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Research Paper

Surface tension and wettability in transdermal delivery: a study on the in-vitro permeation of haloperidol with cyclodextrin across human epidermis

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Abstract

Objectives The aim of this work was to study the effect of surface tension and contact angle on the permeation of haloperidol across human skin using cyclodextrin derivatives.
Methods Surface tension and contact angle of randomly methylated β-cyclodextrin (RM β-CD) and hydroxypropyl β-cyclodextrin (HP β-CD) solutions were measured. Haloperidol solubility and molecular modelling were carried out using the two cyclodextrin derivatives. In-vitro skin permeation was carried out using human skin models.
Key findings The highest increase in drug solubility was observed when the drug was in solution with pH 5 when compared to non-ionised solution, resulting in a 128-fold increase in the intrinsic solubility of the drug. Surface tension measurements indicate a surface-active effect for RM β-CD and HP β-CD. Contact angle measurements showed that vehicles with higher skin wettability increased the contact of the drug with the skin surface and therefore resulted in higher drug permeation across human epidermis.
Conclusions It is concluded that transdermal flux of a drug through the skin may be optimised by controlling surface tension, drug solubility and skin wettability.
Keywords drug–cyclodextrin complexation; haloperidol; skin permeability; surface tension; wettability

Introduction

The stratum corneum presents a barrier to transdermal delivery of molecules, leading to sub-therapeutic drug effect. Chemical enhancers have therefore been used to increase the permeation of drug molecules. According to Fick's law of diffusion, the delivery rate of molecules is dependent on their physicochemical properties, partitioning coefficients and solubilities. Diffusion of a drug across the skin is a function of its solubility. Enhancers can modify drug solubility in the vehicle by means of increasing drug thermodynamic activity or drug concentration in the donor phase to help increase drug penetration across the skin.[1,2]

Haloperidol is a neuroleptic drug for schizophrenia, mania and similar psychotic states. This drug is practically insoluble in water and has a basic pK of 8.3. Haloperidol is a hydrophobic molecule (log P = 3.49) with a low molecular weight of 375.9 Da, making it a suitable candidate for transdermal application.[3,4]

Current approaches to solubilise water-insoluble drugs are complex formation with cyclodextrins, liposomes, microemulsion-based drug-delivery systems and supersaturation. Cyclodextrins (CDs) are attractive candidates for increasing the aqueous solubilities of lipophilic drugs. They are cyclic oligosaccharides of D-glucopyranose units in the shape of cones, each with an outer hydrophilic surface and an inner hydrophobic cavity. The solubilisation effect of CDs is due to the formation of a non-covalent water-soluble inclusion complex, which makes drug–CD complexes easily dissociated and in equilibrium with free drug.[4,5]

Due to the solubility, hygroscopicity and toxicity concerns regarding CDs, they have in general been modified and examples are hydroxypropyl β-CDs (HP β-CDs) and randomly methylated β-CD (RM β-CDs).[5–7] CD derivatives can influence the solubilities of drugs.[4,5,8] They can decrease local irritation at the site of application[9–11] as well as

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stabilise photosensitive drugs.[12] Some investigators have reported that CDs increase the skin permeation rates of drugs by extracting the lipid from the skin,[13–16] while others have reported that CDs do not show any enhancing effect on the flux rates of drugs through the skin.[17–19]

The pH of the vehicle influences the solubility and partitioning of the drug into the skin, implying that the ionised and unionised moieties of a drug influence its solubility and partitioning through the stratum corneum and hence affect the flux of drugs.[20–22] Wagner's group reported that pH values of donor and receptor compartments influence skin pH and change the skin permeability of the drug.[23] On the other hand, Sznitowska's team reported that there were no significant differences in the permeability of hydrocortisone in the pH range of 1–10 and only extreme pH values affected drug permeation across the skin.[24]

Drug absorption is directly related to the drug partition between the vehicle and the skin surface. Adhesion and wettability of the formulation to the skin surface are critical factors in therapeutic efficacy and can be determined from contact angle measurements. This defines the process used to counter the surface tension between drug vehicle and the skin surface to allow complete contact over the entire delivery surface.[25–28] The surface tension of human skin is 27–28 dyne/cm, and transdermal formulations with surface tension value equal to or less that this amount can therefore adhere to the skin surface. Reducing interfacial tension between the topical drug delivery system and the skin improves the contact between the drug and skin surface and facilitates drug transfer across the skin.[29–31]

