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Transdermal permeation of WIN 55,212-2 and CP 55,940 in human skin in vitro

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Abstract

Synthetic cannabinoids have a promising future as treatments for nausea, appetite modulation, pain, and many neurological disorders. Transdermal delivery is a convenient and desirable dosage form for these drugs and health conditions. The aim of the present study was to investigate the in vitro transdermal permeation of two synthetic cannabinoids, WIN 55,212-2 and CP 55,940. Transdermal flux, drug content in the skin, and lag times were measured in split-thickness human abdominal skin in flow-through diffusion cells with receiver solutions of 4% bovine serum albumin (BSA) or 0.5% Brij 98. Differential thermal analysis (DSC) was performed in order to determine heats of fusion, melting points, and relative thermodynamic activities. The in vitro diffusion studies in 0.5% Brij 98 indicated that WIN 55,212-2 diffuses across human skin faster than CP 55,940. The WIN 55,212-2 skin disposition concentration levels were also significantly higher than that of CP 55,940. Correspondingly, CP 55,940 was significantly metabolized in the skin. WIN 55,212-2 flux and skin disposition were significantly lower into 4% BSA than into 0.5% Brij 98 receiver solutions. There was no significant difference in the flux, lag time, and drug content in the skin of CP 55,940 in 4% BSA versus 0.5% Brij 98 receiver solutions. The DSC studies showed that CP 55,940 had a significantly lower melting point, smaller heat of fusion, and corresponding higher calculated thermodynamic activity than the more crystalline WIN 55,212-2 mesylate salt. The permeation results indicated that WIN 55,212-2 mesylate, CP 55,940, and other potent synthetic cannabinoids with these physicochemical properties could be ideal candidates for the development of a transdermal therapeutic system.

Keywords: WIN 55,212-2; CP 55,940; Transdermal delivery; Percutaneous absorption; Cannabinoids

1. Introduction

Cannabinoids are useful for the alleviation of nausea and vomiting caused by chemotherapeutic agents (Dronabinol, PDR, 1996). One notable advantage of the cannabinoids is that many of the patients who are protected from the acute phase of chemotherapy-induced emesis also respond well during the delayed phase of chemotherapy-induced emesis, which serotonin receptor antagonists poorly control (Dalzell et al., 1986; Chan et al., 1987; Abrahamov et al., 1995). Cannabinoids decrease emesis mainly as a result of agonist action at the cannabinoid CB_1 receptor (Darmani, 2000, 2001). Preclinical studies demonstrate that cannabinoids may also be useful in the symptomatic treatment of spasticity and tremor in chronic-relapsing autoimmune encephalomyelitis (Baker et al., 2000; Croxford, 2003). The synthetic analogues WIN 55,212-2 and CP 55,940 (Fig. 1) are potent cannabinoid receptor agonists (Gold et al.,

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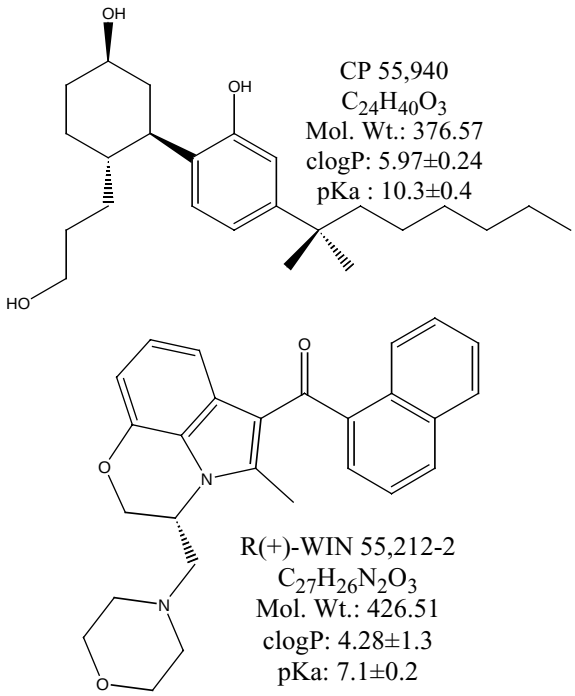

Fig. 1. Chemical structures of WIN 55,212-2 and CP 55,940. Calculated log *P* from Advanced Chemistry Development Software Solaris V4.76.

