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Percutaneous penetration characteristics of amethocaine from novel bioadhesive and pressure-sensitive patch devices

G. P. MOSS, A. D. WOOLFSON* AND D. F. MCCAFFERTY*

*School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, and *School of Pharmacy, The Queen's University of Belfast, Lisburn Road, Belfast BT9 7BL*

Percutaneous amethocaine gels have been shown to provide clinically effective local anaesthesia of intact skin for up to six hours, following a forty minute application (McCafferty and Woolfson 1988; Woolfson et al 1990). Recently, Woolfson and co-workers (1998) formulated an integrated bioadhesive amethocaine patch and demonstrated that this exhibits a similar clinical profile to established gel formulations. The aim of this study is to determine the percutaneous penetration profile of amethocaine from candidate patch formulations across excised porcine skin *in vitro* and compare them to amethocaine gels and drug release from novel pressure-sensitive transdermal patches.

Bioadhesive films were cast from aqueous gels as described previously (Woolfson et al 1998). Pressure-sensitive patches were constructed from acrylic adhesives in either acetone or ethyl acetate. Flux across excised neonatal porcine skin was measured via modified Franz-type diffusion cells. The effect of several formulation parameters on amethocaine flux (as mg cm^{-2} min^{-1}) was investigated. Amethocaine and its degradation products were determined by HPLC (Woolfson et al 1992). The statistical significance of results was determined by single-factor analysis of variance.

In general, several distinct trends were observed. For a total of 29 bioadhesive systems, increasing the concentration of bioadhesive (poly(methyl vinyl ether/maleic anhydride) - PMVE/MA (1:1)) from 1% w/w to 5% w/w significantly decreased flux from 0.142 to 0.031 ($p < 0.05$). Increasing the concentration of viscosity builder (hydroxyethylcellulose - HEC) from 0.5% to 2.5% also significantly ($p < 0.05$) decreased flux from 0.191 to 0.041. Both changes are probably due to the increase in viscosity and its relationship with flux, as described by the Stokes-Einstein equation. Varying the casting gel pH from pH 5 to pH 10 yielded two significantly different sets of results. Patches formulated at pH 5 to pH 7 demonstrated comparable flux (0.055 to 0.071). Patches formulated at pH 8 to pH 10 demonstrated comparable flux (0.082 to 0.139). Both sets of results are significantly different from each other ($p < 0.05$). These results correspond to the percentage drug ionised at each pH. Gels formulated at pH 8 - 10, where amethocaine is predominantly present as the lipophilic, insoluble free base, produced significantly better flux than gels formulated at pH 5 - 7 where amethocaine is present predominantly as a water-soluble salt. Addition of glycerol to the patch (up to 2.5% w/w) had no significant effect on flux. As expected, increasing drug loading significantly ($p < 0.05$) increased flux, from 0.051 (0.5% w/w amethocaine) to 2.035 (10% w/w amethocaine). Lag times of formulations exhibited similar trends.

The maximum flux observed from a total of 16 different pressure-sensitive drug-in-adhesive formulations was 0.012 mg cm^{-2} min^{-1}. Flux from bioadhesive amethocaine films containing 2% w/w PMVE/MA, 1.5% HEC and 1% amethocaine at pH 9 exhibited similar flux to amethocaine gels (Woolfson et al 1992).

These results indicate that novel bioadhesive amethocaine patch formulations exhibit a similar drug release profile to amethocaine gel formulations, whereas pressure-sensitive systems demonstrate significantly lower flux ($p < 0.05$). This difference may be accounted for by the absence of the amethocaine phase-change system (Woolfson and McCafferty 1993) in the pressure-sensitive formulations, ensuring that the drug does not undergo a depression in melting point (from 42°C to 29°C) and hence may not penetrate skin at body temperature as readily as bioadhesive or gel systems that do exhibit such a depression in melting point.

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