The aim of the present work was to investigate the solubility and skin permeation of haloperidol from CD solutions. For this purpose the complexation of haloperidol with two derivatives of β-CD (RM β-CD and HP β-CD) was studied by the phase solubility method. Molecular modelling was conducted using dimethyl-β-cyclodextrin (DM β-CD) and HP β-CD. Surface tension and contact angle measurements were carried out to further elucidate the effect of CDs on the permeability of haloperidol though human epidermis. The effect of concentrations of RM β-CD alone and then combined with limonene on the skin permeation were studied. To elucidate the influence of pH of the donor phase on skin permeability, further experiments using phosphate buffer at pH 5 in the donor compartment, alone and also in combination with RM β-CD, were carried out. Then, RM β-CD was added to the receptor solution to maintain a sink condition, while the donor compartment consisted of solutions of haloperidol in RM β-CD or propylene glycol.

Materials and Methods

Materials

Haloperidol, droperidol, limonene and propylene glycol were purchased from Sigma, Singapore. 2-hydroxypropyl-β-cyclodextrin (HP β-CD) (degree of substitution of about 0.6) and RM β-CD (degree of substitution of about 1.8) were kind gifts from Roquette (Lestrem, France) and Wacker (Burghausen, Germany), respectively. HPLC grade acetonitrile was obtained from Tedia (USA). Milli-Q water (18 MΩ·cm at 25°C), generated from a Millipore Direct-Q ultra-pure water system (Billerica, USA), was used to prepare the buffer solutions and other aqueous solutions.

HPLC analysis

Haloperidol concentration was quantified by HPLC using a Shimadzu (Kyoto, Japan) 2010A. The analysis was carried out using a reversed-phase Waters Symmetry Shield column (3.5 μm, 3.0 mm × 100 mm). The mobile phase was a 55:45 volume ratio of acetonitrile and 0.05 M phosphate buffer adjusted to pH 3 using phosphoric acid, flowing at a rate of 0.4 ml/min. UV detection at wavelength 254 nm, injection volume 100 μl gave a retention time of 3.5 and 5 min for the internal standard (droperidol) and haloperidol, respectively. Standard solutions of haloperidol (0.05–2 μg/ml) and droperidol (0.2 μg/ml) were prepared in 0.03% v/v lactic acid.[3]

Phase solubility studies

Drug–CD inclusion complexes were prepared by adding an excess concentration of haloperidol (15 mg/ml), dissolved in water or buffer phosphate (pH 5), using RM β-CD and HP β-CD solutions of different concentrations (0, 0.01, 0.05, 0.1, 0.2, 0.3 M). The suspensions were shaken on a horizontal rotary shaker in the absence of light for 7 days and finally filtered through a membrane filter (Millipore filters, 0.45 μm pore size, 25 mm diameter) to obtain clear solutions. All samples were prepared in triplicate. The concentrations of haloperidol in the inclusion complexes were determined by HPLC assay.

Molecular modelling

Molecular modelling was carried out to elaborate the complexation modes. DM β-CD was adopted as a substitute for RM β-CD (degree of substitution = 1.8) to facilitate the determination of the stable structure of the haloperidol–RM β-CD complex because RM β-CD is a mixture of different structures. HP β-CD with a degree of substitution of 0.6 was used for the experimental study; four 2-hydroxypropyl groups were added on the primary hydroxyl groups of β-cyclodextrin.[32] The structures of haloperidol, DM β-CD and HP β-CD were individually minimised by MMFF94s force field using SYBYL software, version 7.2 (Tripos Co., USA). After thorough minimisation, docking experiments were carried out on all molecules using the 'Dock' module in SYBYL. This allowed the haloperidol to move within the energy field of the DM β-CD or HP β-CD in order to find its preferred binding geometries. The haloperidol molecule in its favourable conformation was introduced into the respective DM β-CD and HP β-CD cavities and the interaction energies were computed. The most likely conformation of each complex was the one with the lowest interaction energy.

Measurements of surface tension and contact angle

Surface tensions of solutions were measured by the Du Nouy ring method at room temperature (20 ± 2°C) using a digital tensiometer (Sigma 700 KSV Instruments, Helsinki, Finland).

