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RESEARCH ARTICLE

Magnetophoresis in combination with chemical enhancers for transdermal drug delivery

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Abstract

Purpose: The objective of the present work was to investigate the effect of combination of a novel physical permeation enhancement technique, magnetophoresis with chemical permeation enhancers on the transdermal delivery of drugs.

Methods: The *in vitro* drug transport studies were carried out across the freshly excised abdominal skin of Sprague-Dawley rats using transdermal patch systems (magnetophoretic and non-magnetophoretic) of lidocaine hydrochloride (LH). LH gel prepared using hydroxypropyl methylcellulose (HPMC) was spread over the magnets as a thin layer. To investigate the effect of chemical permeation enhancers, menthol, dimethyl sulfoxide, sodium lauryl sulfate and urea (5% w/v) were incorporated in the gels prior to loading on the patch system.

Results: The flux of lidocaine from magnetophoretic patch was ~3-fold higher (3.07 ± 0.43 μg/cm^2/h) than that of the control (non-magnetophoretic patch) (0.94 ± 0.13 μg/cm^2/h). Incorporation of chemical permeation enhancers in the gel enhanced the magnetophoretic delivery flux by ~4 to 7-fold.

Conclusions: The enhancement factor due to combination of chemical permeation enhancer was additive and not synergistic. Mechanistic studies indicated that magnetophoresis mediated drug delivery enhancement was via appendageal pathway.

Keywords: Transdermal patch system, magnetophoresis, chemical permeation enhancers, lidocaine hydrochloride, *in vitro* drug permeation

Introduction

Transdermal drug delivery route has been preferred over other routes of drug delivery due to ease of drug administration, avoidance of first pass effect, controlled and prolonged drug delivery and ease of termination of therapy. However, transdermal drug delivery is limited due to the barrier property of the outer most layer of the skin, stratum corneum. The drug molecule has to penetrate across the stratum corneum barrier in order to reach the deeper dermal region[1–3]. Until now, various chemical enhancers and physical permeation enhancement techniques have been investigated for overcoming the stratum corneum barrier and enhancing the transdermal delivery of drugs[4–9]. In general, physical permeation enhancement techniques are more efficient than chemical enhancers. Several research groups have studied the effect of combination of chemical enhancers and physical permeation enhancement techniques like iontophoresis, electroporation and ultrasound to assess the plausibility of deriving synergistic benefits. Use of a combination of enhancers is reported to mutually enhance the efficacy and also increase the safety of enhancers. Oh et al. have reported that the transdermal transport of zidovudine was enhanced synergistically when iontophoresis was used in combination with chemical enhancers like propylene glycol and oleic acid[10]. Ganga et al. showed that the combination of Azone and iontophoresis enhanced transdermal permeation of metoprolol synergistically[11]. Combination of ultrasound and sodium lauryl sulfate (SLS) was reported to result in

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synergistic enhancement in permeation of mannitol by Mitragotri et al.[12]. Magnetophoresis is a phenomenon of enhancing drug permeation across the biological barriers by application of magnetic field. Previous work by Murthy et al. has shown that magnetophoresis leads to enhanced transdermal drug delivery in *in vitro* and *in vivo* studies[13]. The predominant mechanism for drug permeation enhancement was found to be magnetokinesis and enhanced partitioning of drug into stratum corneum.

The main objective of this study was to investigate the effect of chemical enhancers on the magnetophoretically mediated transdermal drug delivery. The other objective was to investigate the potential mechanisms contributing to the drug delivery enhancement across the skin in case of magnetophoresis. In this manuscript, the experimental data regarding permeation enhancement of lidocaine hydrochloride (LH) using chemical enhancers and magnetic field will be provided first followed by mechanistic studies[14,15].

Materials and methods

Materials

LH was obtained from Spectrum Chemicals (New Brunswick, NJ). Estradiol, ferric pyrophosphate (FPP), menthol, dimethyl sulfoxide (DMSO) and SLS were purchased from Sigma-Aldrich Inc. (St. Louis, MO). PBS 10x liquid concentrate and urea were procured from EMD Chemicals Inc. (Cincinnati, OH) and all other chemicals and reagents were obtained from Fischer Scientific (Fairway, NJ). Neodymium magnets were purchased from K&J Magnetics Inc. (Jamison, PA).

