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Molecularly imprinted polymers as nicotine transdermal delivery systems

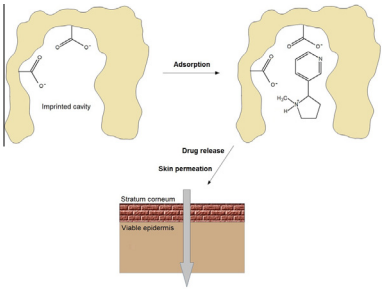
André Luís Morais Ruela *, Eduardo Costa Figueiredo, Gislaine Ribeiro Pereira

Faculdade de Ciências Farmacêuticas, Universidade Federal de Alfenas, Unifal, MG, Brazil

HIGHLIGHTS

- The feasibility of MIPs was evaluated as carriers for nicotine delivery in the skin.
- The drug–polymer interactions were established between the nicotine and the polymer.
- The selective adsorption of drug within the imprinted matrix modifies its diffusion.
- Selective sites on the imprinted matrix led to minor deviations in permeation assays.

GRAPHICAL ABSTRACT



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ABSTRACT

The aim of the present study was to prepare molecularly imprinted polymers (MIPs) with nicotine as the template drug and to evaluate the feasibility of these materials as excipients for the controlled transdermal delivery of nicotine. To achieve this goal, MIPs were synthesised by a free radical polymerisation method using methacrylic acid as the monomer and ethylene glycol dimethacrylate as the cross-linker. Polymer particles were prepared and included in transdermal systems with vehicles of different polarities. Characterisation studies employed the appropriate techniques, such as scanning electron microscopy, infrared spectroscopy and thermal analysis, to study the morphology of the particles, drug–polymer interactions and compatibility. Based on the results, in the MIP particles, non-covalent drug–polymer interactions were established by nicotine adsorption, mainly in non-polar vehicles. The drug release kinetics was fitted to Higuchi model, indicating drug diffusion from polymer matrix. Additionally, the diffusion of the drug from the polymer matrix can be modified by selective sites in the imprinted polymer carrier. Therefore, MIPs can be considered as suitable candidates for the controlled transdermal administration of nicotine.

1. Introduction

Nicotine is a suitable drug candidate for transdermal administration because it is highly lipid soluble and permeates the skin easily [1]. The transdermal delivery of nicotine has been suggested as an aid to smoking cessation therapy. The underlying hypothesis is that a constant plasma level of nicotine reduces the craving for nicotine and therefore, aids in the abstinence from smoking [2]. Moreover, nicotine administration via injection or skin patches has been shown to significantly improve attention, learning, and memory in patients with Alzheimer's diseases [2,3]. The slow and sustained absorption of drugs via the skin and the maintenance of low plasma drug concentrations is also desirable, especially in case of drugs that act on the brain [4]. However, there are substantial problems to be overcome in the development of a nicotine transdermal patch. Many of the common materials, such

* Corresponding author. Address: Rua Gabriel Monteiro da Silva, 700, CEP 37130-000, Alfenas, MG, Brazil. Tel.: +55 35 3299 1337; fax: +55 35 3299 1350.
E-mail address: andre.ruela@yahoo.com.br (A.L.M. Ruela).

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as backing, adhesives, and membranes, are attacked or degraded by nicotine. Polymers have been utilised in different layers of transdermal patches but polymers that can withstand the physical or chemical attack of nicotine frequently exhibit high nicotine permeability. This makes the retention of nicotine within the system a problem [5,6]. Most substances that can permeate the skin easily can also permeate most synthetic polymer films even more easily. Thus, it is difficult to find suitable materials and components and to create systems that can hold sufficient nicotine in a safe and controlled fashion [1].

In recent studies, molecularly imprinted polymers (MIPs) have been used to develop drug delivery systems [7–12]. Although imprinted drug delivery systems have not yet reached clinical application, this technology has a huge potential for creating satisfactory dosage forms and devices that may be useful in closely related fields, such as diagnostic sensors. The utility of these systems for administering drugs by different routes, such as oral, ocular or transdermal, has already been reviewed and is receiving increased attention for its ability to enable controlled and prolonged drug release [13–18].

MIPs are synthetic polymers with high thermal stability possessing selective molecular recognition properties. The recognition properties are due to recognition sites within the polymer matrix that are complementary to the template molecule in terms of the shape and positioning of functional groups [19,20]. The imprinting technique is based on the development of either non-covalent or reversible covalent interactions between a template molecule and suitable functional monomers during the pre-polymerisation step [21]. Once the template is removed, the resulting product is a cross-linked copolymer matrix with specific recognition elements for the template molecule. Molecular imprinting is a well-developed tool in the analytical field, and has mainly been used in the determination of very different substances, including drugs and bio-active molecules, in different samples [13]. MIPs for analytical nicotine determination have already been previously described [21–26]. Although the application of MIPs have been reported for isolation and quantification of nicotine in environmental samples [21,22] and biological fluids [23–26], these materials have not been studied as drug delivery systems. The application of MIPs as drug delivery systems may offer a safe and effective strategy to control the release of nicotine. These polymers can be applied as a matrix with a higher affinity for the drug and consequently nicotine diffusion can be modulated from transdermal patches.