The precision of the force transducer of the tensiometer was 0.01 mN/m. A Du Nouy ring with a platinum–iridium ring having a mean diameter of 9.545 mm was employed. Following each measurement, the ring was washed with Milli-Q water and subjected to a high temperature flame to ensure complete removal of residues. Maximum surface tension values of each concentration and a total of three surface tension measurements for each solution were obtained. The surface tensions of RM β-CD and HP β-CD were measured using 17 different concentrations. The surface tension of each formulation used in the permeation study was also measured using the same method.

The wettability of the excised human skin sample was determined by sessile drop contact angle using a Rame-Hart 100 goniometer (USA). For contact angle measurements, excised human skin was employed. Skin samples were prepared as those for the permeation studies; this was done because of its potential for elucidation of the mechanism of drug permeation studies.

Preparation of human epidermis

Skin samples of adult females were obtained, with patient consent and ethics approval, after abdominal reduction surgery. This study was approved by the Institutional Review Board (IRB) of Singapore General Hospital, Republic of Singapore (IRB Reference Number 196/2006). This IRB operates in accordance with the International Conference on Harmonization/Singapore Guideline for Good Clinical Practices, and with the applicable regulatory requirements.

Subcutaneous fat was carefully separated from the stratum corneum and epidermis after immersing the whole skin in 60 ± 5°C distilled water for 2 min. Samples were stored at −80°C until use. Prior to the permeation studies the skin samples, stratum corneum side facing upwards, were equilibrated in 0.9% w/w sodium chloride solutions containing 1% v/v antibacterial antimycotic solution.[33]

In-vitro skin permeation studies

Permeation studies of the drug, alone or as complexes with RM β-CD, were performed using a flow-through diffusion cell apparatus. A flow-through diffusion cell, used for the measurement of permeability of small tissue samples, is a modified Franz diffusion cell equipped with an automated flow-through system with high solvent-flow rate and a large donor compartment.[34]

The donor compartment was filled with 1 ml of formulations containing 2 mg/ml of the drug. The first receptor phase was isotonic phosphate buffer saline 0.02 M (pH 7.4), and then the receptor phase was changed to 0.1% w/v of RM β-CD for the second series of studies. The exposed surface area of the skin for the permeation of the drug was 0.785 cm^2. Samples from the receptor phase were collected every 6 h over a 30-h period, and the amount of haloperidol permeated was analysed by HPLC. The cell temperature was kept at 37 ± 0.5°C throughout the experiment. The steady state flux (J) was estimated from the slope of the straight line portion of the profile of cumulative haloperidol absorbed against time. Experiments were carried out in triplicate.

The effect of RM β-CD on the skin permeation of haloperidol was studied using two sets of experiments. First a concentration-dependent effect of RM β-CD (0, 0.01, 0.05, 0.1 M) in the donor compartment was studied, with 0.02 M phosphate buffer saline (PBS) at pH 7.4 as receptor solution. A synergistic effect of RM β-CD in combination with limonene 0.1% v/v in propylene glycol (PG) solution was also investigated. The pH-effect on the permeability of the drug was studied at pH 5. The buffer solution was prepared by using 0.05 M sodium phosphate monobasic monohydrate with the final pH adjusted by adding potassium hydrogen orthophosphate 3-hydrate. The combined effect of pH and 0.01 M RM β-CD was also observed. In another set of experiments, PBS in the receiver solution was replaced by 0.01% w/v RM β-CD, while the donor compartment consisted of haloperidol in 0.01 M RM β-CD or PG solutions.

Statistics

The values are expressed as mean ± SD ($n = 3$). Comparisons were made using one-way analysis of variance, ANOVA (Graph Pad Prism, Version 2), followed by the Tukey's post-test to determine the differences between treatment groups. The differences were considered statistically significant when $P < 0.05$.

Results and Discussion

Solubility

The solubilities of haloperidol in aqueous phosphate buffer solutions at pH 5, with and without RM β-CD or HP β-CD, are presented in Figure 1. This pH was selected as it is the same pH as the skin and may therefore minimise skin irritation. The highest increase in drug solubility occurred for RM β-CD, indicating that this oligosaccharide complexed more of the drug than HP β-CD. The solubilisation profile in Figure 1 is linear for all formulations, indicating the formation of a 1:1 complex irrespective of the ionisation of the drug. Drug solubility was assessed in two different solutions (aqueous solution and aqueous solutions with pH adjusted to pH 5). In solutions of pH 5, the drug is ionised and therefore more soluble when compared to the aqueous solution, resulting in a 128-fold increase of the intrinsic solubility of the drug. When phase-solubility experiments were performed with CD in the presence of buffer, the change in solubility was higher than in the presence of CD alone, indicating a synergistic effect. It is evident that the methylated CDs increased the solubility of haloperidol due to their strongly surface-active behaviour. Methylated CDs have been observed to have larger cavity volumes than HP β-CD. Consequently, RM β-CD can easily accommodate hydrophobic drugs such as haloperidol.[35]

