Expert Opinion

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Photosensitiser delivery for photodynamic therapy. Part 1: Topical carrier platforms

Ryan F Donnelly†, Paul A McCarron, Desmond IJ Morrow, Stéphane A Sibani & A David Woolfson

†*Queens University Belfast, School of Pharmacy, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL, UK*

Background: Photodynamic therapy (PDT) is a medical treatment in which a combination of a photosensitising drug and visible light causes destruction of selected cells. Due to the lack of true selectivity of preformed photosensitisers for neoplastic tissue and their high molecular weights, PDT of superficial skin lesions has traditionally been mediated by topical application of the porphyrin precursor 5-aminolevulinic acid (ALA). *Objective*: This article aims to review the traditional formulation-based approaches taken to topical delivery of ALA and discusses the more innovative strategies investigated for enhancement of PDT mediated by topical application of ALA and preformed photosensitisers. *Methods*: All of the available published print and online literature in this area was reviewed. As drug delivery of agents used in PDT is still something of an emerging field, it was not necessary to go beyond literature from the last 30 years. *Results/conclusion*: PDT of neoplastic skin lesions is currently based almost exclusively on topical application of simple semisolid dosage forms containing ALA or its methyl ester. Until expiry of patents on the current market-leading products, there is unlikely to be a great incentive to engage in design and evaluation of innovative formulations for topical PDT, especially those containing the more difficult-to-deliver preformed photosensitisers.

Keywords: 5-aminolevulinic acid, drug delivery, photodynamic therapy, preformed photosensitisers, topical application

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1. Photodynamic therapy

Photodynamic therapy (PDT) is a medical treatment in which a combination of a photosensitising drug and visible light causes destruction of selected cells, mainly through generation of highly cytotoxic reactive oxygen species [1-5].

A vast array of photosensitising agents have been investigated *in vivo* and *in vitro*, with early work involving the application of sunlight and hematoporphyrin derivative [6], before the use of Photofrin® (a purified haematoporphyrin derivative; QLT Phototherapeutics), and, subsequently, second-generation preformed photosensitisers. Due to the relatively high molecular weights of preformed photosensitisers, such as porphyrins, chlorins, phthalocyanines and texaphyrins, these agents have historically been administered parenterally in suitable formulations. While carriers and targeting systems have been used in some of these formulations, lack of true selectivity for rapidly proliferating cells has led to prolonged cutaneous photosensitivity for many preformed photosensitisers [6]. This is clearly undesirable, especially when treating superficial neoplastic skin lesions, or using PDT in palliative treatment.

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2. 5-Aminolevulinic acid

Topical application of 5-aminolevulinic acid (ALA) allows successful PDT of superficial neoplastic skin lesions, while avoiding widespread prolonged cutaneous photosensitisation. ALA is a small, water-soluble prodrug that is a naturally occurring intermediate in the haem biosynthetic pathway and a metabolic precursor of the potent endogenous photosensitiser protoporphyrin IX (PpIX) [3,7]. Administration of excess exogenous ALA avoids the negative feedback control that haem exerts over its biosynthetic pathway. Due to the limited capacity of ferrochelatase to convert PpIX into haem, the presence of excess exogenous ALA in cells induces accumulation of PpIX [8-10]. It has been shown that sufficient PpIX can be synthesised by exogenous ALA administration to produce a photodynamic effect on exposure to light, both *in vitro* and *in vivo* [7-11], and that PpIX accumulation is more pronounced in malignant cells compared with their normal counterparts [5]. Although debate exists over the exact reason for this, reports have suggested that the activity of the rate-limiting enzyme porphobilinogen deaminase is increased [12-14], while the activity of ferrochelatase is decreased [12,15,16].

PDT, based on topical application of ALA, has been successfully used in the treatment of basal cell carcinoma [7,17-21], actinic keratosis [20-22], Bowen's disease [23-25], vulval intraepithelial neoplasia [26-28], vulval Paget's disease [29] and cervical intraepithelial neoplasia [30]. PDT using topically applied ALA, in addition to producing successful therapeutic outcomes with excellent tissue preservation and no scarring, does not give rise to cutaneous phototoxicity [17,31]. Thus, ALA-PDT can be repeated often without causing accumulation of PpIX in normal skin [32]. This is particularly important when the aim of treatment is primarily palliative. This is in contrast to conventional PDT using the older preformed sensitisers, such as hematoporphyrin derivative. Repeated administration of such agents leads to high photosensitiser levels in normal skin and severe phototoxic reactions after skin exposure [6,7].

