipore, Milford, Massachusetts) was used for the preparation of aqueous solutions.

Analytical Instrumentation

The chromatographic system consists of an HPLC Agilent 1100 Series instrument equipped with a G1311A quaternary pump, a G1379A degasser, a G1329B standard autosampler (1200 Series), a G1315B diode-array detector furnished with a 13-mL flow-cell, a G1321A fluorescence detector, and an Agilent Chem Station for data acquisition and analysis (Rev. A 10.12), all of them from Agilent Technologies (Waldbronn, Germany). The analytical column was a reverse phase C_{18} (Synergi Hydro-RP, Phenomenex, 150 × 4.6 mm^2 d.i., 4 μm particle size). Naproxen was eluted isocratically with 10 mM of formic acid/formate aqueous solution (pH 3.2) + MeOH (20/80, v/v) as a mobile phase. The flow rate was maintained at 1 mL × min^{-1} and the injection volume was 20 μL. Ultraviolet (UV) spectrophotometric detection was carried out at 270 nm. Fluorescence detection was carried out at 270 and 357 nm as excitation and emission wavelengths, respectively. A magnetic stirrer IKA® RCT basic (Staufen, Germany) was used for controlling the release conditions.

Standard solutions for calibration were prepared in methanol in the concentration range from 5.2×10^{-7} to 3.9×10^{-5} M. For UV spectrophotometric detection, a good linearity in the studied range was found with a regression coefficient $r^2 = 0.9989$. Detection limit estimated for a signal-to-noise ratio of three was 1.8×10^{-7} M. Repeatability expressed as relative standard deviation (RSD in %) for the peak area was calculated from eight replicates at a concentration of 2.5×10^{-6} M and was 2.1%. For fluorescence detection, the linearity was found with a regression coefficient $r^2 = 0.9988$. Detection limit was 1.1×10^{-7} M and repeatability was 1.5%. The chromatographic method was used in both the determination of the impregnation percentage and in the monitoring of the drug release.

A differential scanning calorimeter (DSC-822e/400, Mettler Toledo, Greifensee, Switzerland) was used to determine melting and glass transition temperatures. Thermograms were obtained at a heating rate of 10°C × min^{-1} from 30°C to 250°C under a N_2 purge of 50 mL × min^{-1}.

A confocal microscope Leica TCS SPII (Leica Microsystems, Wetzlar, Germany) operating in both reflectance and fluorescence modes was used. Excitation was at 351 and 364 nm using UV lasers and reflectance, and emission intensities were recorded in the range of 400—800 nm. The objective used was a 10 × 0.3 N.A. HCPL FLUOTAR lens (Leica Microsystems). Images were processed using the ImageJ (NIH Image; www.rsb.info.nih.gov/ij) and Photoshop 7.0 software (Adobe Corp., San Jose, California). Transversal sections were taken every 2.4 μm.

Preparation of Working Solutions and Naproxen Impregnated Patches

The working solution of rhodamine for preliminary impregnation studies consisted of 1.5 mg dissolved in 100 mL of sodium phosphate buffer solution (PBS)