INVESTIGATING THE POTENTIAL OF ALOE VERA AS PENETRATION ENHANCER FOR TRANSDERMAL DELIVERY

KIRAN SHARMA1*, ASHU MITTAL2, SHEIKH MURTUZA3 & PRIYANKA AGRAHARI4

ABSTRACT

Skin penetration enhancers reversibly decrease the barrier resistance of the stratum corneum and allow drugs to penetrate more readily to the viable tissues and the systemic circulation. There are synthetic permeation enhancers and natural permeation enhancers which will help in improving the transdermal permeation of poorly absorbed drugs. Among the various natural permeation enhancers the most effective and investigated one is Aloe Vera gel. This review describes the enhancement potential of Aloe Vera gel on drug permeation through the skin which was dependent upon the molecular weight of the drug in formulation. Aloe Vera gel increased the in vitro skin penetration of compounds with an apparent inverse correlation between enhancement ratio and molecular weight of the compound. Some constituents of the Aloe Vera gel itself also penetrated the skin and this was interestingly dependent on the molecular weight of the co-applied compounds. The penetration enhancement effect of the aloe gel may be explained by a probable pull effect of complexes formed between the compound and the enhancing agent within the aloe gel or through facilitated permeation i.e. transient reduction in barrier resistance of stratum corneum and intracellular transport by dekeratinization of corneocytes which may be attributed to the presence of triglycerides as constituents of Aloe Vera. Therefore, it is feasible to deliver therapeutically effective dose of drug via transdermal route using Aloe Vera. as penetration enhancer.

KEYWORDS

Aloe Vera gel; Penetration; Enhancer; Skin permeation; Transdermal.

AUTHORS FOR AFFILIATION

*Corresponding author:

Kiran Sharma, Assistant Professor, KIET School of Pharmacy, 13 km stone Ghaziabad-meerut road, Ghaziabad. 201206 (U.P.)

Phone: 7838269630, E-mail: kiran.sharma@kiet.edu
INTRODUCTION

The transdermal route of drug administration offers many advantages, such as avoiding first-pass metabolism, needing less frequent dosing regimens as they produce release for long periods of time, availability of a relatively large surface area for absorption and increased patient acceptability because of its non-invasiveness. However, the outermost layer of the skin, the stratum corneum (SC), offers a formidable physical barrier to molecular transport. This layer is very specific with regards to the type of molecule that can be transported across the skin and therefore only molecules with certain physicochemical properties can readily cross the skin. This limits the range of potential drugs that can be administered transdermally, which emphasizes the need for formulations to incorporate penetration enhancers to assist in the effective delivery of a larger variety of drugs across the skin.

There are many approaches were employed to enhance the skin permeation rate of active moieties. However, the most convenient and widely implemented approach is the use of penetration enhancer. They are used to enhance the penetration rate of drugs across the skin by means of two possible mechanisms of action. Firstly, the penetration enhancer can work by altering the solubility properties of the skin, thereby increasing the solubility of the drug within the SC; secondly, the enhancer disrupts the ordered nature of the skin lipids, which consequently influences diffusion across the SC.

There are synthetic permeation enhancers and natural permeation enhancers which will help in improving the transdermal permeation of poorly absorbed drugs. Chemical penetration enhancers such as DMSO, DMF, azone, ionic surfactants, but their use are also associated with unpleasant and toxic side effects. In recent years there has been a search for natural compounds as permeation enhancers to improve drug permeation that also exhibit low toxicity while maintaining their enhancing activity.

The natural absorption promoters documented so far include essential oils, terpenes, terpenoids, fatty acid esters, fatty acid glycols, and herbal extracts. The essential oils are nontoxic, non-allergic, and compatible with drug and excipients have received much attention of researchers and found one of the promising groups of candidates to be employed as clinically acceptable penetration enhancers. Essential oils present a large range of chemically acceptable and relatively safe penetration enhancers to aid percutaneous drug delivery and are considered as GRAS (generally regarded as safe) compounds for medicinal use. They have been reported to use for permeation enhancement of both hydrophilic and lipophilic drugs. They cause no skin toxicity or if any, only mild irritation.

The use of natural products as effective and safe drug permeation enhancers is receiving considerable attention. One such a natural product, *Aloe Vera* (*Aloe barbadensis* Miller) juice, has shown potential to enhance the permeation of certain drug molecules through porcine ear skin membranes. *Aloe* is a genus consisting of more than 400 different species belonging to the Xanthorrhoeaceae family. *A. vera* has generally been researched to a larger extent for its medicinal properties and other applications of all the aloe species. It is therefore important to include more aloe species in further investigations. It was suggested that the mucilaginous gel of the aloe, consisting mainly of polysaccharides, holds the secret to some of the medicinal properties and biological effects of this family of plants, which was confirmed for drug absorption enhancement across intestinal epithelial cells.
Pathway of transdermal permeation

Permeation can occur by diffusion via:–

1. Transdermal permeation, through the stratum corneum.
2. Intercellular permeation, through the stratum corneum.
3. Transappendaged permeation, via the hair follicle, sebaceous and sweat glands\textsuperscript{37}.