Drug transport from transdermal patch systems

The *in vitro* transport of LH from transdermal patch systems across the freshly excised rat abdominal skin was studied using vertical Franz diffusion cells (diffusional area of 0.64 cm^2 and receiver compartment volume of 5 mL). The barrier integrity of rat skin was confirmed by measuring the electrical resistance according to previously published methods, and pieces of skin that had a resistance >20 $k\Omega \cdot cm^2$ were only used for the drug transport studies[16]. Electrical resistance is considered to be an equally suitable method compared to tritiated water flux method and has the advantage of being more sensitive than TEWL for confirming barrier integrity of skin[17].

The design of transdermal patch system was similar to our recent publication by Murthy et al.[13]. LH (2% w/w) containing gel was prepared in HPMC base (4% w/v) using deionized water and was spread over the magnets as a thin layer, which acts as drug reservoir. DMSO, urea and SLS were incorporated in the gels prepared in deionized water, whereas menthol was incorporated in gel prepared in hydroalcoholic solution (water:alcohol, 70:30). The receiver compartment of diffusion cell was filled with PBS and drug transport studies were carried out by placing gel-filled transdermal patches over the skin with samples withdrawn at regular intervals of time over a period of 8 h.

Drug transport studies across sandwich epidermis model

The mechanistic studies were carried out across the sandwich epidermis model prepared using stratum corneum and porcine epidermis obtained from porcine skin. Sandwich epidermis model includes a layer of stratum corneum overlaid on porcine epidermis. Stratum corneum samples were prepared from porcine epidermis floated overnight on a aqueous solution containing 0.0001% w/v of trypsin and 0.5% w/v sodium bicarbonate at 37°C according to method followed by Essa et al. and El Maghraby et al.[14,15].

Passive and iontophoretic delivery of LH, estradiol and FPP were carried across sandwich epidermis and single layer epidermis and the steady state flux was calculated. In case of LH transport studies, the receiver compartment of diffusion cell was filled with 5 mL of PBS, pH 7.4 and donor compartment was filled with 0.5 mL of LH (10 mg/mL) in PBS, pH 7.4. In case of estradiol transport studies, the receiver compartment was filled with 5 mL of PBS, pH 7.4 containing 10% HPßCD and the donor compartment was filled with 0.5 mL of estradiol (0.25 mg/mL) in PBS, pH 7.4 containing 40% alcohol. In case of FPP transport studies, the receiver compartment was filled with 5 mL of PBS, pH 5 and the donor compartment was filled with 0.5 mL of FPP (50 mg/mL) in PBS, pH 5. Anodal iontophoresis was carried out for LH and estradiol, whereas cathodal iontophoresis was used for FPP. In all the cases, 0.3 mA/cm^2 of electric current was applied using an Iomed Phoresor.

Analytical method

The amount of LH and estradiol were analyzed by high performance liquid chromatography and FPP was analyzed by UV spectrophotometer. The HPLC system (Waters, MA) consisted of a chromatographic pump (Waters 1525), autosampler (Waters 717 plus) and an UV absorbance detector (Waters 2487). Symmetry® C18 column (4.6 × 150 mm) was used for analysis of LH and the mobile phase consisted of a mixture (14/86 v/v) of acetonitrile and potassium dihydrogen phosphate 0.05 M (pH adjusted to 4.0) with a flow rate of 1.3 mL/min at 216 nm[18]. Phenomenox® Luna C18 column (4.6 × 150 mm) was used for analysis of estradiol and the mobile phase consisted of mixture of acetonitrile and 0.1% ortho-phosphoric acid (6:4) with a flow rate of 1 mL/min at 212 nm[19]. FPP samples were analyzed at 510 nm using UV spectrophotometer after the addition of Ferrover® reagent[20].

Statistical analysis

Statistical analysis was carried out using GraphPad InStat 3 software. Unpaired t-test was performed and $P < 0.05$ was considered as the level of significance. All the data

are represented as average of 3–5 trials with standard deviation.

Results and discussion

Development of transdermal patch system incorporated with chemical enhancer and magnetic backing

The design of patch systems was similar to that discussed in the recent publication[13]. In brief, the magnetophoretic patch system consists of magnets arranged in parallel on the adhesive backing membrane. A row of magnetic blocks was used instead of a single magnet mainly to impart flexibility to the patch system. Magnets in the backing membrane were replaced with nonmagnetic pieces in case of non-magnetophoretic patches. The patches containing nonmagnetic backing were used to study the effect of chemical permeation enhancers on the delivery of drug from the patch system. The drug along with chemical enhancers incorporated in the gel was filled into the cavity of adhesive backing membrane. About 200 mg of gel was loaded onto the patch system, which contained LH equivalent to 2 mg.

