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Skin permeation enhancement potential of Aloe Vera and a proposed mechanism of action based upon size exclusion and pull effect

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Abstract

The aim of this study was to determine in vitro the potential of Aloe Vera juice as a skin permeation enhancer; a secondary aim was to probe the extent to which Aloe Vera itself permeates the skin. Saturated solutions of caffeine, colchicine, mefenamic acid, oxybutynin, and quinine were prepared at 32 °C in Aloe Vera juice and water (control) and used to dose porcine ear skin mounted in Franz diffusion cells with water as receptor phase. Receptor phase samples were taken over a 48 h period and permeants determined by reverse-phase HPLC. For caffeine and mefenamic acid no significant enhancements occurred between Aloe Vera and water as vehicles ($p > 0.05$). However, for colchicine, oxybutynin and quinine the presence of Aloe Vera within the formulation provided enhancements ($p \leq 0.05$). Enhancement potential was dependent upon the molecular weight of the drug in formulation, with the enhancement effect attributable to as yet unidentified components within the Aloe Vera. Colchicine, with a molecular weight of 399.44, achieved the best enhancement with an enhancement ratio of 10.97. No correlation with lipophilicity was apparent. In a further experiment, where freeze-dried Aloe Vera was reconstituted at 200% residue level, permeation of quinine was 2.8× that from normal Aloe Vera, providing further evidence for the presence of an enhancing factor within Aloe Vera. Certain, although unidentified, components of Aloe Vera readily permeated skin and the relative amount by which they permeated skin was inversely related to the molecular weight of the drug in solution, thus enhancement ratio. A new mechanistic rationale is proposed whereby larger drug solutes inhibit the permeation of Alove Vera components, but also are then able to interact more effectively with the enhancing factor and be subject to the pull effect.

Keywords: Aloe Vera; Skin; Permeation; Penetration enhancer; Permeation enhancer; Caffeine; Colchicine; Mefenamic acid; Oxybutynin; Quinine

1. Introduction

There is currently particular interest among the general public for medications that either are, or contain components, of natural origin. Aloe Vera (*Aloe barbadensis* Miller*)* is part of the Lilaceal family and is a perennial succulent cactus-like plant, which grows in hot, dry climates (Choi and Chung, 2003). This plant is often referred to as a 'healing' plant and is the source of two products. The first is an exudate from the cut leaf base which contains a high concentration of anthraquinone compounds and when dried is used as a potent cathartic and lacquer to inhibit nail biting. The second product, Aloe Vera, is pressed from the whole leaf and is a clear mucilaginous gel possessing diverse putative pharmacological activity (Pugh et al., 2001). Aloe Vera is thus incorporated into many products and is used for various medicinal, cosmetic and nutraceutical purposes (Ni et al., 2004), with topical applications featuring prominently.

In recent years the potential of using skin as an alternative route for administering systemically active drugs has received considerable interest (Moser et al., 2001). With transdermal delivery becoming more popular, research has focused on improving the absorption of such drugs, as delivery rates tend to be below therapeutic levels due to the barrier function of the skin. In particular, chemical penetration enhancers have received much attention and an enhancement system based upon a product such as Aloe Vera appears an attractive prospect due to its purported 'skin friendly' and humectant properties (Meadows, 1980).

At present there is minimal literature evidence to suggest that Aloe Vera has any skin penetration enhancement properties, although one paper mentions its use as a vehicle for other substances (Reynolds and Dweck, 1999). However, two recent United States patents have been filed which claim that Aloe Vera is responsible for increased skin penetration of co-formulated

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drugs. A 2004 US patent concerned the use of fresh macerated leaves of *Aloe barbadensis* formulated with fentanyl and claimed that when Aloe Vera oil (Aloe Vera extract macerated in soybean oil) was incorporated into the formulation the amount of fentanyl permeating the skin was increased by up to 50%, compared to formulations lacking Aloe Vera oil (Tisa-Bostedt et al., 2004). A further patent described the skin permeation enhancement of oxybutynin by Aloe Vera (Finckh et al., 2004). However, the experimental data contained within both patents can best be described as limited, with no information relating to QSAR or the role of Aloe Vera constituents.

