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Design and evaluation of a water-soluble bioadhesive patch formulation for cutaneous delivery of 5-aminolevulinic acid to superficial neoplastic lesions

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ABSTRACT

Photodynamic therapy of superficial neoplastic lesions generally uses high aminolevulinic acid (ALA) loadings (20%, w/w) in emulsion-type systems under occlusion. This approach makes ALA dosing difficult and delivery to demanding areas, such as the vulval, perineal and perianal skin, are seldom possible. This work evaluated a water-soluble bioadhesive patch, loaded with ALA, which can adhere to both intact skin and mucous surfaces. ALA loading in the patch (38 mg cm^{-2}) was chosen using a simple comparative procedure. Tensile measurements showed that large ALA loadings did not adversely affect adhesion to porcine skin, achieving a mean strength of 1.7 N cm^{-2}. Increasing the loading was, however, shown to lower break strength and enhance percentage elongation at break. Water uptake studies showed an initial, rapid weight gain followed by gradual patch dissolution over 60 min. Drug release studies demonstrated that 57% of ALA was released across an aqueous semi-permeable membrane within 6 h, compared to 42% released from a proprietary cream formulation. The patch designed in this work is suited to definable ALA delivery to diverse regions, such as the lower female reproductive tract and lesions on exposed skin. Adhesion is sufficiently tenacious to allow photodynamic therapy (PDT), without the need to immobilise patients for up to 6 h, as was common with the cream-under-occlusion approach.

1. Introduction

The efficacy of photodynamic therapy (PDT) in the treatment and clinical management of a wide range of neoplastic disease states has been demonstrated clearly (Ost, 2003; Zeitouni et al., 2003; Brown et al., 2004). The therapy encompasses a tripartite interaction between a photosensitising drug substance, light of a specific wavelength and molecular oxygen. This brings about the triggering of a cascade of photochemical and photobiological events, causing irreversible and selective damage to tumour tissue. Superficial lesions, in particular, are readily amenable to PDT as drug and light application are relatively straightforward. As a consequence, topical administration of 5-aminolevulinic acid (ALA) has become an established procedure for the treatment of epidermal neoplastic lesions. Although not a photosensitiser per se, cellular absorption of exogenous ALA leads to rapid and highly specific production of protoporphyrin IX (PpIX) in neoplastic cells (Kennedy et al., 1996). Cells with a predominance of this endogenous intracellular photosensitiser become sensitive to certain wavelengths of visible light, such as that of 630 nm, and cell death occurs after appropriate illumination.

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Effective cutaneous delivery of ALA is problematic, given that it is a small, polar molecule with significant aqueous solubility. As a result, permeation through intact skin is low, with typically reported penetration depths in the region between 1 and 2 mm (Casas et al., 2000; Malik et al., 1995; Pahernik et al., 2001). These features have been influential in shaping current practice that relies on application of semi-solid delivery systems containing high concentrations of ALA for extended periods, typically in the region of between 2 and 6 h (Peng et al., 1997; Morton et al., 1998). This is typified by the ubiquitous 20% (w/w) ALA in an o/w cream (Morton et al., 2002; Jeffes et al., 1997; Fabbrocini et al., 2001; Pollock et al., 2004). Indeed, additional steps are often required to enhance penetration further and the use of occlusive dressings is commonplace and reported often (Morton, 2001).

It is plausible that combined application of an ALA-loaded semi-solid dosage form and use under occlusion gives rise to variations in drug flux across skin. Thin occlusive dressings cannot provide any sort of mechanical support so that changes in the thickness of the encased cream occur readily, primarily as a result of the initial securing of the dressing. The amount of drug available per unit area of underlying skin cannot be controlled with any degree of certainty. With no reproducible control over the ALA dosing to neoplastic lesions, then it is inevitable that potential variations in therapeutic outcome after PDT can become difficult to reconcile. This potential drawback is best illustrated in recent clinical reports, indicating a range of applied doses that extend between 10 and 200 mg of the ALA-containing vehicle applied per square centimetre of lesion (Cairnduff et al., 1994; Morton et al., 1996, 2000, 2001; Fritsch et al., 1998; Dijkstra et al., 2001; Markham and Collins, 2001; Moan et al., 2001).