Molecular modelling

The hypothetical structures of the complexes formed by haloperidol and the various cyclodextrins are presented in Figure 2. For the haloperidol–DM β-CD complex, the computed total energy is –40.7 kcal/mol and the steric energy is −30.587 kcal/mol. For the haloperidol–HP β-CD complex, total energy is −39.6 kcal/mol and the steric energy

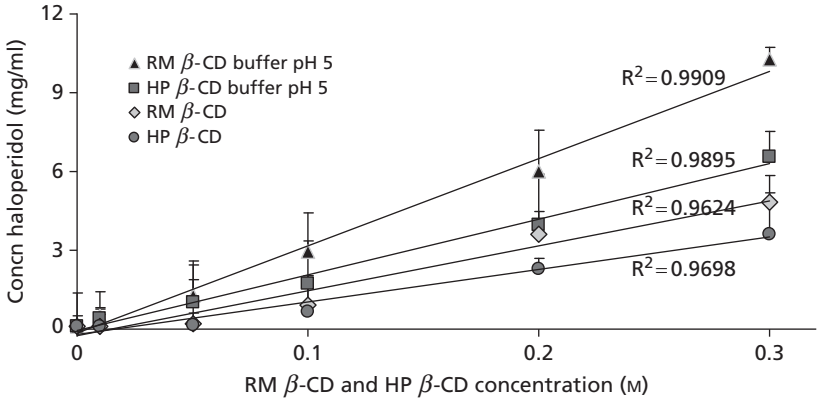

Figure 1 Phase solubility of haloperidol in cyclodextrin solutions. HP β-CD, hydroxypropyl β-cyclodextrin; RM β-CD, randomly methylated β-cyclodextrin

