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Research Paper

In-vitro transdermal penetration of cytarabine and its N4-alkylamide derivatives

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Abstract

Objectives The aim of this study was to synthesise and determine the transdermal penetration of cytarabine alkylamide derivatives and assess the correlation of flux with physicochemical properties.

Methods The alkylamide derivatives of cytarabine were synthesised by acylation at the N4-amino group by the mixed anhydride method. The in-vitro permeation studies were performed using the Franz diffusion cell methodology. Furthermore, partition coefficients (*n*-octanol–water) and aqueous solubility of the N4-alkylamide derivatives of cytarabine were determined in order to obtain information about their lipophilicity and hydrophilicity.

Key findings The N4-alkylamides of cytarabine (acetyl, butanoyl, hexanoyl, octanoyl, and decanoyl derivatives) showed decreased hydrophilicity and increased lipophilicity. The log D values of the alkylamides were higher than that of the parent compound and increased linearly as the alkyl chain lengthened. N4-hexanoyl-4-amino-1-[(2R,3S,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl] pyrimidin-2-one) showed the highest median steady-state flux (J_{ss}) of 89.0 nmol/cm^2 per h in the series, which shows a high statistical difference with the parent compound flux value (3.70 nmol/cm^2 per h).

Conclusions The prodrug approach appears to be a promising strategy for the enhancement of transdermal penetration of cytarabine.

Keywords alkylamides; cytarabine; in vitro; transdermal penetration

Introduction

Cytarabine (Figure 1) is a nucleoside analogue of deoxycytidine that is extensively used in the treatment of both acute and chronic myeloblastic leukaemias. It is a geometric isomer of cytidine and differs in that the 2′-hydroxyl group is oriented in the trans position.[1] The major impediments to a broad clinical use of cytarabine include the rapid metabolism of the drug in plasma to its inactive metabolite uracil arabinoside (ara-U) by the enzyme deoxycytidine deaminase and its cell cycle (S-phase) specificity.[2] A prolonged exposure of cells to cytarabine's cytotoxic concentrations is essential to achieve maximum activity since it is a cell-cycle-specific drug. In practice it is administered by repetitive schedules or continuous intravenous infusion in order to achieve a sustained supply.[1] These modes of administration are inconvenient and invasive, and could therefore contribute to increased patient non-compliance.

Transdermal drug delivery (TDD) offers several advantages over more traditional dosage forms such as oral and intravenous infusion. These include the potential for sustained release, which is useful for drugs with short biological half-lives requiring frequent oral or parenteral administration, and controlled input kinetics, which are indispensable for drugs with narrow therapeutic indices.[3] TDD can achieve consistent plasma concentrations similar to intravenous infusion without the inconvenience. Due to its unfavourable physicochemical properties, cytarabine will not easily permeate the skin without chemical modification.

Many approaches have been explored to protect cytarabine from deamination, including chemical modifications. Among others, N4-acylation has been shown to prevent inactivation by cytidine deaminase.[4,5] N4-acylation of cytarabine with long chain fatty acids such as stearic acid and behenic acid lead to lipophilic amide derivatives of cytarabine, which exhibit greater antileukaemia activity than native cytarabine.[6]

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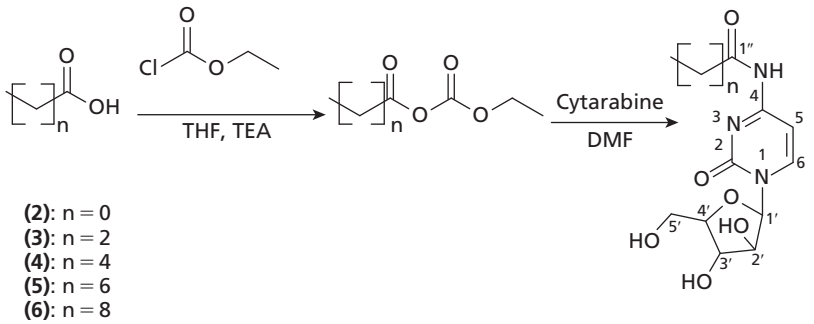

Figure 1 Synthesis of N4-alkylamide derivatives of cytarabine

In studies performed on a structurally related compound (gemcitabine), the amide linkage was shown to have extreme chemical stability in pH range 4–9 and yet is bioreversible.[7] Therefore amide is a plausible linker for N4-prodrugs of cytarabine.