This work sought to investigate the in vitro skin permeation enhancement potential of Aloe Vera extract using excised skin and a series of model drugs with different molecular weights and lipophilicities: caffeine, colchicine, mefenamic acid, oxybutynin and quinine (Table 1).

2. Materials and methods

2.1. Materials

Aloe Vera gel (Holland and Barrett, batch 18462) was purchased from a local store. Quinine, potassium phosphate, mefenamic acid, colchicine, oxybutynin HCl and aqueous phosphoric acid (85%) were purchased from Sigma–Aldrich Company (Poole, UK). Caffeine was purchased from Fluka (Gillingham, UK). Oxybutynin hydrochloride tablets (Tillomed Laboratories Limited, Cambridgeshire, UK) were purchased through Cardinal Health (Glamorgan, UK) and the drug was liberated by aqueous extraction with a purity of >99%. HPLC-grade methanol and acetonitrile were obtained from Fisher Chemicals (Loughborough, UK). High vacuum grease was obtained from DOW Corning (Barry, UK); nylon membrane filters (0.45 μm) were purchased from Whatman (Maidstone, UK). Freshly excised porcine ears were obtained prior to steam cleaning from a local abattoir.

2.2. Preparation of porcine skin membranes

Porcine ear skin has been proposed as a useful model for human skin (Simon and Maibach, 2000) and used in many works ever since. The ears were gently cleaned under running warm water and hairs shaved using electric clippers. Using a scalpel the skin was carefully liberated from the dorsal side of the ear and then cut into approximately 2 cm square sections, which were stored on aluminium foil at −20 °C until required (<1 week). The use of frozen-thawed skin has been used as a standard model for some time although questions have been raised in terms of its metabolic/enzyme activity (Thomas and Heard, 2006) and appropriateness for polar permeants (Sintov and Botner, 2006).

2.3. Preparation of saturated solutions

Saturated solutions of caffeine, colchicine, mefenamic acid, quinine and oxybutynin were prepared in both Aloe Vera juice and deionised water. Drug was added incrementally to Eppendorf vials containing either Aloe Vera juice or deionised water

Table 1
Physicochemical properties, solubility ($n = 3$, ±S.D.) and skin permeation data ($n = 5$, ±S.D.) for caffeine, mefenamic acid, quinine, oxybutynin and colchicine in Aloe Vera and water vehicles and applied to excised porcine ear skin

Drug	MW	$c\log P$	Vehicle	Solubility (μg ml^{-1})	P	Lag time (h)	P	J_{ss} (μg cm^{-2} h^{-1})	P	ER$J_{ssAV}/J_{sswater}$	kp (cm h^{-1})
Caffeine	194.14	−0.04	Aloe Vera	383423 ± 8235	0.1143	1.98 ± 0.32	0.115	7.37 ± 2.44	0.29	0.68	19.22
			Water	367570 ± 7434		2.38 ± 0.25		10.80 ± 4.1			29.49
Mefenamic Acid	241.29	5.287	Aloe Vera	9.83 ± 0.643	0.1143	1.3 ± 0.6	0.654	0.035 ± 0.018	0.151	0.78	3.52×10^{-3}
			Water	10.70 ± 0.810		0.8 ± 0.5		0.045 ± 0.003			4.21×10^{-3}
Quinine	324.42	1.575	Aloe Vera	3348 ± 63.443	0.3429	13.2 ± 1.48	0.674	0.11 ± 0.04	0.0159*	2.75	0.03×10^{-3}
			Water	3295 ± 177.11		12.8 ± 1.15		0.04 ± 0.01			0.012×10^{-3}
Oxybutynin	357.49	4.867	Aloe Vera	338848 ± 5921	0.4857	1.08 ± 0.6	0.20	40.69 ± 7.6	0.0159*	4.36	0.12×10^{-3}
			Water	340883 ± 4371		1.83 ± 0.9		9.33 ± 5.0			0.03×10^{-3}
Colchicine	399.44	1.195	Aloe Vera	68515 ± 5429	0.9999	1.87 ± 1.2	0.40	2.68 ± 1.7	0.0079*	11.2	39.12
			Water	67906 ± 3618		2.96 ± 0.70		0.24 ± 0.16			3.53

* $p < 0.05$.