1992; Rinaldi-Carmona et al., 1994; Pertwee, 1997), 20–30 times more potent than Δ^9-THC. WIN 55,212-2 and CP 55,940 possess superior anti-emetic activity to Δ^9-THC (Darmani, 2001; Darmani et al., 2003). In a clinical trial, glaucoma patients resistant to conventional therapies have experienced significant decreases in intraocular pressure with 25 and 50 μg topical WIN 55,212-2 doses (Porcella et al., 2001). Additionally, preliminary studies in mice show that WIN 55,212-2 could be an effective therapeutic agent for the treatment of multiple sclerosis and deep tissue hyperalgesia (Croxford and Miller, 2003; Kehl et al., 2003).

In vitro metabolism studies in mouse liver microsomal preparations indicate that WIN 55,212-2 and CP 55,940 undergo significant metabolism similar to that of the other cannabinoids (Thomas and Martin, 1990; Zhang et al., 2002). Transdermal delivery of WIN 55,212-2 and CP 55,940 would bypass first-pass hepatic elimination, decrease dose-related side effects, allow easy termination of drug input, as well as maintain therapeutic concentrations for long durations with non-invasive zero-order release. However, the human skin provides a remarkable barrier to the therapeutic transdermal delivery of many drugs. Studies done in human skin, as opposed to animal skin, provide a more accurate prediction of permeation and potential cutaneous metabolism. Therefore, the present study was carried out to investigate the in vitro permeation of the two potent cannabinoids, WIN 55,212-2 and CP 55,940, across human skin.

2. Materials and methods

2.1. Chemicals

R-(+)-WIN 55,212-2 mesylate, Hank's balanced salts modified powder, bovine serum albumin (BSA), anhydrous monobasic potassium phosphate, and sodium bicarbonate were obtained from Sigma (St. Louis, MO). CP 55,940 was obtained from Tocris (Bristol, UK). Triethylamine, ammonium acetate, propylene glycol, 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid (HEPES), gentamicin sulfate, and acetonitrile were obtained from Fisher Scientific (Fairlawn, NJ).

2.2. Instruments

Equipment consisted of PermeGear® flow through diffusion cells of area 0.95 cm^2 (PermeGear, Riegelsville, PA), an Isotemp 2006S water circulator (Fisher Scientific, Fairlawn, NJ), a Retriever IV fraction collector (ISCO Inc., Lincoln, NE), a Pumppro® MPL Static pump (Watson Marlow, Wilmington, MA), a Padgett dermatome (Padgett Instruments, Kansas City, MO), an HPLC with a 200 series autosampler and UV detector model 785A (Perkin-Elmer, CT), and a Waters Alliance 2690 HPLC with a Micromass ZQ2000 detector (LC/MS, Waters, Milford, MA). The differential scanning calorimeter was a model DSC 2920 (TA Instruments, Inc., New Castle, DE).

2.3. In vitro permeability studies

2.3.1. Preparation of receiver solutions

2.3.1.1. HHBSS with BSA. HEPES buffered-Hank's balanced salt solution (HHBSS) was prepared and filtered. 50 μg/mL of gentamicin sulfate was dissolved

in the receiver solution to minimize microbial contamination. 4% w/v of bovine serum albumin was added to the HHBSS solutions. All the glassware used was sterilized with 70% v/v ethanol.

2.3.1.2. Brij 98 solution. Five grams of Brij 98 (for 0.5% w/v) was weighed out and dissolved in 1000 mL of filtered distilled water to make the receiver solution. This solution was used to examine the influence of receiver solution on the permeation of the hydrophobic drugs.

2.3.2. Preparation of drug solutions

The *R*-(+)-WIN 55,212-2 mesylate formulation contained a saturated drug solution of WIN 55,212-2 in propylene glycol and water in the ratio of 1:2 v/v, pH 5.5. The CP 55,940 formulation contained a saturated drug solution of CP 55,940 in propylene glycol:water in the ratio of 3:2 v/v, pH 5.2.

2.3.3. Preparation of human skin

Human skin samples from abdominoplasty surgery were obtained from the National Cancer Institute's Cooperative Human Tissue Network (CHTN). The samples were dermatomed immediately upon arrival to a thickness of approximately 200 μm. The samples were either used immediately or frozen at −20 °C.