As ALA is a small molecule (167.6 Da), its diffusion into cutaneous tissue from a topical delivery system is favourable. However, its hydrophilic nature (octanol : water partition coefficient 0.03) [33] does impair permeation of normal stratum corneum markedly [34,35]. Fortunately, the disordered stratum corneum and epithelial barriers overlying neoplastic lesions allow enhanced ALA penetration. This further improves the selectivity of PpIX accumulation and explains why ALA can be successfully employed for diagnostic procedures, where neoplastic tissue is clearly demarcated by red PpIX fluorescence upon ultraviolet or blue light illumination while the surrounding tissue appears blue. However, its low lipophilicity does prevent effective penetration into hyperkeratotic lesions [17,21] and may even facilitate efflux via the microcirculation from deep nodular lesions.

3. Topical carrier systems for photodynamic therapy

Various physical strategies have been employed to enhance topical penetration of ALA or its chemical derivatives, including intratumoural injection, curettage/debulking of nodular lesions, dermabrasion and tape-stripping [19,36-38]. More recently, sonophoresis [39], iontophoresis [40,41], photomechanical waves [42], needle-free jet injections [43] and microneedle arrays [44] have also been used. With the exception of iontophoresis, where vehicle pH was important, the extent of penetration enhancement observed was a function of the physical technique used rather than the formulation. The purpose of the present work, however, is to concentrate on formulations used in topical delivery, not only of ALA and its derivatives but also of preformed photosensitisers.

3.1 Traditional topical formulations

Most reported work describing ALA/ALA derivative-based PDT for the treatment of surface lesions details topical application, followed by irradiation 2 – 6 h later [40,41]. The drug is dissolved or dispersed in a solution, cream, ointment or gel formulation containing drug concentrations that vary from 10 to 30% w/w [4]. While the most commonly used formulation is 20% w/w ALA in an oil-in-water (o/w) cream [42], Jeffes *et al.* [22] carried out a dose response study and found no significant difference between clinical outcomes for actinic keratosis lesions treated for 3 hwith 10, 20 or 30% w/w ALA in a cream base before irradiation.

With the exception of the Levulan® Kerastick (Dusa Pharmaceuticals), which is based on a hydro-alcoholic solution, topical application of ALA to superficial lesions generally conforms to an archetypical arrangement where an ALA-containing semisolid is applied to the lesion and covered with an occlusive dressing [24,25]. However, no specific details are normally given on the amount of product applied to the area. When topically applied doses are reported, they vary widely between 10 and 200 mg of ALA-containing vehicles per square centimetre of lesion [17,21,24,45,46]. This rather arbitrary approach means that comparing the results from separate studies, and deciding on an optimum dose, is extremely difficult. In addition, application of occlusive dressings causes smudging of applied formulation away from the site of the original application, thus causing additional dosing uncertainty. Delivery of ALA to flat, dry areas of skin is not particularly difficult. However, ALA is increasingly being used in PDT of lesions of the oral cavity, oesophagus, and female genital tract. Clearly, topically applied creams and solutions are not the most suitable drug delivery systems for such moist and irregularly shaped areas, where shear forces may be high.

Limited drug release data are available for semisolid preparations containing ALA or ALA derivatives. McCarron *et al.* [47] demonstrated that only 40% of

drug was release from Unguentum Merck® (Merck) cream containing 20% w/w ALA over 6 h using a model membrane. Similarly limited release was observed from Psoralon® (Hermal Chemie) cream (10% w/w ALA) across excised stratum corneum and epidermis [33]. Only approximately 6.4% of the ALA methyl ester loading was released from Metvix® cream (Photocure; 16% w/w ALA methyl ester) across a model membrane after 6 h [48]. A 4 h lag-phase was observed before significant amounts of ALA were released across excised stratum corneum from Excipal®-Fettecreme (Hans Karrer Gmbh) containing 10% w/w ALA [49]. In a follow-up study, the same group demonstrated extended lag times with a range of cream vehicles, with vehicle hydrophobicity highlighted as influencing ALA permeability [50].