The objective of this study was to synthesise and investigate the transdermal flux of N4-alkylamides of cytarabine. Physicochemical properties were determined and assessed for correlations to transdermal flux values.

Material and Methods

Materials

Cytarabine (98% purity) was purchased from Jingma Chemicals Ltd, China. The carboxylic acid anhydrides and ethylchlorocarbonate were purchased from Sigma-Aldrich South Africa Ltd. HPLC grade methanol was obtained from Labchem South Africa Ltd. All other reagents were of analytical grade and were used without further purification.

General procedures

The ^{1}H, ^{13}C, COSY (correlation spectroscopy), HMQC (heteronuclear multiple quantum coherence) and HMBC (heteronuclear multiple bond coherence) spectra were recorded on a Bruker 600 spectrometer, using deuterated dimethylsulfoxide (DMSO) as solvent. The ^{1}H and ^{13}C spectra were recorded at frequencies of 600.17 and 151.92 MHz, respectively. All the chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane ($\delta = 0$). The splitting pattern abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet) and m (multiplet). The melting points of solid products were determined with a Shimadzu DSC-60A using TA60 (Version 2.11) software. MS spectra were recorded on an analytical VG 7070E mass spectrometer using fast atom bombardment (FAB) as the ionisation technique. Thin-layer chromatography was performed using silica gel plates (60F254 Merck) and flash column chromatography on silica gel (70–240 mesh, G60 Merck).

High performance liquid chromatography

The high performance liquid chromatography (HPLC) system consisted of a Hewlett Packard (HP) Agilent 1100 series auto sampler, HP Agilent 1100 series variable wavelength detector (VWD) and HP Agilent 1100 series pump (Agilent, Palo Alto, CA, USA). A Phenomenex (Luna C-18, 150 × 4.60 mm, 5 μm) column was used with a Securityguard pre-column (C-18, 4 × 3 mm) insert (Phenomenex, Torrance, CA, USA) in order to prolong column life. The wavelength of detection was fixed at 247 nm. Elution was accomplished with gradient at a flow rate of 1 ml/min, with a mobile phase consisting of methanol (solvent A) and 0.005 M heptane sulfonic acid-Na in water adjusted to pH 3.5 with orthophosphoric acid (B). The gradient was started with 30% A, then increased linearly to 95% A in 8 min and held until 11 min, after which the column was re-equilibrated at the starting conditions. A calibration plot of peak area versus drug concentration was constructed for each compound. The plots showed excellent linearity over the concentration range (0.6–200 μg/ml) employed for the assays. The correlation coefficient values $0.998 < r^2 \leq 1$ were found for all calibration plots.

Chemical synthesis

The N4-alkylamide derivatives of cytarabine were synthesised by a mixed anhydride method.[8] Aliphatic carboxylic anhydrides were linked with amino group of cytarabine in a two-step process: by reacting ethylchlorocarbonate (chloroformic acid ethyl ester) and the carboxylic acid in the presence of triethylamine (TEA) to obtain the corresponding very reactive mixed anhydride; and then adding cytarabine solution to the reactive mixture (without isolating the mixed anhydrides) to give the N4-alkylamide derivatives.

Ethylchlorocarbonate (0.56 mmol, 60.8 mg) was added dropwise to an anhydrous tetrahydrofuran (THF) solution of the lipophilic acid (0.56 mmol) and TEA (0.56 mmol, 56.7 mg). The reaction was maintained under stirring at –15°C for 20 min. A solution of cytarabine (0.56 mmol, 136.2 mg) in anhydrous dimethylformamide was added under stirring at –15°C. The reaction mixture was maintained at 5–10°C with stirring until the end of the reaction. The reaction mixture was concentrated to dryness under high vacuum and the residue was purified by silica column chromatography using a mixture of organic solvents as eluting agents (see Figure 2).

