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Microneedle-mediated delivery of donepezil: Potential for improved treatment options in Alzheimer's disease

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ABSTRACT

Transdermal drug delivery is an attractive route of drug administration; however, there are relatively few marketed transdermal products. To increase delivery across the skin, strategies to enhance skin permeability are widely investigated, with microneedles demonstrating particular promise. Hydrogel-forming microneedles are inserted into the skin, and following dissolution of a drug loaded reservoir and movement of the drug through the created channels, the microneedle array is removed intact, and can then be readily and safely discarded. This study presents the formulation and evaluation of an integrated microneedle patch containing the Alzheimer's drug, donepezil hydrochloride. The integrated patch consisted of hydrogel-forming microneedles in combination with a donepezil hydrochloride containing film. Formulation and characterisation of plasticised films, prepared from poly(vinylpyrrolidone) or poly (methyl vinyl ether co-maleic anhydride/acid) (Gantrez®) polymers, is presented. Furthermore, *in vitro* permeation of donepezil hydrochloride across neonatal porcine skin from the patches was investigated, with 854.71 μg ± 122.71 μg donepezil hydrochloride delivered after 24 h, using the optimum patch formulation. Following administration of the patch to an animal model, plasma concentrations of 51.8 ± 17.6 ng/mL were obtained, demonstrating the success of this delivery platform for donepezil hydrochloride.

1. Introduction

Microneedles (MNs)[1] are minimally invasive devices capable of penetrating the skin's *stratum corneum*, overcoming its barrier properties. This increases the potential for transdermal delivery of a greater number of drugs, as the prerequisite for substances to have specific physicochemical properties for passive transdermal delivery is negated [1]. Transdermal drug delivery has numerous well documented benefits, including avoidance of first-pass hepatic metabolism, the offer of controlled drug delivery, and reduction in gastrointestinal side-effects and is particularly useful for patients with dysphagia [2]. Since description of the first studies exploring the delivery capabilities of MNs, interest in the field has grown exponentially [3–5]. It has been acknowledged, that of the various strategies to enhance transdermal drug delivery, MN technology is progressing with the greatest promise, with human studies already conducted for the delivery of vaccines *via* this mechanism [6].

The various MN types have been extensively discussed, with the benefits and limitations of each type identified [7,8]. Hydrogel-forming MNs have several unique characteristics which make them suitable for a broad range of drug delivery applications. They are hard in the dry state, enabling successful insertion into the skin. Once *in situ*, they imbibe interstitial fluid and swell. This creates a porous network through which drug contained within a reservoir can diffuse from, and move into the dermal microcirculation (Fig. 1) [9]. Modification of MN swelling confers the ability to control rate of drug release. The drug reservoir is formulated independently of the MNs allowing further manipulation of the drug delivery system and, as a result, drug loading is not restricted to what can be contained within the needles themselves; a distinct advantage in comparison with dissolving and coated MNs. Aside from MN studies involving the delivery of a vaccine, the majority of drugs used have been for exemplar purposes. As the field continues to progress, the question as to what other applications MNs may have, has been asked [10].

The benefit of transdermal products in Alzheimer's disease has been recognised with a rivastigmine patch currently on the market. This product had an excess of US $400 million in sales in 2014, highlighting the commercial success of transdermal products for patients suffering from this condition [11]. Anti-Alzheimer's drugs

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[1] MNs = Microneedles.

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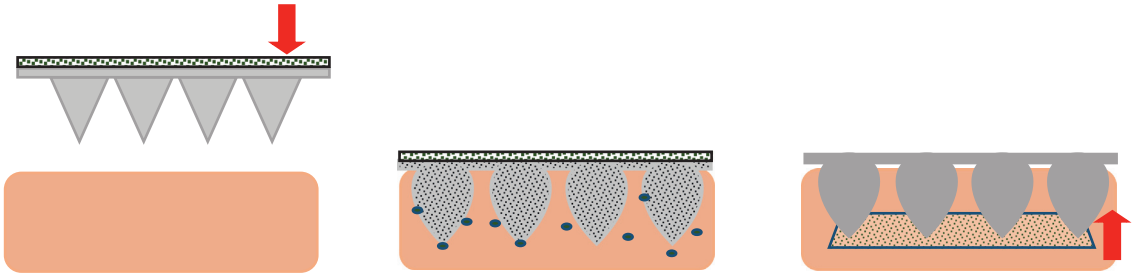

Fig. 1. Schematic representation of the mechanism of action of hydrogel-forming MNs in combination with a drug loaded reservoir.