Different chemical enhancers were incorporated into the gel to enhance the drug permeation across the skin. Menthol, urea, DMSO and SLS were the chemical enhancers investigated in this study. DMSO is known to be an effective permeation enhancer for both hydrophilic and lipophilic drugs. On application to skin, DMSO is known to denature the proteins and change the confirmation of intercellular keratin from α helical to ß sheet and also interacts with the intercellular lipid regions of the stratum corneum[21–23]. Terpenes have been reported to be safe and effective permeation enhancers for both hydrophilic and lipophilic drugs[24]. Menthol has been studied as permeation enhancer for hydrophilic drugs like 5-fluorouracil and propranolol hydrochloride[25,26]. The main reason for enhancement of permeation of hydrophilic drugs by menthol is due to the disruption of the stratum corneum lipids by breakage of hydrogen bonds between the ceramide groups[27]. Urea has been known to act as a skin permeation enhancer by increasing the stratum corneum water content and thus leading to opening of hydrophilic diffusion channels within the stratum corneum[9,23]. SLS is known to solubilize the stratum corneum lipids and also interact with keratin to enhance the overall skin permeability[9].

Magnetophoresis mediated drug delivery enhancement

The passive permeation flux of LH across the rat skin was found to be 0.94 ± 0.13 μg/cm²/h. The permeation flux of LH was enhanced by ~3-fold (3.07 ± 0.43 μg/cm²/h) in case of magnetophoretic patch system compared to that of passive. Previous studies by Murthy et al. carried out across the porcine epidermis resulted in an 8-fold enhancement in permeation flux over control[13]. The difference in enhancement factors between the previous report and the present studies is likely because of the difference in the skin model and nature of the drug reservoir employed in the study.

Effect of chemical enhancers on the drug delivery

Incorporation of chemical enhancers has resulted in an increase in the permeation flux of LH compared to control (gel without any chemical enhancer). The concentration of all the four enhancers used in the present study was at 5% w/v. The drug permeation enhancement factor of different enhancers could be represented in the following decreasing rank order: menthol > SLS > urea > DMSO. Incorporation of menthol in the gel formulation resulted in ~3.7-fold enhancement (3.50 ± 0.69 μg/cm²/h) in the flux of LH. Due to limited solubility of menthol in the aqueous vehicle, 30% v/v of alcohol was used in the gel formulation to incorporate menthol (the flux enhancement by 30% v/v alcohol alone in absence of menthol was found to be ~1.4-fold over control). SLS resulted in ~2.6-fold enhancement (2.44 ± 0.39 μg/cm²/h) in the permeation flux over the control patch. On the other hand, urea and DMSO lead to ~1.7-fold (1.62 ± 0.27 μg/cm²/h) and ~1.1-fold (1.07 ± 0.24 μg/cm²/h) enhancement in the flux over the control patch. Among the enhancers, menthol and SLS resulted in greater enhancement compared to urea and DMSO. Except DMSO, all the other chemical enhancers showed a significant enhancement in the flux of LH (Figure 1). The effect of pretreatment was not considered because the effective pretreatment varies with each chemical enhancer and would not clearly reflect the relative efficiency. Moreover, in real life situation, the patch containing combination of chemical enhancers and magnetophoresis will be applied by the

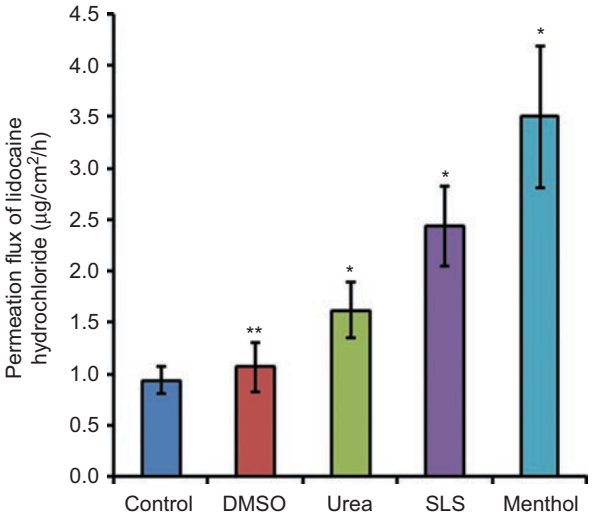

Figure 1. Transdermeal permeation flux of lidocaine hydrochloride from non-magnetophoretic patch systems. 'Control' indicates patch system without any chemical enhancer. **Indicates statistically insignificant and *indicates statistically significant compared to control.