N4-acetyl-4-amino-1-[(2R,3S,4R,5R)-3, 4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl] pyrimidin-2-one (2)

Compound (**2**) was purified by column chromatography using DCM:MeOH (8:1,v/v) as a mobile phase to obtain 1.7 g

(36%) of white powder. m.p. 183°C. ^{1}H NMR (600 MHz, DMSO) δ 2.10 (s, 3H, –HNCOCH$_3$), 3.63 (t, J = 5.3, 2H, 5′), 3.80–3.86 (m, 1H, H-4′), 3.94 (s, 1H, H-3′), 4.07 (dd, J = 7.6, 4.1, 1H, H-2′), 4.92 (t, J = 5.5, 1H, 5′), 5.33 (d, J = 4.3, 1H, OH-3′), 5.35 (d, J = 5.6, 1H, OH-2′), 6.06 (d, J = 4.0, 1H, H-1′), 7.13 (d, J = 7.4, 1H, H-5), 8.03 (d, J = 7.5, 1H, H-6), 10.63 (s, 1H, –HNCO). ^{13}C NMR (151 MHz, DMSO) δ 24.07 (–HNCOCH3), 60.92 (C-5′), 74.59 (C-3′), 76.19 (C-2′), 85.52 (C-4′), 86.72 (C-1′), 93.98 (C-5), 146.35 (C-6), 154.27 (C-4), 161.94 (C-2), 170.57 (C-1″). MS FAB 244.0 (M + H$^+$), 175.9, 153.8, 122.2, 102.0, 74.0, 57.9.

N4-butyryl-4-amino-1-[(2R,3S,4R,5R)-3, 4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl] pyrimidin-2-one (3)

Amide (**3**) was purified by column chromatography using DCM:MeOH (8:1) as a mobile phase to obtain 1.2 g (23%) of white powder. m.p. 193°C. ^{1}H NMR (600 MHz, DMSO) δ 0.90 (t, J = 7.4, 3H, –CH$_2$CH$_3$), 1.59 (h, J = 7.3, 2H, -CH$_2$CH$_3$), 2.39 (t, J = 7.3, 2H, HNCOCH$_2$–), 3.64 (s, 2H, H-5′), 3.85 (td, J = 5.2, 3.1, 1H, H-4′), 3.95 (d, J = 1.8, 1H, H-3′), 4.09 (s, 1H, H-2′), 4.94 (s, 1H, OH-5′), 5.35 (s, 2H, OH-2′&3′), 6.07 (t, J = 4.9, 1H, H-1′), 7.18 (d, J = 7.4, 1H, H-5), 8.05 (d, J = 7.5, 1H, H-6), 10.60 (s, 1H, –HNCO). MS FAB (M$^+$) 313.9, (M + Na)$^+$ 335.9.

N4-hexanoyl-4-amino-1-[(2R,3S,4R,5R)-3, 4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl] pyrimidin-2-one (4)

Compound (**4**) was purified by column chromatography using DCM:MeOH (12:1) as a mobile phase to obtain 3.5 g (63%) of white powder. m.p. 130°C. ^{1}H NMR (600 MHz, DMSO) δ 0.88 (t, J = 7.0, 3H, –CH$_2$CH$_3$), 1.19–1.38 (m, 4H, –CH$_2$CH$_2$CH$_3$), 1.50–1.65 (m, 2H, –COCH$_2$CH$_2$–), 2.40 (t, J = 7.4, 2H, –HNCOCH$_2$–), 3.64 (t, J = 4.5, 2H, H-5′), 3.82–3.87 (m, 1H, H-4′), 3.95 (s, 1H, H-3′), 4.08 (s, 1H, H-2′), 4.93 (s, 1H, OH-5′), 5.35 (t, J = 4.8, 2H, OH-2′&3′), 6.07 (d, J = 4.0, 1H, H-1′), 7.18 (d, J = 7.4, 1H, H-5), 8.04 (d, J = 7.5, 1H, H-6), 10.60 (s, 1H, HNCO). MS FAB 341.7 (M$^+$), 231.7, 210.0, 148.7, 112.0.