Most molecules penetrate through skin via intercellular micro route and therefore many enhancing techniques aim to disrupt or bypass its elegant molecular architecture\textsuperscript{13}. Simplified model of the human skin for mechanistic analysis of skin permeation (Figure 1) shows the protective function of human skin imposes physicochemical limitations to the type of permeate that can traverse the barrier\textsuperscript{9}. For a drug to be delivered passively via the skin it needs to have adequate lipophilicity and also a molecular weight <500 Da. These requirements have limited the number of commercially available products based on transdermal or dermal delivery. Various strategies have emerged over recent years to optimize delivery and these can be categorized into passive and active methods. The passive approach entails the optimization of formulation or drug carrying vehicle to increase skin permeability. Passive methods, however do not greatly improve the permeation of drugs with molecular weights >500 Da\textsuperscript{25}.

\textbf{Aloe Vera}

\textit{Aloe Vera} (syn. \textit{Aloe barbadensis} Mill., Fam. Liliaceae), also known as Barbados or Curaçao. It is the source of two main products, the first is a yellow exudates from the cut leaf base which contains a high concentration of anthraquinone compounds and the second product is the gel which is obtained by pressing the whole leaf. \textit{Aloe Vera} gel is used as an ethno medicine in Trinidad and
Tobago for hypertension\textsuperscript{30}. The most common folk use of aloe has been for the treatment of burn wounds and specifically to aid in the healing process, reduce inflammation, and tissue scarring. The gel was described by Dioscorides and used to treat wounds and mouth infections, soothe itching, and cure sores\textsuperscript{2}.

**Description**

*Aloe Vera* is a succulent plant with thick, fleshy, serrated, lanceolate-shaped leaves of green-grayish color. The *Aloe* leaf can be divided into two major parts, namely the outer green rind, including the vascular bundles, and the inner colorless parenchyma containing the aloe gel\textsuperscript{27}. Description of the inner central part of the aloe leaf may sometimes be confusing, due to the different terms that are used interchangeably such as inner pulp, mucilage tissue, mucilaginous gel, mucilaginous jelly, inner gel and leaf parenchyma tissue. Technically, the term, pulp “or ‘parenchyma tissue refers to the intact fleshy inner part of the leaf including the cell walls and organelles, while gel” or mucilage, refers to the viscous clear liquid within the parenchyma cells\textsuperscript{17}.

The three structural components of the *Aloe Vera* pulp are the cell walls, the degenerated organelles and the viscous liquid contained within the cells. These three components of the inner leaf pulp have been shown to be distinctive from each other both in terms of morphology and sugar composition\textsuperscript{23}.

**Chemistry**

The raw pulp of *A. vera* contains approximately 98.5% water, while the mucilage or gel consists of about 99.5% water. The remaining 0.5 – 1% solid material consists of a range of compounds including water-soluble and fat-soluble vitamins, minerals, enzymes, polysaccharides, phenolic compounds and organic acids (Table 1). It has been hypothesized that this heterogeneous composition of the *Aloe Vera* pulp may contribute to the diverse pharmacological and therapeutic activities which have been observed for aloe gel products\textsuperscript{27}. The dry matter (0.9%) can be divided into 3 distinct fractions: cell wall, micro particles, and liquid gel [accounting for 16.2%, 0.7%, and 83.1% of dry pulp (w/w), respectively]. The predominant sugar component is mannose as mannose-6-phosphate in all 3 fractions [20.4% in cell wall, 32.2% in micro particles, and 62.9% in the liquid gel (% of total sugars)], followed by other sugars in varying concentrations depending on the fraction. Overall, the 5 neutral sugars (ie, arabinose, xylose, mannose, galactose, glucose) account for 69.2% of the total sugars in the gel. Mucopolysaccharides are mainly present as acemannan [a highly acetylated, $\beta$-1-4-linked polysaccharide (> 1kDa) made mainly of mannose] with various side chain glycosylation patterns\textsuperscript{4}. The anthraquinone content should be below 50 ppm and is considered an impurity from the leaf extract of *Aloe Vera*. Other ingredients include various amino acids, enzymes, and vitamins, which have not been quantified. According to a certification program, in which “whole *Aloe Vera* leaf gel” has to adhere to the following specifications: solids (0.46%–1.31%); pH (3.5–4.7); calcium (98.2–448 mg/L); magnesium (23.4–118 mg/L; malic acid (817.8–3,427.8 mg/L); acemannan in raw materials ($\geq$5% by dry weight); isocitrate ($\leq$5% for inner leaf by dry weight); raw materials ash content ($\leq$40%); aloin ($\leq$10 ppm in 0.5% *Aloe Vera* solids solution for oral consumption)\textsuperscript{35}. Quality products should contain high amounts (95%) of pure *Aloe Vera* gel. One way of quantifying aloe polysaccharides is a colorimetric assay, which has been suggested for use in quality control of commercial products. Quality control and identification of commercial *Aloe Vera* products has also been accomplished by nuclear magnetic resonance spectrometry\textsuperscript{14}.
Table 1: Summary of the chemical composition of *A. vera* leaf pulp and exudates.