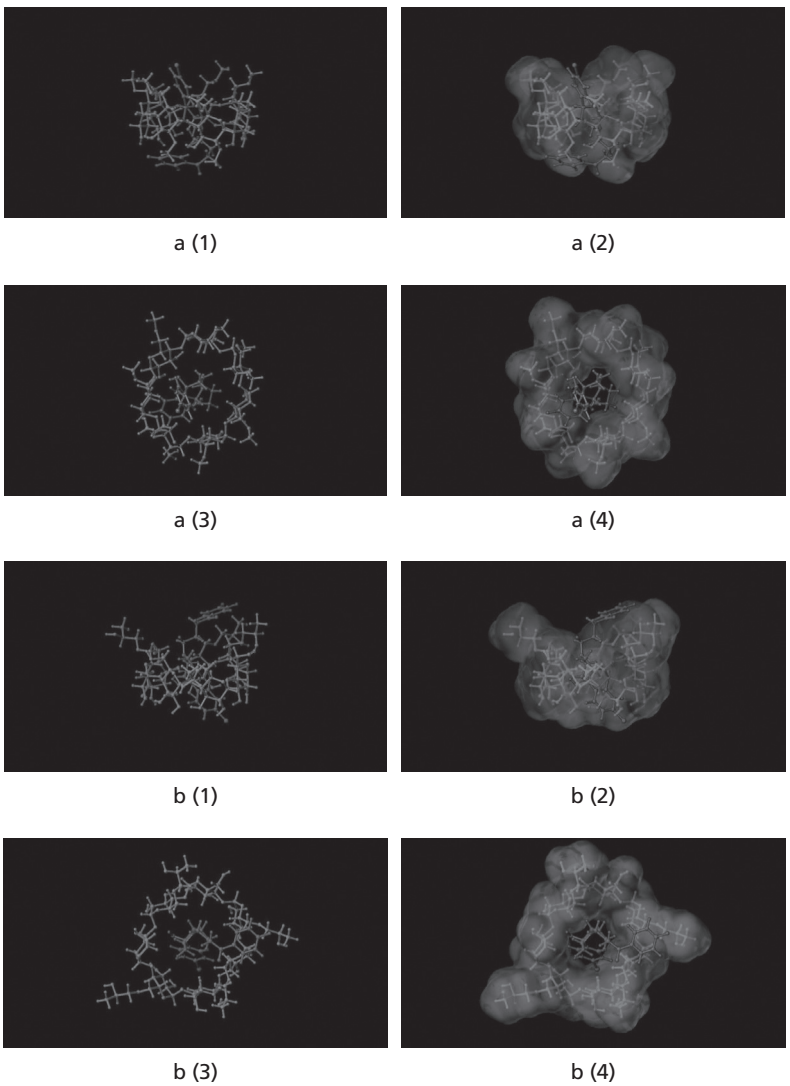

Figure 2 Haloperidol complexes. (a) Hypothetical structure of the haloperidol-dimethyl β-cyclodextrin complex. (b) Hypothetical structure of the haloperidol–hydroxypropyl β-cyclodextrin complex: (1) side view, (2) side view with electron surface, (3) top view and (4) top view with electron surface

is −29.848 kcal/mol. The difference in energy values indicates that the interaction between haloperidol and DM β-CD might be stronger than that of haloperidol and HP β-CD. The molecular modelling that was conducted to support the solubility study showed that the low solubility of haloperidol from the HP β-CD–haloperidol complex is due to the weak binding between haloperidol and HP β-CD whereas the strong interaction between haloperidol and RM β-CD resulted in relatively higher haloperidol solubility.

Surface tension and contact angle

The surface tensions of aqueous solutions of different concentrations (M) of RM β-CD and HP β-CD are shown in Figure 3. A remarkable change in the surface tension of pure water occurred when RM β-CD or HP β-CD was added, indicating that these systems have an effect on the surface tension of pure water. The aqueous solution of β-CD does not have any surface activity, but substitution of native CDs reduces the surface activity of the molecule.[36–39] From Figure 3 it is evident that surface tension reached a constant value after a certain concentration, suggesting the formation of supermolecular aggregates of RM β-CD and HP β-CD.[38,40] Critical micelle concentration (CMC) values were determined from the sharp changes in the slope of the surface tension versus log [CD] plot. CMC values for RM β-CD and HP β-CD were 10 mM (Figure 3).

Based on the above results, a possible mechanism for the formation of large micelle assemblies was deduced, as shown in Figure 4. Particle size analysis, as observed by light scattering, supported this hypothesis.[40] However, due to the short length of the hydrophobic chain in the CD structure, these aggregates may not behave in a similar manner to conventional surfactants.[38,41]

Surface tension and contact angle values of the solutions used are stated in Table 1. It was observed that the surface tension of water (70.3 ± 0.25 mN/m) decreases with increase in the concentration of RM β-CD. The interfacial values of RM β-CD at 0.05 and 0.1 M were of similar values: 54.8 ± 0.31 and 54.1 ± 0.22 mN/m, respectively. However the surface tension of RM β-CD at 0.01 M was 57.5 ± 0.68 mN/m. Buffer phosphate solutions had lower surface tension of 59.2 ± 0.42 mN/m, and an addition of RM β-CD further decreased the surface tension to 56.5 ± 0.03 mN/m. Addition of limonene did not produce any decrease in interfacial tension (36.2 ± 0.06 mN/m) when compared to pure propylene glycol solutions (36.2 ± 0.21 mN/m), indicating that limonene does not possess any surface-active effect. The addition of RM β-CD to PG solution did not change the interfacial tension, mainly due to the very low surface tension of PG, which masks the effect of RM β-CD (see Table 1).

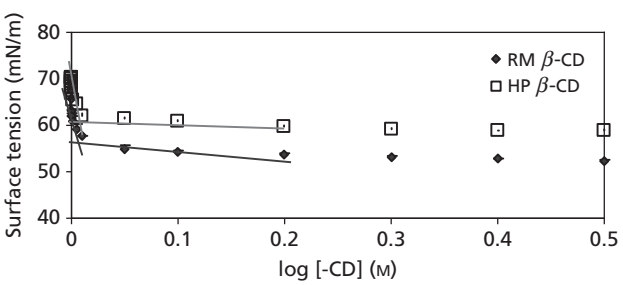

Figure 3 Surface tension of randomly methylated (RM β-CD) and hydroxypropyl β-cyclodextrin (HPβ-CD)