patients. Therefore, the studies included simultaneous application of both the enhancers (chemical enhancers and magnetophoresis) in the patch system to simulate the *in vivo* practice.

Effect of combination of chemical enhancers and magnetophoresis on the drug delivery

Combination of chemical enhancers and magnetophoresis resulted in enhanced permeation flux compared to both individual chemical enhancer effect and magnetophoretic effect and was additive in most of the cases (Table 1). Definitely, there was a significant increase in the enhancement efficiency with this combination approach. Moreover, the results clearly demonstrated the feasibility of incorporating chemical permeation enhancers and magnetophoresis technique in a simple transdermal patch system, which could be of potential benefit in enhancing the transdermal delivery of poorly permeable drugs. The plausible reason for an additive effect is likely due to the difference in the predominant mechanism of drug delivery enhancement between the chemical enhancers and magnetophoresis. Among the enhancers used, menthol and SLS are known to act predominantly on the lipoidal regions, whereas DMSO and urea act on the keratinocytes. Our earlier studies have shown that the magnetically mediated transdermal drug delivery is more likely due to interaction of the magnetic field with the drug molecule than with the stratum corneum barrier. In the mechanistic studies narrated in this paper, we used sandwich epidermis model to elucidate the predominant mechanism of enhancement of drug delivery by the application of magnetic field.

Mechanistic studies

In a recent report, the results of the mechanistic studies clearly demonstrated that magnetokinesis was the predominant mechanism responsible for enhanced transdermal permeation[13]. However, the relative contribution of appendageal pathway in magnetokinesis has not been investigated. Mechanistic studies were carried out using sandwich epidermis model developed by El Maghraby et al. to elucidate the role of appendageal pathway in drug permeation across the skin[14]. In the sandwich epidermis model, the stratum corneum layer overlaid on the epidermal membrane forms the top layer and blocks most of the appendageal pathways present in underlying epidermal membrane (Figure 2).

In this study, porcine epidermis was used to carry out mechanistic studies using sandwich model due to ease of separation of epidermis when compared to rat skin.

El Maghraby et al. have carried out permeation studies across the sandwich epidermis and compared it with that across the epidermis alone[14]. The authors reported that the permeation through sandwich epidermis model would be much reduced in comparison to epidermis if appendageal pathway played an active role in the permeation of drug. It was reported that appendageal pathway played only a minor role in the penetration of liposomal formulations containing estradiol[14]. Essa et al. used the same model to examine the role of skin appendages in the passive, iontophoresis and liposomal penetration of drugs and reported that the appendageal pathway played a major role in the passive permeation of hydrophilic mannitol, whereas it was negligible in case of lipophilic estradiol[15]. The authors also reported that the appendageal pathway had a significant role in the flux enhancement by iontophoresis[14,15].

Initially, a few set of experiments were dedicated to validate the sandwich epidermis model reported by El Maghraby et al. Permeation studies were carried out using LH, estradiol and FPP. LH is a cationic hydrophilic drug and estradiol is lipophilic in nature. FPP represents a high molecular weight anionic hydrophilic compound. Therefore, the three marker drugs differ in their extent and pathways of transdermal permeation.

Passive permeation studies across sandwich epidermis and single layer epidermis

The passive permeation flux ratio of sandwich model to single layer epidermis ($F_{SW/SL}$) would be close to 0.5, if appendageal pathway had no role in drug permeation and the $F_{SW/SL}$ would be <0.5 and close to zero if the drug permeation was via appendageal pathway. In general, highly hydrophilic drugs permeate through skin mainly via appendageal pathway, whereas lipophilic drugs permeate mainly through the bulk of the skin[28,29]. Based on this, one would expect $F_{SW/SL}$ would be <0.5 for LH and FPP which are hydrophilic and 0.5 for estradiol, which is lipophilic in nature.