<table>
<thead>
<tr>
<th>Class</th>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthraquinones/anthrones</td>
<td>Aloe-emodin, aloetic-acid, anthranol, aloin A and B (or collectively known as barbaloin), isobarbaloin, emodin, ester of cinnamic acid</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Pure mannann, acetylated mannann, acetylated glucomannan, glucogalactomannan, galactan, galactogalacturan, arabinogalactan, galactoglucoarabinomannan, pectic substance, xylan, cellulose</td>
</tr>
<tr>
<td>Chromones</td>
<td>8-C-glucosyl-(2’-O-cinnamoyl)-7-O-methylaloediol A, 8-C-glucosyl-(S)-aloesol, 8-C-glucosyl-7-O-methyl-(S)-aloesol, 8-C-glucosyl-7-O-methylaloediol, 8-C-glucosyl-noreugenin, isoaloeresin D, isorabaichromone, neoaloesin A</td>
</tr>
<tr>
<td>Enzymes</td>
<td>Alkaline phosphatase, amylase, carboxypeptidase, catalase, cyclooxida, cyclooxygenase, lipase, oxidase, phosphoenolpyruvate carboxylase, superoxide dismutase</td>
</tr>
<tr>
<td>Inorganic compounds</td>
<td>Calcium, chlorine, chromium, copper, iron, magnesium, manganese, potassium, phosphorous, sodium, zinc</td>
</tr>
<tr>
<td>Miscellaneous including</td>
<td>Arachidonic acid, γ-linolenic acid, steroids (campesterol, cholesterol, β-sitosterol), triglicerides, triterpenoid, gibberillin, lignins, potassium sorbate, salicylic acid, uric acid</td>
</tr>
<tr>
<td>organic compounds and lipids</td>
<td></td>
</tr>
<tr>
<td>Non-essential and essential</td>
<td>Alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, tyrosine, valine</td>
</tr>
<tr>
<td>amino acids</td>
<td></td>
</tr>
<tr>
<td>Proteins</td>
<td>Lectins, lectin-like substance</td>
</tr>
<tr>
<td>Saccharides</td>
<td>Mannose, glucose, L-rhamnose, aldopentose</td>
</tr>
<tr>
<td>Vitamins</td>
<td>B1, B2, B6, C, β-carotene, choline, folic acid, α-tocopherol</td>
</tr>
</tbody>
</table>

**ALOE VERA GEL**

Aloe (often called *Aloe Vera*) produces two substances, gel and latex, which are used for medicines. Aloe gel is the clear, jelly-like substance found in the inner part of the aloe plant leaf. Aloe latex comes from just under the plant's skin and is yellow in color36.
Aloe Vera Gel is the viscous, transparent and colorless mucilaginous gel obtained from the parenchymatous cells in the fresh leaves of Aloe Vera. It is succulent, almost sessile perennial herb; leaves 30–50 cm long and 10cm broad at the base; color pea-green (when young spotted with white); bright yellow tubular flowers 25–35 cm in length arranged in a slender loose spike; stamens frequently project beyond the perianth tube.

**Major constituents**

Aloe Vera Gel consists primarily of water and polysaccharides (pectins, hemicelluloses, glucomannan, acemannan, and mannose derivatives). It also contains amino acids, lipids, sterols (lupeol, campesterol, and β-sitosterol), tannins, and enzymes. Mannose 6-phosphate is a major sugar component.

At present no commercial preparation has been proved to be stable. Because many of the active ingredients in the gel appear to deteriorate on storage, the use of fresh gel is recommended. Preparation of fresh gel: harvest leaves and wash them with water and a mild chlorine solution. Remove the outer layers of the leaf including the pericyclic cells, leaving a "fillet" of gel. Care should be taken not to tear the green rind which can contaminate the fillet with leaf exudate. The gel may be stabilized by pasteurization at 75–80°C for less than 3 minutes. Higher temperatures held for longer times may alter the chemical composition of the gel.