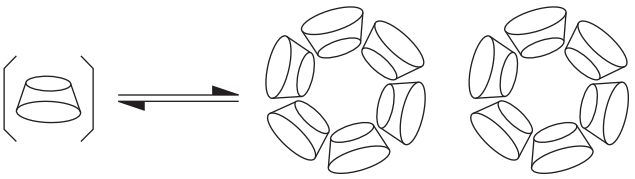

Figure 4 Schematic aggregation of cyclodextrin

From Table 1, water had the highest contact angle of 91.6 ± 3.13°, indicating its low wettability on the skin surface, whereas the contact angle for PG was found to be 40 ± 4.54°, which resulted in higher wettability of the skin surface. The contact angles for RM β-CD 0.1 M and buffer pH 5 were 52 ± 3.82° and 54.11 ± 6.58°, respectively. The contact angles for RM β-CD at 0.05 M and 0.01 M, PG–limonene, PG–limonene–RM β-CD and buffer pH 5–RM β-CD were not measured and were thought to be similar to RM β-CD at 0.1 M, PG and buffer solutions, respectively, as their interfacial values did not differ much.

Permeation studies

RM β-CDs were used in permeation studies due to their significant effect on the solubility of haloperidol compared with HP β-CDs as shown in the solubility results above. Figure 5a shows the effect of different molar ratios of RM β-CD on the permeation of haloperidol. The cumulative haloperidol concentration decreased with increasing RM β-CD concentration. The in-vitro permeation of haloperidol through human stratum corneum showed a similar trend in the presence of both RM β-CD at 0.1 M and 0.05 M, with a low drug penetration through the skin ($P > 0.05$). This is not surprising: it could be that due to the supermolecular arrangement and high concentrations of RM β-CD, the aggregations produced were too large to increase drug permeability. However, at lower concentrations of RM β-CD (0.01 M), an increase in skin permeation flux rate

Table 1 Surface tension and contact angle values of the solutions

Formulations	Surface tension ± SD (mN/m)	Contact angle ± SD
Water	70.3 ± 0.25	91.6° ± 3.13°
RM β-CD 0.01 M	57.5 ± 0.68	–
RM β-CD 0.05 M	54.8 ± 0.31	–
RM β-CD 0.1 M	54.1 ± 0.22	52.0° ± 3.82°
PG	36.2 ± 0.21	40.0° ± 4.54°
PG–limonene	36.2 ± 0.06	–
PG–limonene–RM β-CD	36.2 ± 0.05	–
Buffer pH 5	59.2 ± 0.42	54.11° ± 0.58°
Buffer pH 5–RM β-CD	56.5 ± 0.03	–

PG, propylene glycol; RM β-CD, randomly methylated β-cyclodextrin.

was observed ($P < 0.01$). The flux is due to haloperidol molecules that have not formed complexes with RM β-CD. An increase in RM β-CD concentration causes a decrease in dissociated haloperidol molecules, and therefore the amount of free drug available for permeation decreases.[18,42]

From the phase solubility diagram, it is evident that the CDs are potent solubilisers. However, it is important to use just enough CD to dissolve the drug; addition of too much CD will decrease drug partitioning into the skin.[43]

Previous studies have reported that CD enhances drug permeation by extracting lipids from the skin.[13,15,16] Also, a concentration-dependent effect of cyclodextrin on lipid extraction has been reported.[44] However, the opposite trend was observed in our experiments and also in earlier studies, where drug permeation decreased with increase in cyclodextrin concentrations.[45,46] Divergent results regarding the role of CD derivatives as skin penetration enhancers may be due to the use of different concentrations of these compounds in the various research papers. The surface-active effect and the CMC value of these CD derivatives may help explain the various observations reported in these papers. At concentrations above the CMC point, formation of CD aggregates could decrease the rate of skin permeation of drugs.

CD has been used in combination with chemical enhancers[17,47–49] and electroporation[7] to increase the skin permeation rate of drugs. Previous studies from our laboratories showed that limonene is a good penetration enhancer for the delivery of haloperidol.[3] To investigate the possible use of CD as a co-enhancer, additional tests were carried out by combining limonene with RM β-CD. Permeation, measured by cumulative drug amount, improved when haloperidol was complexed with RM β-CD at 0.01 M in limonene 0.1% v/v and PG solution. As shown in Figure 5b and Table 2, the combination of CD with limonene slightly increased the percutaneous absorption compared to the control, but not significantly ($P > 0.05$). However, the drug permeation profiles were completely different and the lack of a significant difference between the flux in limonene and limonene RM β-CD solution suggests a high enhancing effect of limonene that masks the effect of RM β-CD.