Maintaining ALA-containing vehicles under occlusion on lesions of the trunk, head or limbs does not present much in the way of difficulties. However, the prolonged topical delivery of ALA to gynaecological or oral lesions is more challenging. These sites are moist and undulatory. As an example, photosensitiser delivery to cervical lesions is done using a drug solution in a cervical cap. Treatment failure has been found to occur if the cap becomes dislodged (Monk et al., 1997; Hillemanns et al., 1999). Vulval delivery of ALA is achieved using topically applied creams and solutions covered with occlusive dressings. However, the patient must remain immobilised for up to 4 h as the action of walking will almost certainly dislocate any such device.

ALA is notoriously unstable in topical dosage forms. Reduced pH enhances stability, but exacerbates cutaneous irritation. Careful adjustment of the formulation pH to approximately pH 5 gives a compromise between inducing the rapid dimerisation seen in ALA-containing systems and any irritancy (Franck and Stratmann, 1981; Jaffe and Rajagopalan, 1990; Butler and George, 1992). Nevertheless, established products have an undesirably short shelf-life. Porphin® cream, for example (20%, w/w, ALA in Unguentum Merck®, Crawford Pharmaceuticals, Milton Keynes, UK), must be discarded 6 months after purchase. Inventive strategies to circumvent poor stability, such as dual-compartment roller-ball applicators (Levulan®), nanoparticulate encapsulation (Hurlimann et al., 1998) and multi-lamellar liposomal delivery (Redick et al., 2000) have been described. Pragmatically, these preparations are not ideal for localised delivery to mucous areas.

It is clear that there is a need to design and evaluate an ALA drug delivery system that will address the three main problems highlighted above, namely uniformity of drug flux, stability and delivery to challenging areas. Therefore, the aim of this work is to design and evaluate a novel bioadhesive patch, loaded with aminolevulinic acid, which attempts to address these problems. Patches based on bioadhesive films have been described before for drug delivery to the oral cavity (Gurny et al., 1984), the female reproductive tract (Woolfson et al., 1995a) and to normal skin (Woolfson et al., 1998). In particular, the patch should deliver a defined dose of ALA that is either comparable or better than that released from a commercially available cream (Porphin®, 20%, w/w, ALA in Unguentum Merck®). Such a system would be capable of adhering to either a dry epidermal or moist mucosal surface for prolonged periods of time and offer a clear advantage over the current approach based on semi-solid administration. It is intended that this novel patch system will be ideally suited to topical delivery of ALA to intraepithelial neoplastic lesions, such as those on the vulva, vagina and cervix.

2. Materials and methods

2.1. Materials

Gantrez® AN-139, a copolymer of methyl vinyl ether and maleic anhydride (PMVE/MA) was obtained from ISP Co. Ltd., Guildford, UK. Tripropyleneglycol methyl ether (TPM, Dowanol™) was obtained from Sigma–Aldrich, Dorset, UK. Plastisol®, a medical grade poly(vinyl chloride) (PVC) emulsion containing diethylphthalate as plasticiser, was obtained from BASF Coatings Ltd., Clwyd, UK. Aminolevulinic acid, hydrochloride salt and Porphin® cream (20%, w/w, ALA in Unguentum Merck®), were obtained from Crawford Pharmaceuticals. Female *Balb/c* athymic nude mice were obtained from Bomholt Gaard (Ry, Denmark). All other chemicals and reagents used during the formulation and evaluation work were of a suitable analytical reagent quality.

2.2. Preparation of ALA-loaded bioadhesive patches and films

Aqueous polymer blends were prepared using the required weight of poly(methyl vinyl ether-co-maleic anhydride), which was added to ice-cooled water and stirred vigorously. The mixture was heated and maintained at between 95 and 100 °C until a clear solution was formed. Upon cooling, the required amount of tripropylene glycol methyl ether was added and the casting blend adjusted to final weight with water.

Preliminary investigations indicated that a film cast from an aqueous blend containing 20% (w/w) PMVE/MA and 10% (w/w) TPM possessed the necessary flexibility and conformability to make it ideally suited for vulval application over extended periods of time (McCarron et al., 2004). An amount (4.5 g) of aqueous blend was poured into a glass mould (50 mm × 30 mm) to produce a film of area 15 cm^2. The appropriate amount of ALA was dissolved directly into the aqueous