2.3.4. In vitro experimental conditions

The temperature of the diffusion cells was maintained at 32 °C with a circulating water bath. The diffusion cells were sterilized with 70% v/v ethanol before securing the skin samples into the cell. The diffusion experiment was initiated by charging the donor compartment with 0.25 mL of drug solution. Each donor cell was capped for the duration of the experiment. The receiver solution was pumped through the diffusion cells at a flow rate of 1.1 mL/h for 48 h. The samples were collected with a fraction collector at 6 h intervals. The diffusion samples were refrigerated until analysis. At the end of the experiment, the drug-exposed skin area was excised from the skin sample in order to measure the tissue drug concentration. The formulation was washed off the skin, and the weighed tissue was placed in acetonitrile to shake at room temperature overnight (Challapalli and Stinchcomb, 2002). The extracted drug samples were analyzed by either HPLC or LC-MS as described in Section 2.5.

2.4. Sample preparation

2.4.1. WIN 55,212-2 samples

250 μL of WIN 55,212-2 diffusate sample containing 4% BSA was extracted with 750 μL of acetonitrile. The samples were vortexed for 1 min, sonicated for 15 min, followed by centrifugation at 10,000 × *g* for 20 min. The supernatant was transferred to a silanized autosampler vial and 100 μL of each sample was injected onto the HPLC column. The recovery was 91 ± 6% when compared with that of drug in acetonitrile.

2.4.2. CP 55,940 samples

The samples for CP 55,940 were prepared by addition of 750 μL of acetonitrile to 250 μL of diffusate, vortex mixed for 1 min, sonicated for 15 min, then centrifuged at 10,000 × *g* for 20 min. 500 μL of supernatant was transferred to a silanized culture tube and evaporated under nitrogen at 37 °C. The residue was reconstituted with 500 μL of acetonitrile, sonicated for 15 min and centrifuged (Fisher Scientific, Fairlawn, NJ) at 4000 rpm for 20 min at 15 °C. The clear sample was put into a silanized HPLC autosampler vial insert and 20 μL of each sample was injected onto the column in the LC/MS. The recovery was 89 ± 4%.

2.5. Analytical methods

2.5.1. HPLC analysis of WIN 55,212-2

The HPLC analysis of WIN 55,212-2 was carried out with a mobile phase consisting of acetonitrile and phosphate buffer (25 mM KH_2PO_4 + 0.1% TEA, pH 3.0) in the ratio of 65:35 at a flow rate of 1.5 mL/min. A reversed phase C_{18} column (Brownlee®, 220 mm × 4.6 mm, Spheri-5) with a reversed phase C_{18} guard column (Brownlee®, 15 mm × 3.2 mm, 7 μm particle size) was used for the assay. The run time was 10 min and the UV detector was set at 215 nm. The retention time for WIN 55,212-2 was 5.4 ± 0.15 min. The linearity of the standard curve was within the range of 25–1000 ng/mL, and the assay sensitivity was 25 ng/mL.

2.5.2. LC/MS analysis of WIN 55,212-2

Studies on the in vitro metabolism of WIN 55,212-2 in rat liver microsomes revealed two major and at least six minor metabolites derived from the parent compound (Zhang et al., 2002). The two major

metabolites (structural isomers at *m/z* 461) constituting 60–75% of the total metabolites were identified as dihydrodiol metabolites resulting from the arene oxide pathway. However, the metabolism of WIN 55,212-2 in skin is not known. Hence, the metabolism of WIN 55,212-2 was briefly investigated with the aid of LC/MS by looking for the known *m/z* (M + 1) of the major metabolite (461) in the diffusion samples as well as in the skin disposition samples. A Waters Symmetry C_{18} column (2.1 mm × 150 mm, 5 μm, Waters Corporation, Milford, MA) coupled with a Waters Symmetry C_{18} (2.1 mm × 10 mm, 3.5 μm Symmetry Sentry, Waters Corporation, Milford, MA) guard column was used for this study. The mobile phase was acetonitrile and 2 mM ammonium acetate (70:30 v/v) at a flow rate of 0.25 mL/min. The run time was 12 min. Selected ion monitoring (SIM) was performed in positive mode for ions *m/z* 427 and 461. Capillary voltage was 3.0 kV and cone voltage was 40 V. No significant levels of the potential metabolite at *m/z* 461 were seen in the diffusion samples or skin samples.