In this study, we describe the feasibility of MIPs as a polymer matrix for the controlled release of nicotine and investigated the drug–polymer compatibility and the role of drug–polymer interactions in modifying the profile of nicotine release. Therefore, we prepared imprinted particles and evaluated MIPs as functional pharmaceutical excipients for the controlled transdermal administration of nicotine using *in vitro* studies.

2. Experimental

2.1. Materials

(−) Nicotine (⩾99%, liquid), methacrylcic acid (⩾99%), ethylene glycol dimethacrylate (⩾98%) (EGDMA) and 2,2-azobisisobutyronitrile (AIBN) were purchased from Sigma–Aldrich (USA). Acetonitrile, methylene chloride, methanol, acetic acid and orto-phosphoric acid 85% were purchased from J.T. Baker (USA). Sodium hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, potassium chloride, phosphoric acid and triethylamine were purchased from Vetec (Brazil).

2.2. Synthesis of nicotine-imprinted copolymers and preparation of imprinted particles

The synthesis of the poly (ethlylene glycol dimetacrylate-*stat*-methacrylic acid) polymer was adapted from the bulk polymerisation method previously described [18]. In the first step (pre-polymerisation), 4.0 mmol of methacrylic acid and 1.0 mmol of nicotine were dissolved in 6 mL of methylene chloride (porogenic solvent). To this solution, 20 mmol of EGDMA and 0.24 mmol of AIBN (radical initiator) were added. Next, the solution was purged thoroughly with nitrogen gas for 5 min and the reaction flask was immediately sealed. Then, the mixture was polymerised overnight at 60 °C. After free radical polymerisation, a solid white polymer was obtained. The resulting polymer was crushed, ground in a mortar and sieved (75–106 μm). To remove the nicotine confined in the selective cavities of the polymer particles, successive washings with a mixture of methanol: acetic acid (9:1, v/v) were performed and the level of residual nicotine was monitored by UV at 260 nm. After complete nicotine extraction, the polymer particles were washed exhaustively with water and dried at 40 °C for 24 h prior to use. The same procedure was performed without nicotine as a control for the effect of nicotine imprinting, and the resulting compound was designated as the non-imprinted polymer (NIP).

2.3. Characterisation studies

2.3.1. Fourrier transform infrared spectroscopy (FTIR)

The infrared spectra (IR) of the samples dispersed in KBr were performed using a Prestige-21 Fourier Transform (FT) infrared spectrophotometer (Shimadzu TM, Japan). The spectral data of nicotine, methacrylic acid, polymer particles without drug (MIP and NIP) and polymer particles loaded with nicotine were obtained. The polymer particles were loaded with nicotine solution (10 mg mL^{-1}) in methylene chloride. After 24 h, loaded polymer particles were filtered and the collected powder fractions were dried at 40 °C for 12 h.

2.3.2. Thermal analysis

Differential scanning calorimetry (DSC) was performed using a Mettler Toledo TM instrument model DSC 1 Stare System (Brazil). DSC thermograms were obtained at a heating rate of 10 °C min^{-1} from 25 °C to 500 °C under a N_2 purge of 50 mL min^{-1}. Thermogravimetric analysis (TGA) was performed using an Exstar TG/DTA termogravimetric analyser (Brazil). TGA thermograms were obtained at a heating rate of 10 °C min^{-1} from 30 °C to 600 °C under a N_2 purge of 50 mL min^{-1}. The following samples were analysed: nicotine, polymer particles without drug (MIP and NIP) and binary mixtures drug: polymer particles (1:1, w/w).

2.3.3. Binding experiments in water media

Binding experiments were performed in water media ($n = 3$). Initially, 20 mg of MIP particles were mixed with 2 mL of buffer solutions (20 mM) in closed polyethylene flasks at room temperature. The following buffer solutions with different pH values were prepared: 2.0, 4.5, 6.5 and 9.0. After 48 h, the solutions were filtered through PTFE filters with 0.45 μm pore size. The concentration of free nicotine in the supernatant was determined by high performance liquid chromatography (HPLC), as described in Section 2.6. The amount of nicotine binding on the polymer particles was determined by the difference between the initial (350 μg mL^{-1}) and the equilibrium (supernatant) concentrations.

2.3.4. Adsorption isotherm in organic media

The assays were performed to obtain the maximum adsorption capacity (MAC) of nicotine on the polymer particles (MIP and NIP).