N4-octanoyl-4-amino-1-[(2R,3S,4R,5R)-3, 4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl] pyrimidin-2-one (5)

Amide (**5**) was purified by column chromatography using DCM:MeOH (10:1) as a mobile phase to obtain 2.8 g (43%) of white powder. m.p. 145°C. ^{1}H NMR (600 MHz, DMSO) δ 0.87 (t, J = 7.0, 3H, –CH$_2$CH$_3$), 1.28 (dd, J = 7.5, 3.7, 8H, (–CH$_2$–)$_4$CH$_3$, 1.48–1.67 (m, 2H, –COCH$_2$CH$_2$–), 2.40 (t, J = 7.4, 2H, HNCOCH$_2$–), 3.64 (t, J = 4.6, 2H, H-5′), 3.81–3.87 (m, 1H, H-4′), 3.91–4.00 (m, 2H, H-3′), 4.09 (s, 1H, H-2′), 4.93 (s, 1H, OH-5′), 5.35 (t, J = 4.5, 2H, OH-2′& 3′), 6.07 (d, J = 4.0, 1H, H-1′), 7.18 (d, J = 7.5, 1H, H-5), 8.04 (d, J = 7.5, 1H, H-6), 10.60 (s, 1H, HNCO). MS FAB 370.2 (M + H$^+$), 260.0, 238.0, 112.1.

N4-decanoyl-4-amino-1-[(2R,3S,4R,5R)-3, 4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl] pyrimidin-2-one (6)

Amide (**6**) was purified by column chromatography using DCM:EtOAc:MeOH (6:2:1) as a mobile phase to obtain 1.8 g (28%) of white powder. m.p. 153°C. ^{1}H NMR (600 MHz, DMSO) δ 0.86 (t, J = 7.0, 3H, –CH$_2$CH$_3$), 1.21–1.33 (m, 14H, (–CH$_2$–)$_6$CH$_3$), 1.52–1.60 (m, 2H, COCH$_2$CH$_2$–), 2.39 (t, J = 7.4, 2H, HNCOCH$_2$–), 3.64 (s, 2H, H-5′), 3.81–3.88 (m, 1H, H-4′), 3.91– 3.99 (m, 1H, H-3′), 4.09 (s, 1H, H-2′), 4.93 (s, 1H, OH-5′), 5.35 (s, 2H, OH-2′&3′), 6.07 (d, J = 4.0, 1H, H-1′), 7.18 (d, J = 7.5, 1H, H-5), 8.04 (d, J = 7.5, 1H, H-6), 10.60 (s, 1H, HNCO). MS FAB 397.9 (M$^+$), 390.9, 288.1, 265.8, 265.8, 243.9, 112.3, 60.3.

Physicochemical properties

Solubility determination

The aqueous solubility of the alkylamides was determined by preparing saturated solutions in phosphate buffered saline (PBS) (10^{-2} M, pH 7.4). The slurries were stirred with magnetic bars in a water bath at 32°C for 24 h. It was ensured that an excess of solute was present at all times to provide saturation. The solutions were filtered through 0.2 μm acrodisc filters, diluted appropriately in PBS (pH 7.4) and analysed by HPLC to determine the concentration of dissolved solutes in the PBS.

Experimental log D

The partition coefficients were determined by a method reported by Taylor and Sloan.[9] Equal volumes of *n*-octanol and phosphate buffer solution of pH 7.4 were saturated with each other under vigorous stirring for at least 24 h. An accurately weighed quantity of 30 mg of the amides (**2**)–(**6**) was dissolved in 3 ml of pre-saturated *n*-octanol, stoppered and agitated for 10 min in a 10 ml graduated tube (0.5 ml division). Subsequently 3 ml of pre-saturated buffer was transferred to the tubes containing the previously mentioned solutions. The tubes were stoppered and agitated for 45 min then centrifuged at 4000 rev/min for 30 min. The volume ratio (octanol:buffer) was not discernably different from 1. The octanol and buffer phases were each diluted with methanol and the concentrations of compounds (**2**)–(**6**) were measured by HPLC. The log D values were calculated as logs of the concentration ratios in the two phases. These experiments were done in triplicate. The results expressed as means are listed in Table 1.