The steady state flux of LH was found to be 1.45 ± 0.02 μg/cm²/h across the single layer porcine epidermis. The flux decreased significantly to 0.24 ± 0.01 μg/cm²/h across the sandwich epidermis (Figure 3A). The $F_{SW/SL}$ was ~0.16 indicating that the appendageal pathway

Table 1. Transdermal permeation flux of lidocaine hydrochloride from non-magnetophoretic and magnetophoretic patch system. 'Control' in the table indicates patch system without any chemical enhancer. Enhancement factor is the ratio of permeation flux obtained with respect to flux from control (non-magnetophoretic patch system).

	Non-magnetophoretic patch		Magnetophoretic patch	
Enhancer	Permeation flux (μg/cm²/h)	Enhancement Factor	Permeation flux (μg/cm²/h)	Enhancement Factor
Control	0.94 ± 0.13	1.00	3.07 ± 0.43	3.26
DMSO	1.07 ± 0.24	1.13	3.82 ± 0.48	4.06
Urea	1.62 ± 0.27	1.72	4.85 ± 0.24	5.15
SLS	2.44 ± 0.39	2.59	4.93 ± 0.37	5.24
Menthol	3.50 ± 0.69	3.72	6.06 ± 0.43	6.44

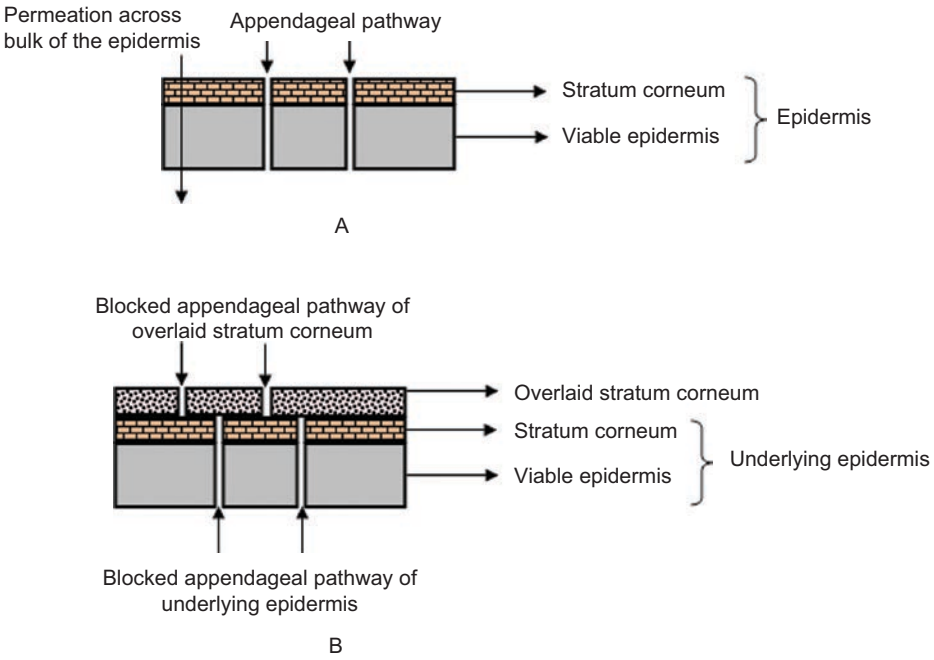

Figure 2. 2A represents single layer epidermis with unblocked appendageal pathway, and 2B represents sandwich epidermis with a stratum corneum layer overlaid on the epidermal membrane. Appendageal pathway of underlying epidermal membrane is blocked by the overlaid stratum corneum layer and appendageal pathway of the overlaid stratum corneum layer is blocked by the underlying epidermal membrane. In case of sandwich epidermis, the permeation flux of hydrophilic drugs which permeate mostly through appendageal pathway would be reduced by less than half and be close to zero due to blockage of appendageal pathway. However, the permeation flux of lipophilic drugs, which permeate mostly through the bulk of epidermis (non-appendageal pathway), would be reduced by half due to increase in thickness of the barrier, in the case of sandwich epidermis.