2.5.3. LC/MS analysis of CP 55,940

The mobile phase of acetonitrile and 2 mM ammonium acetate (70:30 v/v) was degassed and pumped through a Waters Symmetry C_{18} column (2.1 mm × 150 mm, 5 μm, Waters Corporation, Milford, MA) and precolumn (Waters Symmetry C_{18} 2.1 mm × 10 mm, 3.5 μm Sentry, Waters Corporation, Milford, MA) at a flow rate of 0.25 mL/min, and the column temperature was maintained at 35 °C. The run time was 12 min. The data system used for acquisition, storage and calculation was MassLynx Software (Waters Corporation, Milford, MA). Selected ion monitoring (SIM) was performed in the negative mode for the ions of *m/z* 375 [CP-H] (dwell time 0.30 s). Capillary voltage was 3.0 kV and cone voltage was 40 V. Source block and desolvation temperatures were 120 and 250 °C, respectively. Nitrogen was used as a nebulization and drying gas at flow rates of 50 and 450 L/h, respectively. The retention time for CP 55,940 was 5.7 ± 0.1 min. A calibration curve was prepared with each assay at a concentration range of 25–1000 ng/mL, and the regression line had a correlation coefficient of 0.999. The limit of detection was 5 ng/mL.

The in vitro CP 55,940 metabolism studies (Thomas and Martin, 1990) in mouse liver microsomes revealed five monohydroxylated metabolites that differed with respect to the position of hydroxylation on the 1′,1′-dimethylheptyl side chain. CP 55,940 metabolism by side chain hydroxylation is similar to Δ^8-THC and Δ^9-THC. In light of this, we made an attempt to identify the metabolite of CP 55,940 in the diffusion and skin disposition samples with the aid of LC/MS. The masses monitored were for CP 55,940 and its hydroxylated metabolites, *m/z* 375 and 391, respectively. A potential metabolite of CP 55,940 was found in the skin disposition and diffusion samples.

2.6. Stability of WIN 55,212-2 and CP 55,940 in receiver solutions and in donor solvent systems

Stability studies were conducted in the receiver solutions and in the donor solvent systems at room temperature and at 32 °C. Drug solutions of WIN 55,212-2 and CP 55,940 at a concentration of 2.5 μg/mL were prepared in receiver solutions and in donor solvent systems in a 25 mL volumetric flask ($n = 5$). All these flasks were sealed with aluminum foil and placed in an incubator set at 32 °C, and another set of samples ($n = 5$) was incubated at room temperature. One milliliter of sample was removed into a silanized HPLC vial at time points of 0, 1, 2, 6, 12, 18, 24, 48 h and up to two weeks, and stored at 4 °C until HPLC analysis.

2.7. Differential thermal analysis

The heats of fusion, ΔH_f, and melting points for the two drugs were determined with a DSC 2920, TA Instruments. Both of the compounds were in crystalline form. Accurately weighed samples of drug (3–4 mg) were layered evenly over the bottom of an aluminum pan. Heating curves were recorded at 10 °C/min. There were no significant differences in the thermograms for each compound from run to run.

2.8. In vitro data analysis

The permeation data were plotted as the cumulative amount of drug collected in the receiver compartment as a function of time. The fluxes (nmol/cm^2/h) of WIN 55,212-2 or CP 55,940 were calculated from the slope of the plot of the cumulative amount of drug permeated at steady state versus time using linear regression analysis. The statistical analysis of the data was completed with a One-way ANOVA followed by