In-vitro skin permeation experiment

The project ‘In-vitro transdermal delivery of drugs through human skin’ was approved by the Ethics Committee of the North-West University (Potchefstroom Campus, South Africa).

Preparation of donor phase

Donor solutions were obtained by preparing saturated solutions of compounds (**1**)–(**6**) in PBS (10^{-2} M, pH 7.4) at 32ºC. To ensure saturation, the slurries were stirred in a water bath at 32ºC for 24 h.

Skin preparation

The female Caucasian human abdominal skin used for these permeation studies was obtained from Sunwardpark Clinic (Boksburg, South Africa) where it had been removed during a cosmetic procedure. The donor was approximately 40 years old. The skin was stored in a cooler box during transportation and stored in a freezer at –20ºC until time of use (less than 3 months). A scalpel was used to separate the skin from the fat layer. Afterwards, the epidermis was removed by first immersing the skin in 60ºC HPLC water for 60 s.[10] The epidermis was then gently teased away from the skin with forceps. The epidermis was placed in a bath filled with HPLC water, with the outer side facing up, and was then carefully set on Whatman filter paper, left to dry at room temperature and wrapped in foil. The foil containing the epidermis was stored in a freezer at –20ºC and was used within 3 months. Prior to use, the epidermis was thawed and examined by light microscope for any defects, before mounting on the Franz diffusion cells.

Skin permeation determination

Vertical Franz diffusion cells with 2.0 ml receptor compartments and 1.0751 cm^2 effective diffusion area was used for the permeation studies. The epidermis skin layer prepared above was mounted on the lower half of the Franz cell with the stratum corneum facing upwards. Subsequent to that, the upper half of the Franz cell was mounted and vacuum grease applied around the junction of the upper and lower components to prevent possible leakage. A clamp was used to fasten the upper and lower parts of the Franz cell together, with the epidermis separating the donor and receptor compartments. The receptor compartment was filled with PBS (pH 7.4). Special care was taken to ensure that no air bubbles came between the receptor vehicle and epidermis, as this would reduce the effective diffusion area. The donor compartment was filled with 1.0 ml PBS and equilibrated at 32ºC for 1 h in a water bath. Only the receptor compartments were submerged in the water bath and were equipped with magnetic stirring bars. After a period of 1 hour, 1 ml of freshly prepared saturated solution was added to each donor compartment, which was immediately covered with Parafilm to prevent evaporation of any constituent within the solution for the duration of the experiment. An excess of solutes was present in the donor phase at all times during the experimental procedure to ensure that the donor solutions remained saturated. After 2, 4, 6, 8, 10 and 12 h the receptor phase was withdrawn and replaced by fresh buffer (32ºC) to mimic sink conditions as they occur in the human body. The withdrawn samples were immediately analysed by HPLC to determine the concentrations of the compounds which permeated through the epidermis. These experiments were performed in triplicate. The steady-state flux (J_{ss}) was determined by plotting the cumulative drug quantity permeating per unit area versus time and determining the slope of the steady state.

Statistical methods

The following statistical procedures were used to test if there were significant statistical differences between the parent compound′s median flux value and that of the newly synthesised compounds. The reason for comparing the

Table 1 Transdermal data and physicochemical properties of N4-amide derivatives of cytarabine