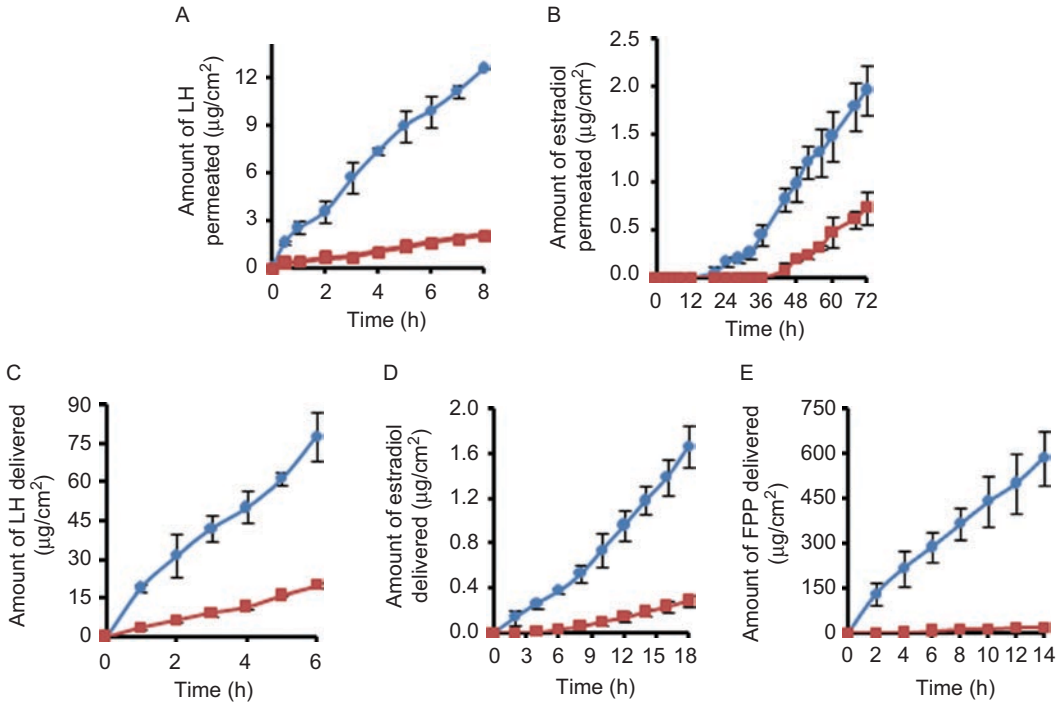

Figure 3. A, B represent the passive permeation, and C, D, E represent the iontophoretic delivery of lidocaine hydrochlodie (LH), estradiol and ferric pyrophosphate (FPP) across single layer epidermis (•) and sandwich epidermis (▪).

had a significant role in the passive permeation of LH (Table 2). However, the diffusion across the bulk of the epidermis is not completely negligible in this case. This is likely because of the presence of unionized fraction of the drug, which tends to selectively diffuse via bulk of the epidermis pathway.

The passive permeation flux of estradiol was found to be 0.042 ± 0.004 µg/cm²/h and 0.023 ± 0.003 µg/cm²/h

Table 2. Steady state flux of lidocaine hydrochloride, estradiol and ferric pyrophosphate following passive permeation and iontophoretic delivery across sandwich and single layer epidermis with corresponding flux ratios.

Drug	Flux (μg/cm²/h)		Flux ratio (sandwich/ single layer)	Role of appendageal pathway
	Sandwich epidermis	Single layer epidermis		
Passive permeation				
Lidocaine Hydrochloride	0.24 ± 0.01	1.45 ± 0.02	0.16	Significant
Estradiol	0.023 ± 0.003	0.042 ± 0.004	0.54	Insignificant
Ferric pyrophosphate	–	–	–	–
Iontophoretic delivery				
Lidocaine Hydrochloride[a]	2.86 ± 0.63	12.54 ± 1.98	0.22	Significant
Estradiol[b]	0.022 ± 0.002	0.111 ± 0.007	0.19	Significant
Ferric pyrophosphate[c]	1.58 ± 0.10	37.69 ± 4.68	0.04	Significant

[a]Anodal iontophoresis, [b]Anodal iontophoresis, [c]Cathodal iontophoresis
The potential mechanisms are electroosmosis and electrorepulsion in case of b and c, respectively. In case of a both electrorepulsion and electroosmosis contribute together.

across single layer epidermis and sandwich epidermis, respectively, with $F_{SW/SL}$ of 0.54 (Figure 3B, Table 2). The results indicate that the appendageal pathway did not play a significant role in the permeation of lipophilic estradiol and hence the flux was reduced by almost half across the sandwich epidermis. This was in agreement with the results reported by Essa et al. for estradiol permeation across the human epidermis[15].