are therefore a logical therapeutic choice when considering a clinically useful MN product. Donepezil (Fig. 2) (2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one) is an acetylcholinesterase inhibitor used in the treatment of mild to moderate dementia in Alzheimer's disease. Alzheimer's disease is the most prevalent form of dementia, which affects 835,000 people in the UK. With an ageing population and improved diagnoses, the number of people suffering from this condition, in the UK, is predicted to increase to over 2 million by 2051 [12]. Alzheimer's disease is associated with a reduction in certain cerebral neurotransmitters, including acetylcholine. The aim of donepezil treatment is to inhibit the hydrolysis of acetylcholine, thereby increasing its concentration in the synaptic cleft, and consequently, improving neurotransmission. It has been hypothesised that donepezil formulated as a transdermal patch, similar to rivastigmine, could provide significant patient benefit. A particular advantage of avoiding the gastrointestinal (GI) tract, by using a patch formulation, is a reduction in GI related side effects. Further to this, dysphagia is a common symptom of Alzheimer's disease, frequently hindering treatment with oral preparations [11]. Poor compliance to medication regimens amongst patients suffering from Alzheimer's disease is commonly reported, with one study finding that, following six months of oral donepezil treatment, only 52% of patients were fully adherent [12]. It has been shown that compliance in the elderly population is greater with transdermal patches in comparison with the oral form [13,14].

The base form of donepezil has a Log *P* of 3.08–4.11 and does not passively traverse the skin at clinically relevant levels [15,16]. To enhance transdermal delivery, various methods have been employed, mainly penetration enhancers [16,17] and iontophoresis [18]. These methods have investigated the delivery of both the free base form of the drug and the hydrochloride (HCl) salt. As it has been demonstrated that MNs can significantly increase the transdermal delivery of small, water soluble drug substances, we hypothesise that MNs could be used to facilitate the transdermal delivery of donepezil HCl (molecular weight: 433.97 g/mol). Our previous work has largely focused on the delivery of compounds with representative physicochemical properties using this novel MN system [9]. In contrast this study examines the modification and development, of this delivery system for a therapeutically relevant compound. The aim of the current study was to develop a novel 'integrated' MN patch consisting of a donepezil HCl loaded film and hydrogel-forming MNs for enhanced *in vitro* and *in vivo* transdermal delivery of this Alzheimer's drug.

2. Materials and methods

2.1. Materials

Gantrez® AN-139 and S-97, copolymers of methyl vinyl ether and maleic anhydride and methyl vinyl ether and maleic acid, respectively (PMVE/MAH and PMVE/MA, with molecular masses

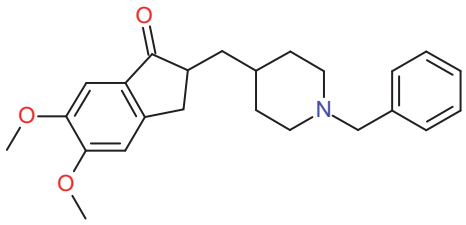

Fig. 2. Molecular structure of donepezil.

of 1,080,000 and 1,500,000 respectively) were gifts from Ashland, Kidderminster, UK. Poly(ethylene glycol) (PEG MW 10,000 Da), poly(vinylpyrrolidone) (PVP, MW 58,000 g/mol), glycerol, tripropylene glycol methyl ether (TPME), triethylamine and HPLC grade methanol and acetonitrile were purchased from Sigma Aldrich, Dorset, UK. Donepezil HCl was purchased from TCI UK Ltd., Zwijndrecht, Belgium. All other chemicals used were of analytical reagent grade.

2.2. Fabrication of hydrogel-forming MNs

MN arrays were fabricated from aqueous blends containing 15% w/w Gantrez® S-97, 7.5% w/w PEG, 10,000 and 3% w/w Na_2CO_3 as previously described [19]. Approximately 500 mg of blend was poured into 11 × 11 MN moulds and these were centrifuged at 2205 g for 15 min and dried at room temperature for 48 h. Crosslinking was induced *via* an esterification reaction, by heating the MNs at 80°C for 24 h [20]. Following this 24 h heating process, moulds were allowed to cool and the arrays extracted, with sidewalls formed by the moulding process removed using a heated blade. The final arrays produced contained 121 needles perpendicular to the base and of conical shape (600 μm in height, with base width of 300 μm and 150 μm interspacing on a 0.49 cm^2 patch).

2.3. Pharmaceutical analysis of donepezil hydrochloride

To analyse donepezil HCl delivered *in vitro*, a reverse phase high performance liquid chromatography (RP-HPLC) method was developed. An Agilent 1200 series system (Agilent Technologies UK Ltd., Stockport, UK) was used for analysis. The column used was a Phenomenex Luna® C18 (ODS1) column (150 mm × 4.6 mm internal diameter, 5 μm packing, Phenomenex, Cheshire, UK) with UV detection at 272 nm (run time per sample = 6 min). The mobile phase consisted of 65:34.5:0.5 acetonitrile:0.025 M potassium dihydrogen phosphate buffer (pH 3.0):triethylamine, at a flow rate of 1 mL/min. Column temperature was maintained at 25°C and injection volume was 20 μL. Agilent ChemStation® Software B.02.01 was used for chromatogram analysis. Correlation analysis along with least squares linear regression analysis was performed on the calibration curves generated, enabling determination of the equations of the line and their coefficients of determination. Limits