Compound	*n*	Mp (°C)	Mr	S_w (± SD) (mg/ml)	S_w (± SD) μmol/ml	Log S_{oct} (μmol/ml)[a]	Log D (*n*-octanol-PBS)	J_{ss} (nmol/cm^2 per h)[b]	J_{ss} (nmol/cm^2 per h)[e]	SD	R_t	*P*-value[f]	*P*-value[g]
1		212	243.2	179.54 ± 8.22	738.18 ± 33.79	0.93	–1.9 ± 0.02	3.70[c]	3.70	1.37	4.4		
2	0	183	285.3	12.10 ± 0.35	42.43 ± 1.2	0.36	–1.27 ± 0.02	19.72[c]	16.60	10.79	2.2	0.005*	0.127(1–2)
3	2	193	313.3	7.95 ± 0.08	25.38 ± 0.26	1.24	–0.17 ± 0.01	nd[d]	nd		4.6		
4	4	130	341.4	4.96 ± 0.24	14.53 ± 0.69	2.07	0.91 ± 0.05	95.93[c]	89.0	55.87	7.1	0.005*	0.005*(1–4)
5	6	145	369.4	0.45 ± 0.00	1.22 ± 0.01	2.23	2.15 ± 0.02	nd[d]	nd		8.8		
6	8	153	397.5	0.03 ± 0.00	0.07 ± 0.01	2.14	3.28 ± 0.06	nd[d]	nd		10.0		

[a]Calculated from $S_{oct} = D \times S_W$; [b]flux mean; [c]each experiment was run on three different cells; [d]each experiment was run on six different cells; [e]flux medians; [f]Kruskal–Wallis *P*-value; [g]multiple comparison *P*-value; nd, not detected; *statistically significant; S_w, aqueous solubility; S_{oct}, octanol solubility; Mr, molecular mass; Mp, melting point; log D, log P at specific pH (7.4).

medians of the flux values instead of the mean was that non-parametric tests were done because normality of the distribution of the data of this study could not be assumed. The usual parametric test to compare means in the case of samples less than 30 can only be applied when normality is assumed.[11]

The non-parametric Kruskal–Wallis test was therefore performed with Statistica[12] to test the statistical significance of differences between the medians of different compounds at a 5% level. Multiple comparisons on the mean ranks of individual groups were performed to determine where the differences occurred. Note that the compounds where no fluxes were detected were not included in the statistical analysis because the conclusion that they were much less efficient than the parent compound is trivial.

Results

Synthesis

The N4-alkylamide derivatives of cytarabine (**2**)–(**6**) with molecular weight ranging from 285.3 to 397.47 were synthesised by the mixed anhydride method in 23–63% yield.

Hydrophilicity and lipophilicity

The physicochemical data of cytarabine amide derivatives are presented in Table 1. The interrelation between octanol solubility, aqueous solubility and partition coefficient are presented in Figures 2 and 3.

Skin permeation

The transdermal penetration parameters of cytarabine and its N4-alkylamide derivatives were determined *in vitro* and are summarised in Table 1.

Discussion

Synthesis of cytarabine derivatives

The ^{13}C NMR spectra of amides exhibit the resonance of carbonyl carbons at around 170 ppm. Due to the electron-withdrawing capacity of the amide linker, H-5 and H-6 signals were deshielded from 5.6 and 7.5 ppm to 7.1 and 8.0 ppm, respectively. This confirms that the acylation took place at the N4-amino group. The deshielding of the signal from 7.1 ppm, assignable to the N4-amino group, to around 10.7 ppm suggests that the N4-amino group is adjacent to an electron withdrawing carbonyl group. Mass spectra confirmed the molecular weights of (**2**), (**3**), (**4**), (**5**) and (**6**) as 244.0, 313.3, 341.7, 370.2 and 397.9, respectively.

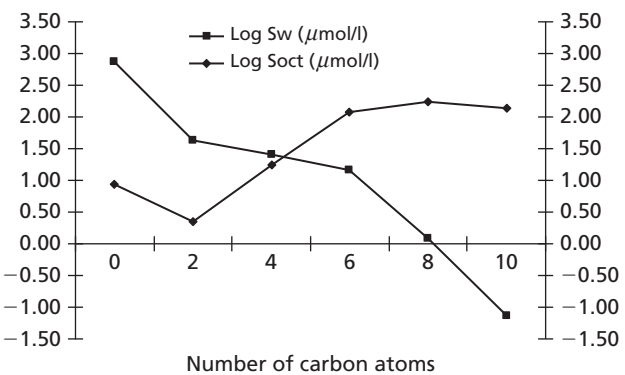

Figure 2 Relationship between aqueous and lipid solubility versus number of carbon atoms on the alkyl substituent