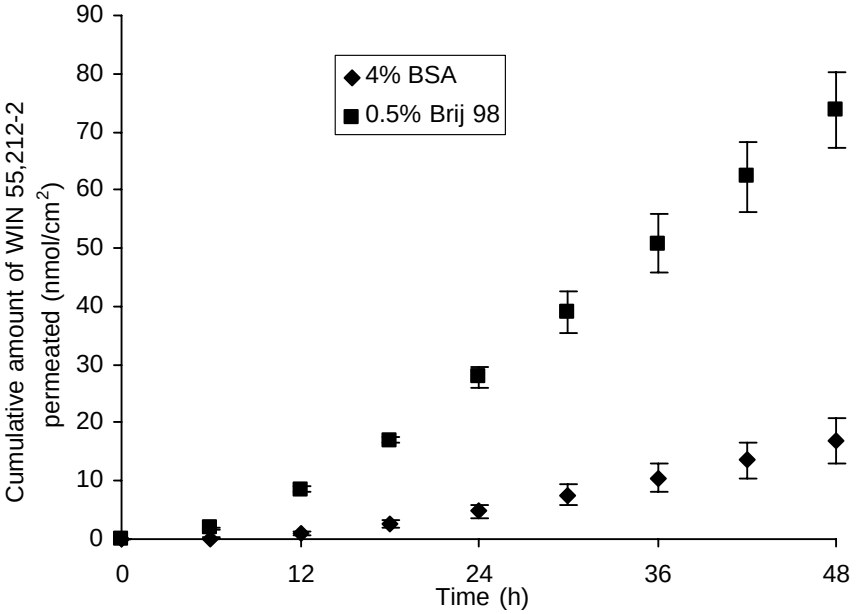

Fig. 2. Mean (±S.D.) cumulative amount of WIN 55,212-2 permeated across the human skin into 0.5% Brij 98 and 4% BSA receiver solutions.

a Tukey post-hoc test using SIGMASTAT (SPSS Inc., Chicago, IL).

3. Results and discussion

The present investigation was carried out in order to assess the transdermal permeation of the two potent synthetic cannabinoids (WIN 55,212-2 and CP 55,940), which may be useful for the treatment of many conditions, including chemotherapy-induced nausea and vomiting in cancer patients. The HPLC and LC-MS methods developed for the quantitation of WIN 55,212-2 and CP 55,940 in skin disposition and diffusion samples were found to be precise and accurate as indicated by a less than 5% coefficient of variation (CV, inter- and intra-day variation). The stability studies indicated that WIN 55,212-2 and CP 55,940 were stable (≤2% degradation in two weeks) in the receiver solutions and in the donor solvent systems. The in vitro diffusion studies were conducted in 4% BSA or 0.5% Brij 98 receiver solutions in order to observe any potential differences in skin permeation of WIN 55,212-2 and CP 55,940, and also to aid in the selection of the right receiver solution for further in vitro/in vivo correlation studies.

The cumulative amounts of WIN 55,212-2 or CP 55,940 permeated in 48 h across the human skin into 4% BSA or 0.5% Brij 98 solutions are shown in Figs. 2 and 3, respectively. In the present study, saturated drug

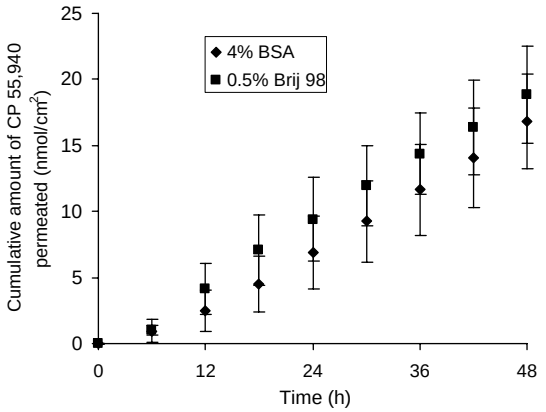

Fig. 3. Mean (±S.D.) cumulative amount of CP 55,940 permeated across the human skin into 0.5% Brij 98 and 4% BSA receiver solutions.

Table 1
Mean (±S.D.) permeation parameters of WIN 55,212-2 and CP 55,940 in human skin using 4% BSA or 0.5% Brij 98 as receiver solutions

Parameter		WIN 55,212-2	CP 55,940
Cumulative amount (nmol/cm^2)	4% BSA	16.9 ± 1.4	16.8 ± 3.0
	0.5% Brij 98	73.8 ± 6.6[a]	15.2 ± 2.0[b]
Flux (nmol/cm^2/h)	4% BSA	0.53 ± 0.08	0.43 ± 0.01
	0.5% Brij 98	1.9 ± 0.1[a]	0.35 ± 0.08[b]
Lag time (h)	4% BSA	13.1 ± 1.8	8.9 ± 7.0
	0.5% Brij 98	9.5 ± 1.1[b]	7.7 ± 4.4[b]
Drug content in the skin (μmol of drug/g of skin)	4% BSA	5.7 ± 2.0	1.4 ± 0.4
	0.5% Brij 98	21.7 ± 3.9[a]	1.1 ± 0.4[b]