(1 ml) on a blood tube rotator (Stuart Scientific, Stone, UK) set-up in a laboratory incubator at 32 °C (average skin surface temperature). Saturation was indicated when the solutions remained cloudy, due to suspended particulate drug. When required, the vials were centrifuged at 1000 × *g* in a mini centrifuge also set-up in the incubator to maintain a constant 32 °C. Using a pipette and tips previously stored at 32 °C a 50 μl aliquot of each solution was carefully transferred to a HPLC autosampler vial for dilution and solubility determination by HPLC; the remainder of the solutions were used to dose the diffusion cells. All experiments were internally consistent by the use of the same batch of Aloe Vera juice.

2.4. Preparation of 'double strength' Aloe Vera

Aloe Vera juice (15 ml) was placed into Pyrex conical flasks and covered with Parafilm, which was then pierced to allow the exit of water vapour. The flasks were placed into liquid nitrogen to accelerate freezing, before being placed in a freeze dryer (Heto-Holten Drywinner 110) for 24 h. This produced Aloe Vera residue of approx. 1.5% (w/v). To produce 'double strength' Aloe Vera, the residue was reconstituted with deionised water, under stirring, to a level of 3% (w/v). This was stored in screw cap containers and stored at −20 °C until required.

2.5. In vitro skin permeation experiments

In vitro skin permeability was determined using all-glass Franz-type diffusion cells (Friend, 1992) incorporating the porcine ear membranes, equally distributed between experiments to eliminate donor variability. The cell flanges were minimally greased with high performance vacuum grease with the skin placed stratum corneum uppermost between the cell chambers and clamped into position. Magnetic stirrer bars were added to the receptor chambers and filled with the receptor phase (de-gassed, de-ionised water) ensuring the exclusion of all air. The cells were then placed on a submersible magnetic stirrer plate (Variomag, Daytona Beach, FL, USA) set-up in a Clifton unstirred water bath set at 37 °C (providing a skin surface temperature of 32 °C by heat dissipation). After 10 min the donor chambers were dosed with 200 μl of the appropriate saturated solution, ensuring minimal temperature change. To avoid evaporation, Parafilm (Whatman, Maidstone, UK) was used to occlude the donor chambers and glass caps were placed over the ends of the sampling arms. At specific time intervals over a 48 h period the whole receptor phases were removed, with 1 ml added to HPLC autosampler vials and stored at −20 °C prior to analysis. Cells were replenished with fresh water stored at 37 °C.

2.6. HPLC analysis

Drug content was quantified using an automated Hewlett Packard 1100 HPLC system, fitted with a Kingsorb 5 μm C18 column, 150 mm × 4.6 mm (Phenomenex, Macclesfield, UK) and detection by UV. Methods were optimised to provide separation of drug and Aloe Vera components from any skin leachate. For caffeine the method was adapted from that in the paper by Heard et al. (2006a). The optimised mobile phase consisted of 0.05% (v/v) TFA solution: acetonitrile 90:10% (v/v). The flow rate was 1 ml min^{-1} and detection at 210 nm. The retention time was 15 min. For colchicine the method was adapted from that in the paper by Rosso and Zuccaro (1998). The optimised mobile phase consisted of 0.01 M potassium phosphate buffer (1.2249 g potassium phosphate, 900 ml deionised water, adjusted to pH 3 with phosphoric acid): methanol 60:40% (v/v). The flow rate was 1 ml min^{-1} and detection at 254 nm. The retention time was 23 min. For mefenamic acid the method was adapted from the mobile phase used for oxybutynin. The optimised mobile phase consisted of 0.01 M potassium phosphate buffer (1.2249 g potassium phosphate, 900 ml deionised water, adjusted to pH 3 with phosphoric acid): acetonitrile 40:60% (v/v). The flow rate was 1 ml min^{-1} and detection at 254 nm. The retention time was 13 min. For quinine the method was that reported by Heard et al. (1998). The mobile phase consisted of methanol: acetonitrile: 0.7% (w/v) ammonium acetate solution, 30:15:55% (v/v). The flow rate was 1 ml min^{-1} and ultraviolet detection carried out at 281 nm. The retention time was 15 min. For oxybutynin the method was adapted from that in the paper by El-Gindy (2005). The optimised mobile phase consisted of 0.01 M potassium phosphate buffer (1.2249 g potassium phosphate, 900 ml deionised water, adjusted to pH 1.5 with phosphoric acid): acetonitrile 70:30% (v/v). The flow rate was 1 ml min^{-1} and detection at 220 nm. The retention time was 14 min.

