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Research paper

Transdermal and dermal delivery of adefovir: Effects of pH and permeation enhancers

Kateřina Vávrová [a,*], Kateřina Lorencová [a], Jana Klimentová [a], Jakub Novotný [a], Antonín Holý [b], Alexandr Hrabálek [a]

[a] Centre for New Antivirals and Antineoplastics, Faculty of Pharmacy in Hradec Králové, Charles University in Prague, Prague, Czech Republic
[b] Centre for New Antivirals and Antineoplastics, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague, Czech Republic

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Abstract

The objective of this work was to investigate feasibility of transdermal and dermal delivery of adefovir (9-(2-phosphonomethoxyethyl)adenine), a broad-spectrum antiviral from the class of acyclic nucleoside phosphonates. Transport of 2% adefovir through and into porcine skin and effects of various solvents, pH, and permeation enhancers were studied *in vitro* using Franz diffusion cell. From aqueous donor samples, adefovir flux through the skin was 0.2–5.4 μg/cm^2/h with greatest permeation rate at pH 7.8. The corresponding adefovir skin concentrations reached values of 120—350 μg/g of tissue. Increased solvent lipophilicity resulted in higher skin concentration but had only minor effect on adefovir flux. A significant influence of counter ions on both transdermal and dermal transport of adefovir zwitterion was observed at pH 3.4. Permeation enhancer dodecanol was ineffective, 1-dodecylazepan-2-one (Azone) and dodecyl 2-(dimethylamino)propionate (DDAIP) showed moderate activity. The highest adefovir flux (11.3 ± 3.6 μg/cm^2/h) and skin concentration (1549 ± 416 μg/g) were achieved with 1% Transkarbam 12 (5-(dodecyloxycarbonyl)pentylammonium 5-(dodecyloxycarbonyl)pentylcarbamate) at pH 4. This study suggests that, despite its hydrophilic and ionizable nature, adefovir can be successfully delivered through the skin.
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Keywords: Skin absorption; Transdermal drug delivery; Permeation enhancer; Adefovir; Acyclic nucleoside phosphonates

1. Introduction

Adefovir (9-(2-phosphonomethoxyethyl)adenine, Fig. 1) is a broad-spectrum antiviral from the class of acyclic nucleoside phosphonates highly effective against herpes-, retro-, and hepadnaviruses. Its bis(pivaloyloxymethyl) ester prodrug adefovir dipivoxil has been approved for treatment of hepatitis B; for reviews on adefovir, see Refs. [1,2]. Due to the polar character of the phosphonate moiety, its resorption from gastrointestinal tract is restricted and there is a continuous search for new prodrug types or delivery options to enhance adefovir bioavailability and improve its pharmacokinetic profile.

Transdermal drug delivery offers numerous advantages over conventional routes of administration [3,4]. Considering the chronic nature of adefovir therapy and the requirement for a substantial commitment from the patients due to a risk of severe acute exacerbations of hepatitis on discontinuation of therapy, less frequent application associated with a transdermal patch would be advantageous. Another concern of adefovir is nephrotoxicity, which limits the oral daily dose to 10 mg of adefovir dipivoxil. Adefovir is actively transported by human renal organic ion transporter 1, which plays a critical role in its kidney toxicity [5]. This secretion is concentration-dependent, thus we hypothesize that more stable plasma levels resulting from

* Corresponding author. Centre for New Antivirals and Antineoplastics, Charles University in Prague, Faculty of Pharmacy in Hradec Králové, Heyrovského 1203, 50005 Hradec Králové, Czech Republic. Tel.: +420 495 067497; fax: +420 495 067166.
E-mail address: katerina.vavrova@faf.cuni.cz (K. Vávrová).

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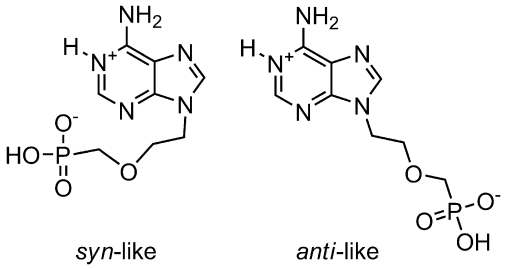

Fig. 1. The *syn*- and *anti*-like structures of zwitterionic adefovir.

transdermal delivery may be beneficial. Moreover, gastrointestinal disturbance, which is another side effect, should be avoided by administration via the skin.