[a] Significantly different when compared with 4% BSA ($P < 0.001$).
[b] ns: not significantly different when compared with 4% BSA.

solutions were used in the donor compartment, providing a maximum thermodynamic activity value of 1. The in vitro permeation parameters of WIN 55,212-2 and CP 55,940 are shown in Table 1. No statistically significant differences in the lag times were observed between WIN 55,212-2 and CP 55,940, drugs of similar molecular size (Table 1). The cumulative amount of WIN 55,212-2 permeated (73.8 nmol/cm^2) and the flux (1.9 nmol/cm^2/h) across the human skin into 0.5% Brij 98 was significantly higher ($P < 0.001$) than that into 4% BSA (16.9 nmol/cm^2 and 0.53 nmol/cm^2/h). The same results were observed for previous Δ^9-THC diffusion studies, and are not the result of Brij 98 damage to the skin barrier (Challapalli and Stinchcomb, 2002). Barrier damage from Brij 98 would have been observed as a significant increase in drug flux for CP 55,940 as well, as compared to flux into 4% BSA. The observed significant difference for WIN 55,212-2 could have been due to the difference in the solubility of WIN 55,212-2 in 4% BSA (0.103 mg/mL solubility) versus 0.5% Brij 98 (1.42 mg/mL solubility) receiver solutions. However, the highest concentration of the WIN 55,212-2 diffusion samples in 0.5% Brij 98 was 889 ng/mL, well below the 4% BSA solubility (<1% of the solubility). The concentration of drug in the skin also corresponds directly with the increase in flux into the Brij 98. The most likely explanation for the difference in receiver solutions seems to be that the Brij 98 partitions into the viable epidermis/dermis and causes an artificial increase in the flux of some drugs that would not likely be seen in vivo. Ongoing in vitro and in vivo studies in our laboratory will provide further information about the most appropriate receiver solution for use in the determination of the best in vitro/in vivo correlation for the highly hydrophobic cannabinoids. In cases like this where we are interested in investigating skin metabolism, the physiological 4% BSA solution is the best choice for a receiver solution.

The heats of fusion, ΔH_f, and melting points for the two drugs were determined by conducting DSC studies. The differential thermal analysis data for the two synthetic cannabinoids, WIN 55,212-2 and CP 55,940, is given in Table 2. Both WIN 55,212-2 and CP 55,940 showed only one thermal transition, and the endotherm peaks corresponded to the melting of the crystals. The heats of fusion were calculated from the areas under the melting peak curves of the corresponding drugs. The melting points and heats of fusion are the prime physicochemical parameters for the determination of intrinsic solubility (Mackay et al., 2001). This solubility of the unionized form or drug solution saturation condition in turn provides the

Table 2
Differential thermal analysis of WIN 55,212-2 and CP 55,940

	WIN 55,212-2 mesylate salt	CP 55,940
Molecular weight (g/mol)	522.6	376.57
T_f, melting point (°C) (±S.D.)	249.5 ± 0.3	83.8
ΔH_f, heat of fusion (kJ/mol) (±S.D.)	27.8 ± 1.8	18.4
a_2, activity of solid at $T = 25$ °C[a]	0.008	0.295

[a] Calculated from $\ln a_2 = (-\Delta H_f/RT)((T_f - T)/T_f)$ (from Hildebrand and Scott, 1950).

maximum thermodynamic activity (a_2) driving force for drug transport across the skin. The reference state thermodynamic activities were calculated from the equation in Table 2 using room temperature (25 °C) (Hildebrand and Scott, 1950; Stinchcomb et al., 1995). The predicted intrinsic solubility of CP 55,940 would be higher than that of WIN 55,212-2, based on its higher calculated thermodynamic activity. This higher thermodynamic activity did not translate into improved flux of CP 55,940 over WIN 55,212-2 from the drug saturated propylene glycol:water solutions, even though WIN 55,212-2 is also fifty percent ionized at the vehicle pH. A slightly higher proportion of propylene glycol in the CP 55,940 vehicle did not cause enhanced permeation over WIN 55,212-2 either.