For each of the drug permeants, HPLC chromatograms determined from receptor phase samples were found to contain significant amounts of additional early-eluting peaks due to the transdermal delivery of components from the Aloe Vera—these were absent from the control (water) solutions indicating that they were not due to skin leachate, but *were* present in when dilutions of Aloe Vera juice were injected. Chromatograms varied greatly in terms of separation of Aloe Vera components and peak areas as different chromatographic conditions were employed for different drugs. In order to estimate the proportions being delivered across skin the total peak areas were expressed as percentages of the amount dosed to the cells.

2.7. Data analysis

Cumulative amounts of caffeine, colchicine, mefenamic acid, quinine and oxybutynin, permeated over the 48 h period (per unit area, μg cm^{-2}) were plotted against time (hours). A period of 48 h is generally acceptable when steady state is found to exist for this period, at least. The linear section of the curve, 12–48 h was used to provide a value for steady state flux (J_{ss}); this and the drug concentration in the formulation (Cv) were used to calculate the permeability coefficient (kp). Lag times until were determined by extrapolating the steady state back to the *x*-axis of the permeation profile. Enhancement ratio was obtained when the flux of a drug in the saturated Aloe Vera formulation was divided by the flux of the drug in the saturated water formulation. Statistical analyses were carried out using Instat 3 for Macintosh (GraphPad Software, Inc.), where non-

parametric Kruskal–Wallis ANOVA was employed to determine differences between data sets, and Mann–Whitney tests used to compare data pairs.

3. Results

3.1. Solubilities

Drug concentrations of saturated solutions in water and Aloe Vera were determined as detailed in Table 1. The general trend for solubility was caffeine > oxybutynin > colchicine > quinine > mefenamic acid. A Mann–Whitney statistical test showed that for all analytes there were no significant differences ($p > 0.05$) between solubility in water and Aloe Vera.

3.2. Permeation from Aloe Vera versus water vehicles

For caffeine the highest steady state flux was observed from a water vehicle, with a mean value of 10.84 $\mu g\,cm^{-2}\,h^{-1}$ and a standard deviation of 4.10. The Aloe Vera formulation gave a flux of 7.37 $\mu g\,cm^{-2}\,h^{-1}$, and a permeability coefficient of 19.22×10^{-6} cm h^{-1}. The enhancement ratio was 0.68 although a Mann–Whitney test revealed that there was not a statistically significant difference between the formulations, with the p-value being 0.2857. Similarly, lag times were statistically equal ($p = 0.1152$) for Aloe Vera and water, 1.98 and 2.38 h, respectively.

For colchicine the highest steady state flux was observed for the Aloe Vera formulation. This gave a mean value of 2.68 $\mu g\,cm^{-2}\,h^{-1}$ with a standard deviation of 1.701. The permeability coefficient was 39.12×10^{-6} cm h^{-1}. The water formulation gave a flux of 0.24 $\mu g\,cm^{-2}\,h^{-1}$. This formulation gave a permeability coefficient of 3.53×10^{-6} cm h^{-1}. For the steady state fluxes a Mann–Whitney statistical analysis test demonstrated that there was a statistically significant difference between the formulations, p-value = 0.0079. The enhancement ratio was 11.2. Lag times were statistically the same with mean values of 1.87 and 2.96 h ($p = 0.4000$).