In transdermal systems, variables including drug thermodynamic activity, partitioning, ionization, and ion pairing may be efficiently controlled in contrast to the absorption from gastrointestinal tract. Furthermore, skin barrier properties may be temporarily decreased by chemical substances known as permeation enhancers. These compounds may act by different mechanisms; the most active ones are believed to incorporate into the stratum corneum intercellular lipids and disturb their packing. For recent reviews on permeation enhancers, see Refs. [6–8].

Even though acyclic nucleoside phosphonates are promising drugs for the treatment of numerous viral skin infections, our knowledge on the extent of the absorption of these highly hydrophilic drugs into the skin and their flux through intact skin into the systemic circulation is limited. Currently, only one member of this group, cidofovir, has been studied with regard to dermal and transdermal transport [9–12]; there are no reports on adefovir except for our preliminary study [13].

The objective of this work was to investigate both transdermal flux and local skin concentration of adefovir and the conditions that may influence these processes including various solvents, pH, and permeation enhancers. Identification of adefovir behavior and optimization of the formulation are necessary for prospective improved administration of this potent antiviral and would be also useful for further studies on other acyclic nucleoside phosphonates.

2. Materials and methods

2.1. Chemicals

Adefovir [14] and permeation enhancers 1-dodecylazepan-2-one (Azone) [15], dodecyl 2-dimethylaminopropionate (DDAIP) [16], and 5-(dodecyloxycarbonyl)-pentylammonium 5-(dodecyloxycarbonyl)pentylcarbamate (Transkarbam 12, T12) [17,18] were synthesized as described previously. Their structure and purity was confirmed by IR and NMR spectra. KH_2PO_4, NaH_2PO_4, Na_2HPO_4, and NaCl were purchased from LachNer (Neratovice, Czech Republic). Isopropyl myristate (IPM) was purchased from Kulich (Hradec Králové, Czech Republic). Ultrapure water was obtained using Milli-Q Water Filtration System (Millipore, Bedford, MA). All other chemicals were purchased from Sigma–Aldrich (Schnelldorf, Germany).

2.2. Skin

Porcine skin was selected for the initial evaluation of adefovir delivery as it is easy to obtain and has barrier properties close to human skin [19]. Porcine ears were purchased from a local slaughterhouse. To ensure integrity of the skin barrier, ears were removed post-sacrifice before the carcass was exposed to the high-temperature cleaning procedure. Full-thickness dorsal skin was excised by blunt dissection and hairs were carefully trimmed. The skin was then immersed in 0.05% sodium azide solution in saline for 5 min for preservation. The skin fragments were stored at −20 °C up to 2 months.

2.3. Donor samples for skin permeation experiments

Donor samples were prepared by stirring 20 mg of adefovir in 1 ml of the pertinent solvent either with or without 10 mg of an enhancer. The samples were allowed to equilibrate at 37 °C for 48 h, and were re-dispersed before the application onto the skin if needed. In pH-adjusted samples, adefovir was dissolved in either 100 mM Tris or phosphate buffer (PB) at pH 7.4. pH was adjusted by 2-(hydroxymethyl)-2-aminopropane-1,3-diol (Tris) and HCl, respectively, for Tris samples and by H_3PO_4 and NaOH, respectively, for the PB-based ones, using a microelectrode HC153 (Fisher Scientific, Pardubice, Czech Republic). Samples containing T12 were prepared by dissolving adefovir in Tris, adjusting the pH at approximately 7.5 and then adding T12 to avoid decomposition of the carbamate by acidic media. This stock sample was adjusted at the desired pH.

For the determination of adefovir solubility in the donor solvent, an excess of adefovir was added to the pertinent solvent, pH was adjusted and the suspension was allowed to equilibrate. After 48 h, the suspensions were centrifuged at 10,000*g* for 5 min; the supernatant was withdrawn, diluted with phosphate buffered saline (PBS) at pH 7.4 if needed, and analyzed by HPLC (see below). Three replicates were performed in each solvent.

2.4. Skin permeation experiments

The skin permeability of adefovir was evaluated *in vitro* using the static Franz diffusion cells [20]. Generally, the use of static cells would yield the same results as the flow-through ones when maintaining the skin viability is not necessary. For a comparison of these two diffusion cell types, see Refs. [21–23]. The skin fragments were slowly thawed immediately before use and carefully inspected for any visual damage. They were cut into squares ca

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