The cumulative amount of drug permeated, the flux, and the drug content in the skin of WIN 55,212-2 into 0.5% Brij 98 were significantly higher ($P < 0.001$) than these parameters for CP 55,940 (Table 1). If Brij 98 in vitro experiments do provide a realistic picture of what happens in vivo, then this flux increase might be due to the difference in the lipophilicities of the two drugs. We have identified that the stratum corneum does provide some resistance to Δ^9-THC skin diffusion, but that the viable tissue provides the rate-limiting step to diffusion of this hydrophobic cannabinoid (Challapalli and Stinchcomb, 2002). Sufficient hydrophilic and lipophilic characteristics are necessary in order to cross the skin barrier efficiently, so that the aqueous viable tissue does not rate-limit the diffusion process (Flynn et al., 1981). Parabolic relationships between partition coefficients and skin flux/permeability have been observed with other groups of compounds (Flynn and Yalkowsky, 1972; Yano et al., 1986; Houk and Guy, 1988). The calculated log octanol/buffer (pH 7, donor vehicle) partition coefficients of Δ^9-THC, CP 55,940, and WIN 55,212-2 are 5.5, 4.6, and 3.4, respectively (Advanced Chemistry Development Software Solaris V4.76). Potts and Guy calculated that compounds with log octanol/water partition coefficients above 4.1 may undergo a rate-limiting viable tissue transfer process, although this was not incorporated into their model of skin permeation prediction since data with these types of compounds is limited (Potts and Guy, 1992). Therefore, WIN 55,212-2 would be predicted to have a faster permeation rate across the skin than CP 55,940, as CP 55,940 has hydrophobicity more similar to Δ^9-THC. The permeability of WIN 55,212-2 into 0.5% Brij 98 from this vehicle was 4.5×10^{-4} cm/h, 10 times higher than Δ^9-THC. The advantage of increased polarity may be the key to the permeation success of this highly hydrophobic compound class.

The in vitro diffusion samples and skin disposition samples were analyzed for masses of known major metabolites of WIN 55,212-2 and CP 55,940 (Zhang et al., 2002; Thomas and Martin, 1990). There was no mass of the known major metabolite seen in the skin samples or diffusion samples of WIN 55,212-2. WIN 55,212-2 may not undergo significant metabolism during human skin transport, and/or may metabolize to compounds with masses that were not scanned in this study. A potential hydroxy-metabolite of CP 55,940 was found in the skin disposition samples, as well as in the diffusion samples. The level of this metabolite was consistent, $17 \pm 2\%$ of the observed peak area for CP 55,940 in the skin disposition samples. However, further efforts to identify and characterize these potential metabolites were not made. It is possible that CP 55,940 was significantly metabolized in the human skin. This could also explain the decreased flux of CP 55,940, as compared to WIN 55,212-2 into the Brij solution. Skin metabolism was occurring, even though the Brij receiver solution is not an ideal media for optimal metabolism studies. It is difficult to predict the permeation of CP 55,940 based on its physicochemical characteristics, because the data is confounded by the significant metabolism that occurred in the skin. Epidermal drug metabolism can decrease the bioavailability of the topically applied compound, but is not necessarily a detriment to drug delivery, especially when metabolites are pharmacologically active as well. Many of the cannabinoids have pharmacologically active metabolites.

4. Conclusions

The in vitro diffusion studies of WIN 55,212-2 and CP 55,940 across the human skin showed that both drugs could be potential candidates for transdermal delivery. Confirmation of the best in vitro receiver solution (0.5% Brij 98 over 4% BSA) with future in vivo data may reveal that WIN 55,212-2 mesylate is a better transdermal candidate than CP 55,940,

especially since significant skin metabolism of CP 55,940 occurred. It appears that WIN 55,212-2 has sufficient hydrophilic and lipophilic characteristics in order to diffuse across the skin at a reasonable rate. Further studies are in progress on formulation modification and patch formulation techniques in order to increase the flux across the human skin to achieve a therapeutic delivery rate range. These cannabinoids are more potent than Δ^8-THC and Δ^9-THC, and may make better candidates for transdermal delivery, as well as provide structural permeability information for future potent synthetic derivative design.

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