ALA, and possibly also its derivatives, exhibits instability when not in an acidic environment [51]. However, due to the risk of severe cutaneous irritation, ALA and ALA derivative-containing dosage forms are not commonly formulated at low pH. Consequently, shelf lives are short. Porphin® (Crawford Pharmaceuticals) cream (20% w/w ALA in Unguentum Merck) and Metvix must be discarded 6 months after purchase. These products must be refrigerated and their cold temperatures can cause discomfort for patients upon application, particularly those with gynaecological lesions.

3.2 ALA derivatives and chemical penetration enhancers

Various other simple semisolid vehicles have been described. Some of these formulations contain chemical penetration enhancers, while others are loaded with ALA derivatives possessing enhanced lipophilicities relative to the parent drug. While enhanced skin penetration has been demonstrated *in vitro* and in animal models in many cases, penetration enhancers and lipophilic ALA derivatives have yet to demonstrate truly verifiable enhanced therapeutic outcomes for patients relative to ALA.

Numerous *in-vitro* and *in-vivo* studies have been carried out to assess the ability of ALA esters, in particular, to enhance penetration and PpIX production. The majority of *in-vitro* investigations reveal that increased amounts of ALA esters, relative to the parent compound, only penetrate the stratum corneum after prolonged application times, sometimes approaching 30 h. Working within a framework of clinically relevant application times, such as 4 or 6 h no significant difference is observed in amounts of ALA or ALA esters penetrating the stratum corneum, regardless of ester alkyl chain length [49,52,53]. The *in-vivo* studies have typically investigated PpIX production in the skin of human volunteers [54-56] or nude mice [57-60] following topical application of ALA or one of its esters. Again, significant lag times are generally observed before PpIX fluorescence induced by ALA esters becomes greater than that induced by ALA. In spite of this, ALA methyl ester has been shown to be effective for PDT of nodular basal cell carcinoma [38,61,62] where ALA PDT has historically produced poor results [63,64]. However, it should be pointed out that these clinical studies used curettage/debulking to remove the stratum corneum and some of the carcinoma before treatment, and also routinely used a treatment cycle that involved two treatments a week apart. Nevertheless, Metvix cream has received market authorisation in the US and Europe.

One notable success story for lipophilic ALA derivatives is in photodiagnosis of dysplasia and early bladder cancer, when the ALA hexyl ester has been shown to not only reduce instillation times but also induce a twofold increase in fluorescence signals with a 20 times lower concentration of ALA hexyl ester compared with ALA [65]. These findings were, however, attributable to the different properties of the urothelial and stratum corneum permeability barriers.

The addition of 20% w/w dimethyl sulfoxide (DMSO) to an o/w emulsion containing 10% w/w ALA has been shown to produce a significant increase in the flux of ALA across skin *in vitro* [66]. Moreover, a 2.5-fold increase in PpIX production was observed *in vivo*, relative to the same formulation without the penetration enhancer. Similarly, glycerol monoleate, an ester of oleic acid, has been shown to increase the *in-vitro* permeation and retention of ALA at concentrations up to 20% w/w [67]. Oleic acid (10% w/w in propylene glycol) itself was shown to significantly enhance ALA penetration into and across porcine ear skin *in vitro* [68]. *In vivo* findings showed that both extracted PpIX and cutaneous PpIX fluorescence was enhanced in a nude mouse model when the formulation contained oleic acid.

Bugaj *et al.* [69] investigated the effect of a range of chemical permeation enhancers on PpIX fluorescence in mouse skin during continuous application of a cream containing ALA methyl ester. DMSO, HPE-101® (Hisamitsu Pharmaceutical Co.) and Labrafac® (Gattefossé) CC (caprylic/capric) were all shown to enhance PpIX fluorescence *in vivo* at a concentration of 10% (w/w). Subsequent work by the same group suggested that Labrafac CC could be used to enhance ALA methyl ester delivery without producing erythema, which is sometimes associated with the use of chemical permeation enhancers [70].