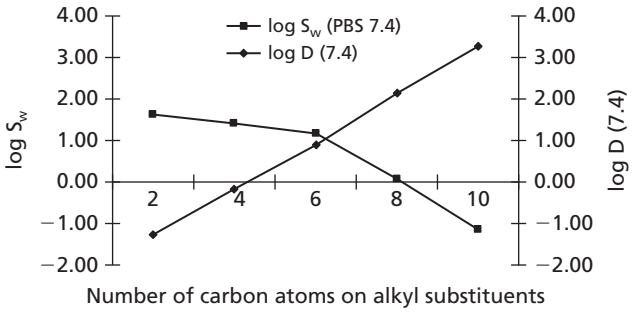

Figure 3 Relationship between number of carbon atoms on N4-alkylamide of cytarabine, log D (7.4) and log S_w

Physicochemical properties

Physicochemical parameters such as aqueous solubility and lipophilicity have been reported to influence the membrane permeation, therapeutic activity and pharmacokinetic profile of medicines.[13] The physicochemical data of cytarabine amide derivatives are presented in Table 1. In this homologous series, octanol solubility values increased while aqueous solubility decreased as the alkyl chain lengthened (see Figure 2). As a consequence, the log D increases as the chain lengthens (Figure 3). This corroborates previous findings in the literature that increasing the non-polar portion of a molecule by extending the length of the chain produces certain characteristic features, such as elevation of boiling point, decreased aqueous solubility and increased partition coefficient.[14] It is noteworthy that compound (**2**) exhibited lower solubility in both water and lipid than the parent compound. Moreover, amide (**2**), the first member of the homologous series, exhibits lesser solubility in octanol than does cytarabine, which is contrary to previous reports that, generally, the first member of a homologous series exhibits increased lipid solubility, thought to be due the masking of hydrogen bond donor.[9] All amides showed lower melting points than the parent compound. Generally, compounds with lower melting points are associated with higher solubility and are known to permeate the skin better than those with higher melting points.[15]

In-vitro skin permeation study

The diffusion experiments showed that there is a varying degree of transdermal permeation between compound (**1**) and its N4-alkylamide (Table 1). There is no clear trend between flux values and molecular weights of compounds. Compound (**4**) penetrated the skin much better than (**2**) and (**3**), despite having a higher molecular weight. This corroborates previous findings in which some members of homologous series with higher molecular weights penetrated the skin better than members with lower molecular weights.[16,17]

Compound (**4**) exhibited a significant enhancement of transdermal penetration compared to cytarabine. It showed a

median steady-state flux of 89.0 nmol/cm^2 per h, which is a significant enhancement. This enhancement may be attributable to the solubility of (**4**) in both aqueous and lipid media (Figure 2). A good balance between lipid and aqueous solubility values is reported to be essential to optimise transdermal flux.[18] The other compounds, (**3**), (**5**) and (**6**), were not detected in the receptor phase, which means they did not permeate the epidermis. The epidermis, especially its outermost layer, is the major source of resistance to the permeation of the skin by drug molecules.[3] It has been reported that the optimal log octanol/water partition coefficient for a drug to penetrate the stratum corneum is approximately 2.[19] However, in this study compound (**5**), with log D of 2.15, exhibited poor percutaneous penetration. This could be due to *inter alia* the hydrogen-bonding phenomenon. The hydrogen bonding functional groups in the permeant tend to slow down transdermal diffusion to due to their interaction with polar head groups of the intercellular lipids present in the skin.[20,21]

Conclusions

The alkylamide derivatives of cytarabine were successfully prepared and their structures were confirmed by NMR and MS techniques. The transdermal data showed no trend in melting point, lipophilicity and hydrophilicity. The amide (**4**), characterised by a good balance of lipophilicity and hydrophilicity, exhibited the highest enhancement of transdermal penetration of cytarabine.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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