FPP did not result in any passive permeation across the porcine epidermis, which could be due to its high molecular size and extremely hydrophilic nature.

Iontophoretic drug delivery across sandwich and single layer epidermis

Anodal iontophoresis would favor the transdermal delivery of LH and at pH over 5, both electroosmosis and electrophoresis contribute to the enhanced transport of drug. In case of estradiol, permeation could be enhanced only by electroosmosis mechanism due to lack of any charge on the molecule[15]. FPP was found to be poorly permeable across the skin by passive diffusion and the permeation could be enhanced significantly by cathodal iontophoresis at pH over 5. In case of FPP, recent studies by Murthy and Vaka have shown that electroosmosis does not play any role in the enhanced permeation and the main pathway for enhanced permeation by iontophoresis is through appendageal pathway[20]. Therefore, in the present study, anodal iontophoresis was carried out for LH and estradiol, whereas cathodal iontophoresis was carried out for FPP. The flux of LH across sandwich epidermis decreased to 2.86 ± 0.63 μg/cm²/h in comparison to 12.54 ± 1.98 μg/cm²/h across single layer epidermis and $^{I}F_{SW/SL}$ (ratio of iontophoretic flux across sandwich model to single layer epidermis) was found to be 0.22 (Figure 3C, Table 2). In case of estradiol $^{I}F_{SW/SL}$ was found to be 0.19 with a flux of 0.022 ± 0.002 μg/cm²/h across the sandwich epidermis model and 0.111 ± 0.007 μg/cm²/h in case of single layer epidermis (Figure 3D and Table 2). Assuming complete blockade of appendageal pathway, $^{I}F_{SW/SL}$ should be close to zero. But permeation of both lidocaine and estradiol was observed which might be due to the electroosmosis mediated transport of drug through the additional pores created in the bulk of the skin by application of iontophoresis. These results are in agreement with that reported by others[14,15]. Murthy and Vaka demonstrated that the iontophoretic delivery of FPP occurs only through appendageal pathway across the rat skin[20]. In this study using porcine epidermis, $^{I}F_{SW/SL}$ of FPP was only 0.04, with flux of 1.58 ± 0.10 μg/cm²/h and 37.69 ± 4.68 μg/cm²/h across sandwich and single layer epidermis, respectively (Figure 3E, Table 2). These results of the validation studies confirm that the appendageal pathway is almost completely blocked in the sandwich epidermis model, and it could serve as an excellent model to investigate the contribution of appendageal pathway in the drug transport. Barry has also proposed that sandwich epidermis model can be applied effectively to analyze appendageal pathway in case of ultrasound and magnetophoresis studies in addition to passive diffusion and electrical methods[30].

Therefore, the sandwich epidermis model was used in case of magnetophoresis mediated studies to elucidate the mechanism of appendageal pathway.

Magnetophoretic delivery of LH across sandwich and single layer epidermis

These studies were carried out to determine the extent of contribution of appendageal pathway in magnetically enhanced drug permeation. Drug permeation studies were carried out across porcine epidermis using transdermal patch system. The flux of LH from magnetophoretic patch system across single layer epidermis and sandwich epidermis was found to be 3.87 ± 0.30 μg/cm²/h and 0.99 ± 0.26 μg/cm²/h, respectively. The $^{M}F_{SW/SL}$ (ratio of magnetophoresis flux across the sandwich model to single layer epidermis) would have been close to 0.5 if appendageal pathway had no significant role in the drug permeation by magnetophoresis. But, $^{M}F_{SW/SL}$ was found to be 0.25 indicating that appendageal pathway played a significant role in the magnetophoretic delivery of LH.

From the mechanistic studies reported earlier and in the present paper, it is more evident that the magnetic field enhances the drug delivery across the skin predominantly by magnetokinesis across the appendageal pathway without significantly affecting the stratum corneum barrier. In addition, the present study indicates

that the use of chemical permeation enhancers, which interact with the bulk of the epidermis (non-appendageal region), would improve the overall drug delivery efficiency.

Conclusions

The results indicate that the magnetically mediated drug permeation enhancement could be further enhanced by incorporation of suitable chemical permeation enhancers. The magnetic systems were found to enhance the drug permeation via appendageal pathway.

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Declaration of interest

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