For mefenamic acid the highest steady state flux was observed for the Aloe Vera formulation. This gave a mean value of 0.0346 $\mu g\,cm^{-2}\,h^{-1}$ with a standard deviation of 0.01891. The permeability coefficient was 3519.8×10^{-6} cm h^{-1}. The water formulation gave a flux of 0.045 $\mu g\,cm^{-2}\,h^{-1}$. This formulation gave a permeability coefficient of 4205.6×10^{-6} cm h^{-1}. For the steady state fluxes it was shown that with a p-value of 0.1508 there was not a statistically significant difference between the formulations; the enhancement ratio was 0.78. Lag times were statistically the same with mean values of 1.3 and 0.40 h ($p = 0.65$).

For oxybutynin the highest steady state flux was observed for the Aloe Vera formulation. This gave a mean value of 40.69 $\mu g\,cm^{-2}\,h^{-1}$ with a standard deviation of 7.588. The permeability coefficient was 120.1×10^{-6} cm h^{-1}. The water formulation gave a flux of 9.33 $\mu g\,cm^{-2}\,h^{-1}$. This formulation gave a permeability coefficient of 27.37×10^{-6} cm h^{-1}. For the steady state fluxes it was shown that there was a statistically significant difference between the formulations, with the p-value of 0.0159. The enhancement ratio was 4.36. Lag times were statistically the same with mean values of 1.08 and 1.83 h ($p = 0.2000$).

For quinine the highest steady state flux was observed for the Aloe Vera formulation. This gave a mean value of 0.106 $\mu g\,cm^{-2}\,h^{-1}$ with a standard deviation of 0.04278. The permeability coefficient was 31.66×10^{-6} cm h^{-1}. The water formulation gave a flux of 0.041 $\mu g\,cm^{-2}\,h^{-1}$. This formulation gave a permeability coefficient of 12.44×10^{-6} cm h^{-1}. For the steady state fluxes it was shown that there was a statistically significant difference between the formulations, with the p-value of 0.0159. The enhancement ratio was 2.75. Lag times were substantially longer in this case, although again statistically equal with mean values of 13.2 and 12.8 h, respectively ($p = 0.6743$).

3.3. Permeation from 'standard strength' and 'double strength' Aloe Vera

Table 2 shows that the highest steady state flux of quinine was observed for the double strength Aloe Vera formulation. This gave a mean value of 0.11 $\mu g\,cm^{-2}\,h^{-1}$ with a standard deviation of 0.019. The permeability coefficient was 310.3×10^{-6} cm h^{-1}. The 'standard strength' formulation provided a flux of 0.045 $\mu g\,cm^{-2}\,h^{-1}$ and a permeability coefficient of 120.8×10^{-6} cm h^{-1}. The enhancement ratio was 2.82 and a Mann–Whitney statistical test produced a p-value of 0.0079, indicating a significant difference and providing further evidence for the presence of an enhancing factor within Aloe Vera. However, a p-value of 0.1376 indicated there was not a statistical difference between the lag times.

3.4. Enhancement ratio in relation to molecular weight and c log P

From Table 1 it is evident that as molecular weight increased the enhancement ratio increased and this is illustrated in Fig. 1. A Kruskal–Wallis statistical test provided a p-value of 0.0016, showing that there was a significant difference between the enhancement ratios of all five drugs tested. No correlation was apparent involving drug lipophilicity ($c \log P$).