The formation of a neutral ion pair is a strategy used to overcome the poor permeation of charged drug molecules through the stratum corneum [71]. A neutral complex is formed by combining the charged permeant with an oppositely charged, lipophilic species. Enhanced partitioning into the stratum corneum is followed by dissociation to yield the charged species once again [72]. Anuer *et al.* [73] used lipophilic counter ions, in combination with the penetration enhancers, phloretin and 6-ketocholestanol, to increase permeation of ALA through porcine skin *in vitro*. Cationic and anionic counter ions enhanced ALA permeation at pH 7.0 and 4.0, respectively, and the combination of 6-ketocholestanol and cetylpyridinium chloride at pH 7.0 was considered a potential strategy for increasing ALA penetration. The benefits of employing ion pairs or chemical penetration enhancers have yet to be demonstrated clinically, however.

3.3 Patches containing ALA or its derivatives

Patch-based systems can be tailored to deliver a defined amount of drug per unit area. Consequently, drug dosing is standardised and reproducible. Occlusion can be a component feature of the formulation itself, normally achieved using an impermeable backing layer. Given that the stratum corneum acts as an efficient and impedimental barrier to ALA penetration, the use of a rate-controlling membrane is not required. Therefore, the most appropriate patch design is one based on a drug-in-adhesive or matrix type system. The first report of ALA being incorporated into a patch was in 1996 [74]. Crystalline ALA was dispersed throughout a pressure-sensitive adhesive (PSA) matrix. Drug-release studies demonstrated a 20 h lag phase before appreciable amounts of ALA penetrated hydrated sheets of stratum corneum *in vitro*. Using polarising microscopy, the authors reported that ALA was present in the crystalline form. Hence, water was required to infiltrate the relatively hydrophobic matrix of the PSA to dissolve the ALA, before the drug can diffuse to, and partition into the stratum corneum. Lieb *et al.* [33] also formulated ALA in a PSA patch containing the reasonably hydrophilic polymer Eudragit® NE (Degussa) and the plasticiser acetyl tributyl citrate. Owing to poor drug solubility in the polymer matrix, ALA crystals were observed on the film surface. Water ingress mediated by Eudragit NE allowed rapid dissolution of the surface crystals and meant no lag phase was observed in the drug release profile across excised stratum corneum and epidermis. However, only 2.5% of the ALA loading was released from the formulation after 5 h. There was no mention of drug release from a similar system described by Pons *et al.* [75]. However, pressure-sensitive patches containing ALA were used in the successful PDT of actinic keratosis, basal and squamous cell carcinomas. Such systems may be capable of maintaining stability of ALA or its esters on prolonged storage, due to the fact that the drug is in the solid state. However, the poor release and the inability of PSA-based systems to adhere in moist environments may limit their commercial success.

Valenta *et al.* [76] reported ALA drug release from a film produced by lyophilisation of a cubic phase gel mixed with a carrageenan hydrogel. *In-vitro* drug release profiles across dermatomed pigskin were extremely encouraging, with approximately 70% of ALA loading penetrating the membrane after 24 h However, stability studies demonstrated that over 60% of the drug loading had degraded after only 14 days.

An alternative approach to patch production was described by McCarron *et al.* [47]. The authors described a novel bioadhesive patch cast from an aqueous gel containing poly(methyl vinyl ether/maleic anhydride). Unlike PSA-based formulations the ALA existed in the solution phase, and rather than compromising adhesion, moisture ingress was shown to initiate both adhesion and accelerate drug release. No lag time was observed in the ALA release profile. The patch released approximately 60% of its drug loading across a model membrane over 6 h. The system was subsequently shown to be capable of delivering high levels of ALA down to depths of approximately 2.5 mm in vaginal tissue [77]. The formulation was highly flexible and capable of adhering even in wet environments and was used in the successful PDT of extra-mammary Paget's disease, lichen sclerosus of the vulva and vulval intraepithelial neoplasia [29,46,78]. Patient evaluation demonstrated comfort and firm attachment to the vulval area when the patch was applied for up to 4 h in mobile patients [79].