Figure 5c shows the effect of pH on the permeation rate of haloperidol alone and in combination with RM β-CD. The flux of the ionised drug at pH 5 and RM β-CD at 0.01 M concentration was enhanced over that when the buffer was used alone ($P < 0.05$, Table 2). The higher flux is a result of increased solubility of the drug. Synergistic effects can be achieved by adjusting the pH and concentration of RM β-CD to obtain improved solubility and therefore skin permeability of the drug.[21,22,50] The pH of the stratum corneum is about 4.8–6.[24,51] Some authors have reported that the skin permeability does not change in the pH range of 3.5–8.5,[24,51] while others have shown that the maximum drug flux through the skin occurrs at the pH where ionised species of the drug exist in large amounts.[20] Both ionised and unionised moieties of drug molecules contributed to the total flux (J_{tot}), which can be calculated using the following equation:

$$J_{tot} = K_{punion} \times C_{union} + K_{pion} \times C_{ion} \quad (1)$$

where K_{punion} and K_{pion} are the dependent drug permeabilities and C_{union} and C_{ion} are the dependent concentrations of

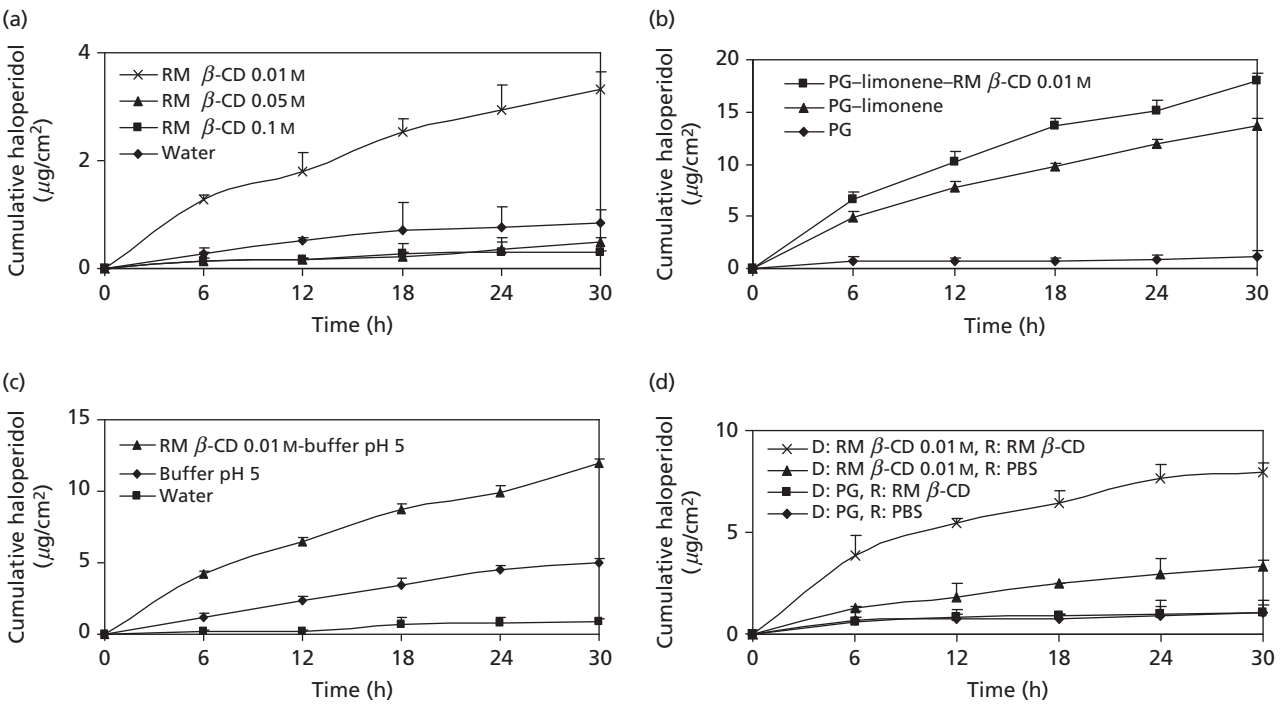

Figure 5 Permeation profile of haloperidol across human epidermis. Influence of (a) different randomly methylated β-cyclodextrin (RM β-CD) concentrations, (b) limonene and RM β-CD, (c) ionisation and RM β-CD and (d) RM β-CD and sink condition in receptor compartment. R and D denote receptor and donor compartment of the flow through diffusion cells, respectively. PBS, phosphate-buffered saline; PG, propylene glycol