Table 2
Data for the permeation of quinine across porcine skin from Aloe Vera and Aloe Vera residue reconstituted at double level

Formulation of Aloe Vera	Lag time (h)	p-Value	Flux ± S.D. ($\mu g\,cm^{-2}\,h^{-1}$)	Lower 95% confidence limit	Upper 95% confidence limit	ER (double/single)	p-Value	Kp ($\times 10^{-6}$ cm h^{-1})
Standard strength	13.2 ± 0.84	0.1376	0.045 ± 0.003	0.041	0.049	2.82	0.0079	120.8
Double strength	14.1 ± 0.54		0.11 ± 0.019	0.089	0.138			310.3

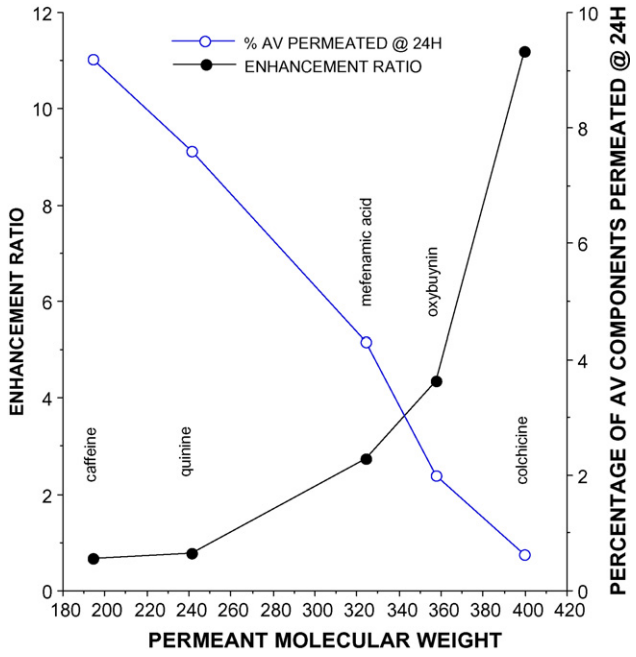

Fig. 1. Double Y plot showing that drug enhancement ratio varies proportionately with molecular weight but inversely with % permeation of Aloe Vera constituents.

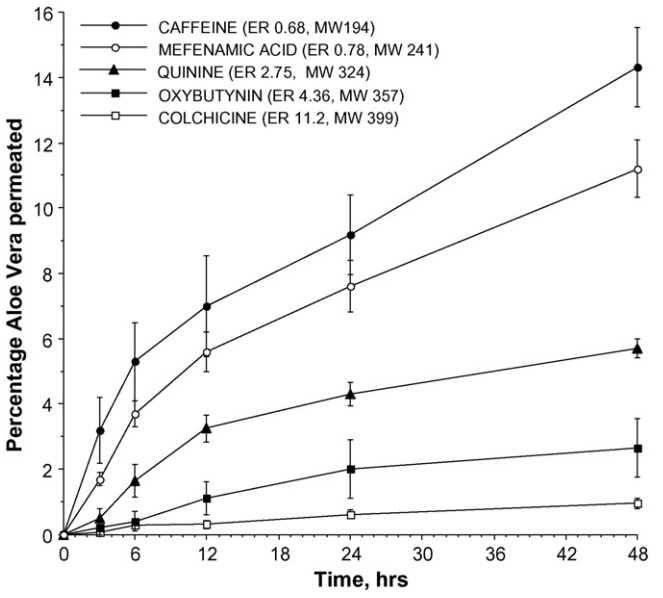

Fig. 2. Plot of the percentages of initial Aloe Vera permeated as function of time and drug ($n = 5$, ±S.D.).

3.5. Permeation of Aloe Vera constituents

In the case of each drug permeant, substantial amounts of compounds from Aloe Vera were found to be present in the receptor phase samples (Fig. 2 and Table 3). However, it is clear that the percentages permeating skin varied greatly, and dependently upon the solute drug. When the cumulative percentage of Aloe Vera (at 24 h) was plotted against drug molecular weight a relationship once again emerged although on this occasion it was clearly inverse relative to molecular weight and enhancement ratio (Fig. 1).