Donnelly *et al.* [80] highlighted that a bioadhesive patch containing ALA resulted in reduced drug penetration through normal stratum corneum *in vitro* when compared with a conventional semisolid. Importantly, however, patches performed as well as the semisolid in skin above subcutaneously implanted tumours. Furthermore, PpIX fluorescence was found to be localised to the area of application when the patch was used. The authors concluded that components within the cream were acting as penetration enhancers, facilitating enhanced ALA penetration through normal skin. This delivery system was subsequently shown to enhance selective delivery of the ALA methyl ester (m-ALA) [48]. An *in vivo* study by the same group compared PpIX production induced by m-ALA formulated in creams, bioadhesive patches and PSA patches [81]. At low drug loadings m-ALA-containing PSA patches induced higher PpIX levels than either the cream or the bioadhesive film. PSA patches performed extremely well at short application times and, importantly, restricted photosensitiser accumulation to the site of application. However, when the m-ALA loading in the PSA patch was increased, PpIX fluorescence was reduced, due to drug crystallisation.

3.4 ALA-loaded bioadhesive gel delivery systems

It has been proposed that the use of ALA-containing bioadhesive gels for the PDT of Barrett's oesophagus could be utilised as a means of targeting the necessary cells, enhancing oesophageal retention time, and improving oral ALA absorption [58]. Bourre *et al.* [82] suggested a thermosetting gel containing ALA which, when administered as an oral liquid, may, upon gelation, provide sustained delivery to the oesophageal mucosa. It was shown that it was possible to incorporate ALA into Pluronic® (BASF) F-127 based systems. Such systems were stable with regards to thermosetting for up to several months and enhanced PpIX production in comparison to ALA solutions.

3.5 Cubic phase photosensitiser delivery systems

The introduction of an amphiphilic lipid (e.g., monoolein or phytantriol) into an aqueous environment results in its spontaneous rearrangement into various thermodynamically stable, three-dimensional, liquid crystalline phases, in a temperature and water-dependent manner [83,84]. The structure of this 'cubic phase', with a three-dimensional

bicontinuous lipid bilayer separating two congruent networks of water channels [83], allows for the incorporation of both hydrophilic and hydrophobic molecules [85,86].

Turchiello *et al.* [85] investigated the potential of the cubic phase as a topical delivery system for prodrugs and photosensitisers used in PDT of cutaneous diseases. The ALA, its ester derivatives (hexylester, octylester and decylester), a second-generation preformed photosensitiser (m-THPC), and also the endogenous photosensitising agent PpIX were incorporated into a gel cubic phase (monoolein:water, 70:30 w/w). It was shown that ALA and its ester derivatives remained stable in the cubic phase gel formulation over the 30-day period of investigation, while m-THPC and PpIX remained stable for 90 and 126 days, respectively. Furthermore, no sign of bacterial contamination was observed in the cubic phase gel up to 6 months. *In-vivo* work carried out on patients observed enhanced PpIX production following application of a 2% w/w ALA-containing monoolein cubic phase gel formulation compared with application of a traditional ALA cream formulation (20% w/w).

Bender *et al.* [84] have also confirmed the ability of lipid cubic systems, incorporating ALA and its ester derivative m-ALA, to significantly increase PpIX production upon topical administration compared with standard ointments *in vivo*. It was reported that the choice of both drug and the lipid used may play an important role in the subsequent topical penetration enhancement. For application times less than 4 h the increase in PpIX fluorescence was more pronounced when using m-ALA, while systems based on monoolein improved the amount of drug delivered transdermally compared with those systems based upon phytantriol. It was shown that the monoolein systems contained a greater amount of water in comparison to those based on phytantriol (40% compared with 28%, respectively). This implies that the phytantriol systems would have more narrow water channels in the tortuous structure. Being water-soluble drugs, ALA and m-ALA, will reside within these water channels. It is known that the release of water soluble drugs from cubic phase systems decreases with decreasing water pore diameter [70], supporting the above findings.

3.6 Sponge phase formulations containing ALA or its derivatives

As discussed above, the addition of an amphiphilic lipid into an aqueous environment results in the formation of various liquid crystalline phases. Another of these phases that has recently been proposed as a transdermal delivery system is the so-called sponge phase [87]. The sponge phase is a clear liquid with a bicontinuous structure consisting of one congruent lipid bilayer 'swimming in a sea of solvent', similar to that of the cubic phase [88]. However, it is considered to be the liquid analogue, or melted version, of the cubic phase [89,90], with larger aqueous pore dimensions (10 – 15 nm) than the cubic phase [91]. The same advantageous characteristics as the cubic phase with regards to transdermal drug delivery apply to the sponge phase. The sponge phase is thermodynamically stable, and with its amphiphilic character possesses the ability to incorporate a wide variety of drugs of differing polarity, as well as the inherent skin penetration enhancement properties of the solvents involved in making the formulation [87,88,91].