Table 2 Flux value of haloperidol across human epidermis

Formulation	Mean flux ± SD ($\mu g/cm^2$/per h)
(a) Water (control)	0.18 ± 0.01
RM β-CD 0.1 M	0.04 ± 0.01
RM β-CD 0.05 M	0.11 ± 0.03
RM β-CD 0.01 M	0.49 ± 0.12
Phosphate buffer pH 5	0.90 ± 0.14
Phosphate buffer pH 5, RM β-CD 0.01 M	1.71 ± 0.22
(b) PG (control)	0.12 ± 0.01
PG–limonene 0.1% v/v	1.98 ± 0.35
PG–limonene 0.1% v/v, RM β-CD 0.01 M	2.74 ± 0.14
(c) PG	0.09 ± 0.01
RM β-CD 0.01 M	0.77 ± 0.13

In (a) and (b), receiver solution is phospahate-buffered saline; in (c), receiver solution is randomly methylated β-cyclodextrin (RM β-CD) 0.01% w/v. PG, propylene glycol.

ionised and unionised moieties respectively.[20] The results from the drug solubility profiles showed that the ionised moieties of the drug have higher solubilities and therefore greater impact on the total flux of the drug. Results from our study suggest that the simultaneous presence of both RM β-CD and phosphate buffer pH 5 at suitable concentrations could be exploited to improve drug solubility and permeability, resulting in enhanced permeation of the drug though the skin when compared to unionised drug solution.

Physiological buffer solutions with pH 7.4 are normally placed in the receptor compartment of the flow-though cell. However, for a less water-soluble drug, sink conditions and therefore total flux may increase with changes in the receptor phase. Our next approach was to study the possible promoting effect of the CDs in receptor solutions. Sclafani and co-workers reported that γ-CD in receiver solutions influenced the permeation rate of progesterone.[52] In our study, RM β-CD (0.1% w/v) was chosen because of its significant enhancement of the solubility of haloperidol. Figure 5d compares the cumulative drug amount permeated when RM β-CD 0.01% w/v was placed in the donor solution. A substantial increase in haloperidol permeability was obtained by using 0.1% RM β-CD as the receptor solution and RM β-CD at 0.01 M in the donor compartment (Table 2).

Critical contact angle value, which distinguishes between penetration and non-penetration, helped to optimise the drug permeation rate. From Figure 5 and Table 1, it can be seen that a PG solution, with lower contact angle value, results in a higher drug permeation rate when compared with pure water. Addition of RM β-CD to the vehicle reduced the interfacial tension of the aqueous system to allow good wetting of drug on the skin surface and a higher permeability of the drug. All aqueous formulations showed an improvement in wetting properties and skin permeability compared with that obtained using pure water. The lowest values for interfacial tension were obtained for the formulations containing 0.01 M RM β-CD at pH 5, which promoted the drug permeation.

Before any molecule can penetrate through the skin, it has first to adhere to the skin surface. The wetting rates and the viscosities of these formulations therefore influence the penetration rate of the drug. As a result, the physicochemical characteristics of the vehicle and other ingredients in a formulation have a great impact on skin permeation rate.[53,54]

Conclusions

The influence of RM β-CD and pH on the permeation of a drug through isolated human skin was studied. RM β-CD and HP β-CD significantly increased the aqueous solubility of haloperidol in a linear manner. There was a concentration-dependent effect on the permeation enhancement and the flux of the drug decreased with increasing concentration of RM β-CD, therefore sufficient CD must be added to dissolve the drug. Addition of more CD (above its CMC value) will result in molecular aggregation and decrease the drug permeation rates. Contact angle measurements showed that vehicles with higher skin wettability increased the contact of the drug with skin surface and therefore increased drug permeation rate. Absorption of drug through the skin is affected by the drug partitioning between the formulation and the skin surface, thus complete skin contact throughout the application period is thought to be necessary. Drug transfer to the skin will be fast if the formulation has a high affinity to the skin surface. Adjustments of pH with addition of CD could synergistically enhance drug permeation.

Declarations

Conflict of interest

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

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