4. Discussion

As Aloe Vera is some 98.5% water, the appropriate control vehicle was water. Using drug solutions at saturation ensured that any change in the donor concentration was minimal, i.e., the doses applied were effectively infinite. The statistically equal solubilities of each drug in water and Aloe Vera was important, as it demonstrated that the saturated solutions used to dose cells were not only equitable in terms of concentration, but also thermodynamic activity. Therefore, the drug permeating from the two vehicles was doing so from the same starting point and any differences in permeation must have been attributable only to differences between water and Aloe Vera, specifically the solutes present in Aloe Vera juice. Aloe Vera is a succulent plant and the juice is comprised mostly of water, with only 1.5% (w/v) of extract, thus very similar solubilities would be expected. Furthermore, any enhancement observed could not be attributable to water alone.

As the in vitro permeation investigations demonstrated that Aloe Vera does have the potential to increase the permeation of certain model permeants the drug physiochemical properties that may influence this enhancement were examined, in particular $c \log P$, and molecular weight. These parameters are of significance, for example in the Potts Guy equation (Guy and

Table 3
Percentage of Aloe Vera components permeating skin after 24 h in presence of co-permeating oxybutynin, colchicine, caffeine, mefenamic acid and quinine

Drug	Permeant	Mean % permeated at 24 h	Ratio of % permeated AV/water	J_{ss} in AV (μmol cm^{-2} h^{-1})
Oxybutynin	Aloe Vera	1.99	13.33	0.114
	Oxybutynin	0.15		
Colchicine	Aloe Vera	0.66	38.13	0.0067
	Colchicine	0.02		
Caffeine	Aloe Vera	9.30	58.84	0.038
	Caffeine	0.16		
Mefenamic acid	Aloe Vera	4.63	110.08	0.00015
	Mefenamic acid	0.04		
Quinine	Aloe Vera	8.01	679.2	0.000339
	Quinine	0.01		

Potts, 1993), although, no correlation was apparent between $c \log P$ and the enhancement ratio. However, Fig. 1 does show a relationship between molecular weight and enhancement ratio. Inspection of Fig. 1 suggests enhancement may not occur for solutes of <260 approximate MW; it is further speculated that the relationship would diminish as the MW approaches the generally accepted ceiling of ~500. The aforementioned US patents claim that the permeation of both fentanyl and oxybutynin can be enhanced by Aloe Vera, and data from this study indeed supports the claimed permeation enhancement of oxybutynin. Fentanyl has a molecular weight of 366.5 and interpolation of this value using Fig. 1 suggests it too may indeed be enhanced by Aloe Vera by a factor of ~6.

With the knowledge that Aloe Vera had the potential to enhance the permeation of certain solutes, the effect of increasing the amount of Aloe Vera residue within formulations was determined. As there was no statistical difference between the solubilities of quinine in standard and double strength Aloe Vera (Table 2) direct comparisons could be made. The double strength Aloe Vera, which contained 3% (w/v) of Aloe Vera residue compared to 1.5% (w/v), gave ~2.8× greater permeation of quinine compared to standard strength Aloe Vera ($p = 0.0079$). These data confirm the permeation enhancement was attributable to one or more of the solutes within Aloe Vera.

From Fig. 2 it is clear that Aloe Vera (or at least a substantial proportion of its solute constituents) permeated the skin in relatively high proportions. As a natural product, Aloe Vera contains a diverse array of component compounds, including anthraquinones, saccharides, polysaccharides, lignin, and numerous low molecular weight compounds such as vitamins and salicylic acid (Femenia et al., 1999); in addition to recently discovered compounds such as bioactive maloyl glucans (Esua and Rauwald, 2006). Though the more lipophilic components of the Aloe Vera may penetrate the stratum corneum more readily and modulate it in some way, in line with how other chemical enhancers work, it would be expected that the same permeation profile of Aloe Vera would be observed regardless of what drug it is formulated with. However, this was clearly not the case and could indicate increased hydration due to increased population of humectant compounds delivered into the skin from the Aloe Vera. However, if this were so one might anticipate a positive correlation of enhancement with hydrophilicity, but not an inverse correlation with molecular weight. Consequently the following alternative mechanism may be proposed.