Merclin *et al.* [90] investigated the iontophoretic and passive transport of ALA and m-ALA through porcine ear skin from a lipid sponge phase consisting of monoolein, propylene glycol and water. It was proposed that the bicontinuous structure of the sponge phase would make it useful for iontophoresis since it would be possible for ions to move freely through the aqueous domains of the phase. Incorporation of low drug loadings (0.25% w/w) in sponge phases of differing monoolein, propylene glycol and water composition, in combination with iontophoresis, resulted in delivery comparable to that achieved with the more concentrated products (20% w/w ALA and 16% w/w m-ALA) used in clinical practice.

3.7 Topical delivery systems for preformed photosensitisers

Preformed photosensitisers offer a number of advantages over ALA-induced PpIX. For example, compared with porphyrins, such as PpIX, the absorption spectrum of the phthalocyanines is shifted to longer wavelengths, typically around 700 nm [92]. Light fluence through tissue is known to reduce exponentially with thickness. This decrease is determined by absorption and scattering. The average light penetration depth is 1 – 3 mm at 630 nm and 2 – 6 mm at 700 – 850 nm [93]. The increased penetration depth of light of longer wavelength is a major incentive for the development of new photosensitisers which absorb strongly at such wavelengths. Compounds with this property would be of particular use in diseases, such as nodular basal carcinoma and cervical intraepithelial neoplasias, when lesions can extend to at least 5 mm below the surface [56]. In addition, a number of these preformed drugs are much more potent photosensitisers than PpIX, being more efficiently excited by light and having much greater singlet oxygen quantum yields [94]. This means that enhanced cytotoxic effects can be obtained with lower drug doses. Preformed photosensitisers do not accumulate to the same extent in nerve cells as ALA-induced PpIX, meaning pain upon irradiation could be reduced. If such agents could be rapidly delivered, then patient and clinician convenience would also be greatly increased, due to the reduced waiting time between drug and light administration. This is because PpIX takes several hours to reach phototoxic levels in neoplastic cells upon topical application of ALA or its derivatives. Rapid delivery of a preformed sensitiser would allow prompt irradiation.

Intravenous administration of preformed photosensitisers typically causes prolonged and severe cutaneous photosensitivity,

with the consequence that patients must remain indoors for periods up to several weeks after treatment [74,95]. In addition, photosensitisers, such as haematoporphyrin derivative, temoporfin and Zn(II)-phthalocyanine can take 2 – 3 days to accumulate in tumours before irradiation can take place [95], meaning that patients must return to the clinic for a second time. Successful topical application of preformed photosensitisers would, clearly, offer considerable advantages over their systemic administration and also over topical ALA. Accordingly, it is not surprising that several groups have carried out studies in this area.

Bretschko *et al.* [74] examined the permeation profile of Photofrin (haematoporphyrin derivative) across human stratum corneum. It was reported that only 0.8 μg cm^{-2} crossed the barrier after 50 h. Several studies have used qualitative techniques, such as fluorescence microscopy, to show penetration of preformed photosensitisers into excised skin *in vitro* [96-98]. However, penetration beneath the stratum corneum was minimal in each case and such studies do not provide any quantitative insights. Kaestner *et al.* [99] examined topical penetration of a zinc (II) phthalocyanine into mouse skin *in vivo*. After 1 h application, the surface of the skin was cleaned and immediately excised. The skin sample was homogenised and the photosensitiser extracted using 2% w/w sodium dodecyl sulfate solution. The authors reported that approximately 4.6% w/w of the applied photosensitisers was recovered. However, no attempt was made to determine the actual depth of penetration or whether the drug had simply accumulated in the stratum corneum. To date, successful treatment of patients using topical administration of a preformed photosensitiser has not been reported. However, this may change in the near future, as recent reports have demonstrated true intradermal delivery of preformed photosensitiser using needle-free jet injection and microneedle arrays [43,100].

