Design and *In Vivo* Evaluation of a Patch System Based on Thiolated Polymers

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ABSTRACT: A new oral patch delivery system has been designed to increase the overall oral bioavailability of drugs within the gastrointestinal tract. The patch system consists of four layered films: a mucoadhesive matrix layer, a water insoluble backing layer, a middle layer and an enteric surface layer. The separation layer between the two matrix layers contained lactose, starch and confectioners' sugar. The matrix layer, exhibiting a diameter of 2.5 mm and a weight of 5 mg, comprised Polycarbophil-cysteine conjugate (49%), fluoresceine isothiocyanate-dextran (26%), glutathione (5%), and mannitol (20%). A standard tablet formulation consisting of the same matrix served as control. Entire fluoresceine isothiocyanate-dextran (FD_4) was released from the delivery system within 2 h. For *in vivo* studies patch systems were administered orally to Male Sprague–Dawley rats. Maximum FD_4 concentration in blood of the patch system was 46.1 ± 8.9 ng/mL and was reached 3 h after administration. In contrast c_{max} of control tablets displayed 50.5 ± 14.9 ng/mL after 2 h and the absorption of FD_4 after administration in oral solution was negligible. The absolute bioavailability of orally administered patch systems and control tablets was 0.54% and 0.32% respectively. Results of this study indicate that a prolonged and higher oral bioavailability of FD_4 is obtained with patches thou with tablets. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:620–627, 2009

Keywords: patch system; polycarbophil-cysteine; FD_4; controlled release; *in vivo* study

INTRODUCTION

The efficiency of transfer of orally given drugs from the site of administration to the site of action may be limited by several factors. These include the release of the drug from the administered formulation and the changing conditions that the drug has to pass on its way to the target receptor.[1] Therefore many efforts have been devoted in the past to develop drug delivery systems (DDS) that include several layers which perform different tasks including adhesion, controlled release and protection from the surroundings.[2,3] While all these approaches have been shown to improve the oral bioavailability of large molecules, none of them offers a complete solution for adequate and safe oral administration.

One promising approach for incorporating the desired functionalities is the use of multilayered patch systems. Patch systems are designed with layers of thin, flexible membranes: an impermeable backing layer consisting of water insoluble polymer to protect drug from the attack of digesting enzymes, a drug containing layer containing drug and mucoadhesive polymer, a surface layer consisting of an enteric pH sensitive polymer that dissolves at an optimum site for absorption of drug in the small intestine and a

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separation layer between middle and surface layer.[4] Over the past decade, several new patch systems have been developed to provide more effective oral drug delivery.[5] One proposed approach for inducing greater levels of absorption by patch systems at the intestinal epithelium is the use of thiolated polymers as matrix layer.[4,6] Thiolated polymers, or designated thiomers to simplify matters, exhibit improved mucoadhesive, controlled release, permeation enhancing and enzyme inhibitory properties.[7] They represent a new generation of mucoadhesive and permeation enhancing polymers. For example permeation studies with hydrophilic model drugs across intestinal mucosa demonstrated that the combination of thiolated polymers with glutathione (GSH) led to a significantly improved drug uptake in the presence of thiomers.[8]

Due to the fact that major causes of the low oral bioavailability of macromolecular drugs are on the one hand generally luminal enzymatic hydrolysis and on the other hand low membrane permeability[9] the idea was the combination of both promising strategies, patch systems and thiomers, by the use of thiomers as multifunctional layer with the protective coating of a patch system.[4] After encouraging *in vitro* results[4] a patch system consisting of thiomers was utilized to enhance the oral bioavailability of insulin *in vivo*.[6] Although promising results were achieved it could not be evaluated if these results were obtained on the basis of the utilized thiolated polymer or the utilized patch system due to missing controls. So the aim of this study was to show the potential of a patch system based on thiolated polymers by *in vitro* and *in vivo* evaluation in comparison to a standard tablet formulation.

MATERIALS AND METHODS

Materials

Polycarbophil was kindly donated by Noveon (Raubling, Germany). 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC), *N*-(2-hydroxyethyl) piperazine-*N*-(2-ethanesulfonic acid) (HEPES), 5, 5-dithiobis(2-nitrobenzoic acid), ethylcellulose (EC) and fluoresceine isothiocyanate-dextran (FD_4 medium molecular mass: 4 kDa) were all purchased from Sigma (St. Louis, MO). Eudragit L100 was obtained from Röhm Pharma (Darmstadt, Germany). *N*-Hydroxysuccinimide (NHS) was obtained from Acros (Geel, Belgium). All chemicals were of analytical grade. Male Sprague–Dawley rats were purchased from the medical University of Vienna (Austria). Permeation studies were performed with rats weighed between 258 and 307 g.

Manufacturing of Patches

First, polycarbophil-cysteine (PCP-Cys) conjugate was synthesized as described previously.[10] Degree of modification was determined using Ellman's reagent.[8] Patches were prepared using PCP-Cys (49% w/w) in which FD_4 (26% w/w), glutathione (5% w/w) and mannitol (20% w/w) were incorporated. The granulate for the separation layer was made as described by Lieberman and Lachman[11] After filling 1 mg of the granulate for the surface layer in the tablet press, 5 mg of lyophilized PCP-Cys conjugate in which FD_4, mannitol and glutathione were incorporated, was added and compressed into 6 mg flat-faced tablets (single punch eccentric press-Paul Weber Maschinenbau, Modell 10, Remshalden-Grunbach, Germany). Pressure of 1.5 kN was kept constant during the preparation of all tablets resulting in discs of 0.5–0.8 mm height and 2.5 mm diameter. Tablets were coated in two steps. Each coating step was performed by immersing the tablet four times into the solution of coating material in acetone. First step included coating on the top and on the side with 5% (w/v) ethylcellulose. Tablets coated with ethylcellulose will be named disks in the entire publication. The uncoated side of one disc was stick to the uncoated side of another disc, followed by coating of the whole dosage form with 3% (w/v) Eudragit L100 (Fig. 1). Thereafter, the obtained "sandwich" was coated with hard fat in order to facilitate swallowing during *in vivo* experiments with rats. Patch systems without hard fat coating showed no significant differences regarding the overall oral bioavailability in comparison to patch system with hard fat coating (data not shown). For control tablets 10 mg of PCP-Cys, in which FD_4 (26% w/w), GSH (5% w/w), and 20% (w/w) mannitol were embedded, was compressed as described above and coated with 3% (w/v) Eudragit L100.

In Vitro Release of FD_4 from Patches

Due to the small size of the tablets, the *in vitro* release rate of FD_4 from the patch delivery system