**Skin penetration enhancement activity**

Aloe Vera has an element called “Lignin” which helps it to penetrate right down to the cellular level. It also has another element called “Saponin” which works as a natural cleansing agent. Both these elements working in conjunction reach the cellular level of the skin. In addition to this, it also nourishes the skin and replenishes it with the much needed nutrition that it requires. Along with this it increases the in vitro skin penetration of some compounds depending on their molecular weights, with an apparent inverse correlation between enhancement ratio and molecular weight of the compound. This penetration enhancement effect of the aloe gel was explained by a probable pull effect of complexes formed between the compound and the enhancing agent within the aloe gel, but it was stated that the proposed mechanism of action has to be further investigated and confirmed.

Some constituents of the A. vera gel itself also penetrated the skin and this was interestingly dependent on the molecular weight of the co-applied compounds. The higher the molecular weight of the co-applied compound, the less of the gel components were transported across the skin. This was explained by the probable displacement of A. vera components from the penetration pathways and thereby it inhibits permeation of the gel components more effectively than the smaller compounds. Another proposed mechanism is through facilitated permeation i.e. transient reduction in barrier resistance of stratum corneum and intracellular transport by dekeratinization of corneocytes which may be attributed to the presence of triglycerides as constituents of Aloe Vera.

**Other proposed Mechanisms of Action**

- Stimulation of macrophage and fibroblast activity, increased collagen and proteoglycan synthesis.
• Mannose-6-phosphate binds to growth factor receptor on fibroblasts and enhances their activity\(^6\).

• Macrophage activation through increased nitric oxide synthases activity by acemannan, leading to release of fibrogenic cytokines\(^{24}\).

• Up regulation of phagocytosis and fungicidal activity of macrophages by acemannan\(^{28}\).

• Acemannan and other cell wall biomaterial may promote stability of growth factors and prolong stimulation of granulation tissue\(^{11}\).

• Inhibition of Thromboxan A\(_2\)\(^{23}\).

• May promote hypoglycemic effect by normalizing membrane-bound enzyme activities of phosphatases and hydrolases and increased glucose metabolism; potential active\(^{29}\) compounds include the phytosterols lophenol, cycloartenol and their alkylated derivatives

• Anti-inflammatory effect of plant sterols like lupeol, campesterol, and \(\beta\)-sitosterol through bradikinase activation, prostaglandin F2 and E2, as well as thromboxane A2 inhibition and inhibition of IL-10 secretion\(^6\).

• Inhibitory effect on release of reactive oxygen species from human neutrophils by reducing intracellular free calcium levels\(^{23}\).

• Increase in mRNA expression of metalloproteinases and plasminogen activator may lead to angiogenic activity in endothelial cells\(^{11}\).

**Adverse Effects**

In general, topical application of *Aloe Vera* preparations has been regarded as safe however; several case reports of the development of hypersensitivity reactions and contact dermatitis in response to topically applied aloe gel preparations. This allergic reaction has been attributed in most cases to anthraquinone contaminations in the gel\(^{21}\). Macrophage infiltration and emesis has been observed in dogs treated intravenously with acemannan. Oral application of *Aloe Vera* gel may lower blood glucose levels and enhance the activity of antidiabetic treatments. No genotoxic effects have been observed following administration of an *Aloe Vera* inner leaf gel. An important factor for adverse effects is the purity of the *Aloe Vera* gel used, since anthraquinones like aloin might be related to the development of hypersensitivity reactions\(^{19}\).

**Drug Interactions**

When *Aloe Vera* gel is administered topical, it is generally regarded as safe. Aloe gel might enhance the ability of hydrocortisone to reduce swelling if applied topically\(^{10}\). If ingested, it might lead to increased hypoglycemia in conjunction with oral antidiabetics or insulin. The American Pharmaceutical Association rates *Aloe Vera* gel for external use in category 2, meaning that “according to a number of well-designed studies and common use, this substance appears to be relatively effective and safe when used in recommended amounts.” *Aloe Vera* inner gel may significantly increase the absorption of vitamins C and E\(^{24}\). *Aloe Vera* gel for systemic application is not recommended in combination with antidiabetic, diuretic, or laxative drugs; sevoflurane; or
digoxin\textsuperscript{20}. In general, if Aloe Vera gel is used with any other prescription drug, the patient should inform the physician and/or pharmacist.

**CONCLUSION**

Penetration enhancers are applied to improve the permeation of the poor permeable drug through the skin. They do not have any therapeutic effect but they enhance the penetration of drugs across the membrane. Aloe Vera seems to enhance the penetration for certain drugs molecules across the skin along with skin hydrating and anti-inflammatory effects. Since the external use of aloe on intact skin is not associated with adverse reactions and is generally regarded as safe, the use of this natural resource as a penetration enhancer is promising.

**REFERENCES**