4. Conclusion

Over the past two decades, photodynamic therapy based on topical application of ALA has enjoyed a period of intense investigation, both in the laboratory and in the clinic. Although still widely considered to be an experimental technique, its status and value within modern clinical practice continues to grow. Comparison of the results of clinical studies based on topical ALA delivery is, however, currently difficult, due to the arbitrary approach taken to topically applied doses. Adhesive patches containing defined drug loadings per unit area are capable of overcoming this problem but no commercially available product of this type currently exists.

PDT, based on topical application of simple semisolids containing ALA, is most effective for treatment of superficial skin neoplasias, where the excellent clearance rates and cosmetic results and lack of scarring are notable advantages over surgical excision of such lesions, which typically occur on the face or lower arms. Poor tissue penetration of ALA currently limits its ability to treat deep or hyperkeratotic skin lesions and use of more lipophilic derivatives or formulation-based approaches, such as inclusion of penetration enhancers, has so far failed to produce a meaningful improvement. The majority of novel formulations have yet to be tested in the clinic. Physical approaches to improving ALA penetration, such as curettage/debulking of tumours and intratumoural injection are unlikely to be reproducible, while sonophoresis and iontophoresis require very specialised equipment. The use of advanced technologies, such as needle-free jet injectors and microneedle arrays, may be one possible solution to not only increasing tissue penetration of ALA or its derivatives but also to allowing successful intradermal delivery of preformed photosensitisers.

5. Expert opinion

Despite the vast number of studies published in the area of topical photodynamic therapy, a rational approach to formulation design has not taken place. This may be because this field is dominated by clinicians and basic scientists, rather than those involved in pharmaceutical formulation development. When formulating a topical drug delivery system, the aim should be to maximise the thermodynamic activity of the drug substance in the vehicle, so as to maximise the concentration drive for diffusion and the partition coefficient between stratum corneum and vehicle. For example, formulating a relatively lipophilic ALA derivative, such as the hexyl ester in an aqueous vehicle, should maximise its flux into skin when applied topically.

Studies published to date on topical application of ALA and its derivatives have used aqueous solutions, oil in water creams, water in oil creams, hydrogels, organogels, sponge and cubic phase formulations and aqueous and solvent-based patches. These dosage forms, which in many cases seem to have been selected at random with little regard for their nature, possess a multitude of different physicochemical properties. This has made comparison of different studies difficult. As a result, the true value of derivatisation of ALA to yield more lipophilic prodrugs, for example, has been blurred somewhat. In addition, the arbitrary dosing approach taken to topical application of ALA has caused further confusion. Adhesive patches, which could overcome this latter problem, have not yet gained acceptability from clinicians and so remain as experimental formulations.

Topical application of preformed photosensitisers may offer considerable advantages over ALA and its derivatives in terms of reduced drug-to-light intervals and less pain on irradiation. However, their high molecular weights mean that sophisticated technologies, such as needle-free jet injections or microneedle arrays will have to be used to allow intradermal delivery.

In the foreseeable future, PDT of neoplastic skin lesions is likely to continue to be based on topical application of simple semisolid dosage forms containing ALA or its methyl

ester. Until expiry of patents on the current market leading products (Levulan and Metvix) approaches, there is unlikely to be a great incentive for pharmaceutical companies to engage in design and evaluation of innovative formulations for topical PDT. Consequently, such research will continue to be the preserve of academic departments, who rarely possess the funds for clinical trials. Ultimately, this may prove to be to the detriment of patients.

Declaration of interest

The manuscript just submitted represents original work and has not been previously published or simultaneously submitted elsewhere for publication. The manuscript has been read and approved by all authors. The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Ryan F Donnelly†, Paul A McCarron, Desmond IJ Morrow, Stéphane A Sibani & A David Woolfson
†Author for correspondence
Queen's University Belfast,
School of Pharmacy,
Medical Biology Centre,
97 Lisburn Road,
Belfast BT9 7BL, UK
Tel: +44 28 90 972 251; Fax: +44 28 90 247 794;
E-mail: r.donnelly@qub.ac.uk