Given the general impermeability of skin it is reasonable to assume there can only exist finite availability of permeation pathways across skin at any given time. In a complex solution of Aloe Vera and drug at saturation, larger drug molecules would be expected to displace components of Aloe Vera from the pathways and inhibit permeation more effectively than smaller molecules. This is clearly supported in the trends of Fig. 2. However, we know from Fig. 1 that the higher the drug size/molecular weight, the higher the enhancement ratio. This phenomenon can be rationalised in terms of the scope for interaction and complexation of the drug with the (unidentified) enhancing factor. Smaller molecules are seemingly less effective at blocking AV from permeation pathways. Thus, if more of an enhancing factor is 'lost' from the solution as a result of its permeation, then there will be reduced opportunity for the drug to interact with it. This is despite what might be perceived as an increase in thermodynamic activity—although without knowledge of the transit of water this is difficult to assess. Conversely, with a larger MW drug, the permeation routes will be more effectively blocked and a consequence of this is that it will allow increased scope for the drug to interact with the enhancing factor and complex with it before being transported across the skin. Such facilitated transport across skin involving relatively large complexes (Karia et al., 2004) is already known and there is increasing evidence of the importance of the pull effect in permeation enhancement (Kadir et al., 1987; Heard et al., 2006b). However, further elucidation of the mechanism of action of permeation enhancement using Aloe Vera cannot be made until the enhancing factors have been identified. A summary of the processes involved in the current work is proposed in Fig. 3.

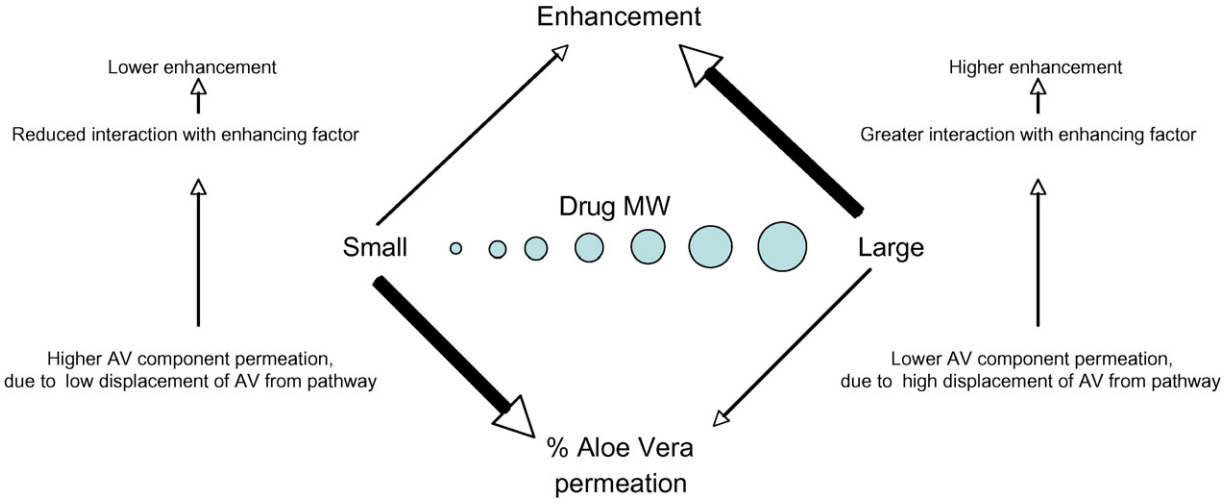

Fig. 3. Flowchart summarising the proposed mechanism behind the observed permeation enhancement behaviour of Aloe Vera.

5. Conclusions

The potential of Aloe Vera to enhance certain co-formulated solutes has been demonstrated. This potential appears to be related to the molecular weight of the solute, with a presumed ceiling value not attained in this work and which is attributable to one or more components of the juice. Certain components of Aloe Vera (as yet unidentified) also readily permeate skin, which may have ramifications on its use as an excipient.

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