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Transdermal therapeutic systems for memantine delivery. Comparison of passive and iontophoretic transport

S. del Río-Sancho[a,b,*], C.E. Serna-Jiménez[a], M. Sebastián-Morelló[a], M.A. Calatayud-Pascual[a], C. Balaguer-Fernández[a], A. Femenía-Font[a], Y.N. Kalia[b], V. Merino[c], A. López-Castellano[a]

[a] Instituto de Ciencias Biomédicas, Departamento de Farmacia, Facultad de Ciencias de la Salud, Universidad CEU Cardenal Herrera, Avenida Seminario s/n, 46113 Valencia, Spain
[b] School of Pharmaceutical Sciences, University of Geneva & University of Lausanne, 1 Rue Michel-Servet, 1211 Geneva, Switzerland
[c] Instituto Interuniversitario de Investigación de Reconocimiento Molecular y Desarrollo Tecnológico (IDM) Universitat Politecnica de València, Universitat de València, Departamento de Farmacia y Tecnología Farmacéutica y Parasitologia, Universidad de Valencia, Valencia, Spain

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ABSTRACT

Memantine is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist used in the treatment of moderate to severe dementia including the symptoms of Alzheimer's disease (AD). It is administered orally but compliance, swallowing problems and the routine use of multiple medications in elderly AD patients means that an alternative route of administration would be of interest.

The aim of the present study was to develop memantine hydrochloride occlusive transdermal therapeutic systems (TTS) for passive and iontophoretic delivery across the skin. Polyvinyl pyrrolidone (PVP) and a mixture with polyvinyl alcohol (PVA) were employed as polymeric matrices. The study involved the TTS characterization in addition to quantification of the memantine transport across porcine skin *in vitro*.

The evaluation of the TTS physical properties suggested that systems were made more mechanically resistant by including PVA (6%) or high concentrations of PVP (24%). Moreover, a linear correlation was observed between the concentration of PVP and the bioadhesion of the systems. Drug delivery experiments showed that the highest transdermal flux provided by a passive TTS (PVP 24% w/w limonene) was $8.89 \pm 0.81\ \mu g\ cm^{-2}\ h^{-1}$ whereas the highest iontophoretic transport was $46.4 \pm 3.6\ \mu g\ cm^{-2}\ h^{-1}$. These innovative TTS would enable two dosage regimens that could lead to therapeutic plasma concentrations.

1. Introduction

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder that brings about severe cognitive deficits in the elderly (Sepulveda et al., 2010). It is estimated that 35.6 million people suffer from AD and this figure is expected to rise to 65.7 million in 2030 and 115.4 million in 2050 (Weiner et al., 2010). As the disease progresses, patients become unable to perform the simplest daily tasks without assistance, thus becoming completely dependent upon care-givers (Forstl and Kurz, 1999).

Memantine is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that acts on the glutaminergic system by blocking NMDA receptors and inhibiting their overstimulation by glutamate (Lipton, 2006; McKeage, 2010; van Marum, 2009) and it has been approved for the treatment of moderate to severe AD (Ebixa® and Namenda®) (Sonkusare et al., 2005).

However, it is reported that only 46.7% of AD patient care-givers said they were satisfied with the approved oral dosage form (Sevilla et al., 2009). These results can be attributed to (i) the inconvenience of oral administration due to the swallowing problems suffered by patients in advanced stages of AD, (ii) the burden placed on the care-giver to ensure that the medicine is taken by the patient and (iii) the posology which requires that the dose be increased in 5 mg increments to 20 mg/day (10 mg twice daily) which accentuates the difficulties imposed by (i) and (ii). An extended release tablet (Namenda® XR) has addressed some of the

* Corresponding author at: Instituto de Ciencias Biomédicas, Departamento de Farmacia, Facultad de Ciencias de la Salud, Universidad CEU Cardenal Herrera, Avenida Seminario s/n, 46113 Valencia, Spain.
E-mail address: sergiodelrio@hotmail.es (S. del Río-Sancho).

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problems (Bassil et al., 2010). However, the issues of adherence and dysphagia remain; therefore, despite an oral bioavailability of almost 100%, there is a need for an alternative route of administration – transdermal delivery could address both concerns and so help to facilitate care and to improve the patient quality of life (Chan et al., 2008).

Given that steady-state plasma concentrations range from 70 to 150 $\mu g\,L^{-1}$ following administration of a daily dose of 20 mg and that the total clearance is 10.2 $L\,h^{-1}$ (Wenk et al., 2000), then in order to maintain steady state levels it is necessary to achieve transdermal input rates of ~0.7–1.5 $mg\,h^{-1}$. Memantine has a molecular weight of 216 and a log P of 3.28 which make it a good candidate for passive transdermal delivery. However, memantine contains a primary amine with a pKa of 10.4, is available as a hydrochloride salt and possesses good aqueous solubility – these physicochemical properties make it an excellent candidate for anodal transdermal iontophoresis. This was confirmed in a previous study that compared the use of chemical penetration enhancers (CPE) oleic acid, laurocapram or R-(+)-limonene (5% w/w in ethanol) for passive delivery and iontophoresis as an active delivery system (del Río-Sancho et al., 2012). Although the CPE increased transdermal flux as compared to the control, the most significant increases were observed using iontophoresis.

The passive and iontophoretic delivery experiments performed during the previous study (del Río-Sancho et al., 2012) were conducted using either ethanolic or aqueous solutions; although suitable for a proof-of-principle, it is clear that more sophisticated transdermal therapeutic systems (TTS) must be developed and tested before any pharmacokinetic studies can be envisaged in humans.

The aim of the present study was to develop, to characterize and to evaluate delivery from a series of TTS with a drug-in-adhesive design (Joshi, 2008). After fabrication, the mechanical properties, *in vivo* bioadhesion, moisture uptake and stability of each TTS were evaluated. Following TTS characterization, transdermal delivery experiments were performed using porcine skin *in vitro* to quantify deposition and permeation of memantine from the passive and active TTS; the studies conducted with the different systems are summarized in Fig. 1.

2. Materials and methods

2.1. Materials

Memantine hydrochloride (MEM; 1-amino-3,5-dimethyladamantane hydrochloride; Ebixa®) was supplied by H. Lundbeck A/S (Valby, Denmark). Eudragit® E100 was supplied by Evonik Industries-Degussa (Darmstadt, Germany). Polyvinyl alcohol (PVA; 83400 Da; degree of hydrolysis 86–89%), Carbopol®, lauric acid and glycerol were obtained from Laboratorios Guinama S.L. (Valencia, Spain). Polyvinyl pyrrolidone K90 (PVP), potassium bicarbonate ($KHCO_3$), potassium hydroxide (KOH), sodium chloride (NaCl), triethanolamine (TEA) and oleic acid were provided by Sigma-Aldrich Química, S.A. (Madrid, Spain). Dansyl chloride (5-(Dimethylamino)naphthalene-1-sulfonyl chloride, DNS) was supplied by Iberlabo, S.A. (Madrid, Spain). Acetonitrile (ACN), methanol and ammonium di-hydrogen phosphate (96–102%, w/w) were obtained from Análisis Vínicos, S.L. (Ciudad Real, Spain), hydrochloric acid (HCl) was purchased from J.T.Baker (Deventer, Holland) and HEPES (*N*-[2-Hydroxiethyl] piperazine-N'-[2-ethanesulfonic acid]), adipic acid (1,6-hexanodioic acid) and R-(+)-limonene were acquired from Sigma-Aldrich Co. (Missouri, USA). Laurocapram (1-dodecyl-azacycloheptan-2-one) was obtained from Netqem (North Carolina, USA). All the compounds were of analytical grade. The silver chloride (99%, AgCl) and one millimeter silver (Ag) and platinum (Pt) wires (99.9%) employed to manufacture Ag/AgCl electrodes and the ultrapure electrophoresis grade agarose were purchased from Sigma-Aldrich Co. (Missouri, USA). Ultrapure water used to prepare all solutions was obtained via a Barnstead NANOpure system (Barnstead International, Massachusetts, USA).

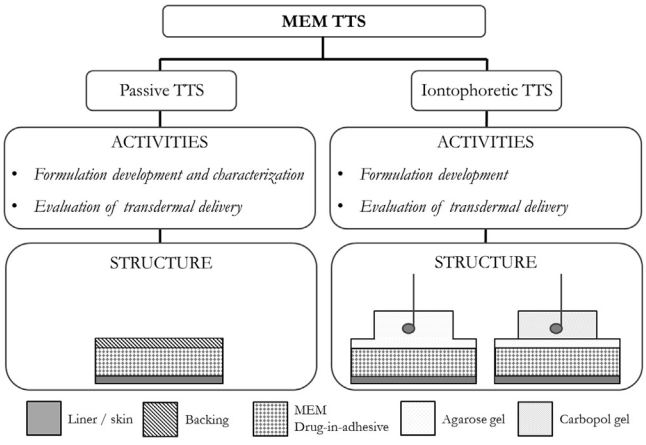

Fig. 1. Schematic of MEM drug-in-adhesive TTS prepared, the different techniques evaluated and a cross-sectional diagram showing major structural components.

2.2. Preparation of MEM TTS

Drug-in-adhesive type TTS were prepared via a lamination method (Balaguer-Fernandez et al., 2010; Padula et al., 2009) using PVP (12 or 24%) or PVP-PVA (6:6% or 16:6%) as a polymeric mixture; the TTS configurations are shown in Fig. 1.

The adhesive Plastoid E35H used in the formulations was prepared according to a procedure described previously (Serna-Jimenez et al., 2015). Concisely, 14% of Eudragit® E100, 8.4% of lauric acid and 1.7% of adipic acid were added to hot water (78–82 °C) until a clear dispersion was obtained. Finally, 9.3% of glycerol was added before storing the adhesive in hermetically closed plastic vessels.

2.2.1. Passive TTS

Briefly, a primary mixture containing MEM, sorbitol, Plastoid® E35H adhesive solution, PVA and the specific CPE was prepared according to the desired formulation composition. Then, PVP was incorporated into the primary mixture under 12 h continuous stirring. Final concentration of MEM was 0.5% when in wet mixture or 300 $\mu g\,cm^{-2}$ once dried in all passive TTS formulated. The composition of the different formulations is shown in Table 1, which presents the final percentage of each component in the wet mixtures (% w/w). The TTS were divided into three groups: Group I (no (−) MEM/no (−) CPE; Blank), Group II (with (+) MEM/no (−) CPE; a MEM control), and Group III (with (+) MEM and (+) CPE; CPE group). All mixtures obtained were manually laminated at 600 μm on an occlusive layer (Scotchpack™ 9733 backing) and allowed to dry at room temperature, in darkness.

2.2.2. Iontophoretic TTS

The iontophoretic TTS were formulated with PVP at a concentration of 24% and three different MEM concentrations (0.17, 0.34 and 0.5% when in wet mixture or 100, 200 and 300 $\mu g\,cm^{-2}$ once dried) (Table 1).

Two different configurations of iontophoretic TTS were prepared: a) an agarose gel (agarose 3% (w/v), NaCl 150 mM) with an embedded anode placed directly in contact with the drug-in-adhesive matrix and b) an agarose laminate (800 μm; agarose 3% w/v; NaCl 150 mM) on the drug-in-adhesive matrix (PVP 24% (w/