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Transdermal formulation of 4-benzylpiperidine for cocaine-use disorder

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ABSTRACT

Cocaine-use disorder is a major public health problem, yet there is no FDA approved treatment. The distinguished preclinical efficacy of 4-benzylpiperidine as substitute agonist for cocaine-use-disorder along with the therapeutic benefits of transdermal delivery, make it an excellent candidate for transdermal delivery. The purpose of this study was to investigate the *in vitro* transdermal delivery of 4-benzylpiperidine across dermatomed human skin. Mathematical models were used to calculate the theoretical and experimental drug percutaneous absorption. Gels were formulated with varying amount of gelling agent and subjected to rheological analysis. Franz cells were used to investigate the *in vitro* permeation. Transdermal permeation of 4-benzylpiperidine from propylene glycol solution (1, 10, 20 and 50 mg/mL) corresponded to 16%–31% delivery (49.45 ± 11.60, 258.47 ± 48.50, 600.26 ± 74.18, 1945.20 ± 405.59 μg/cm^2). The average cumulative amount of drug delivered from gel formulation was 1824.90 ± 425.12 μg/cm^2. Thixotropic test demonstrated 2% hydroxyl propyl cellulose based gel to have the highest structure recovery ratio. The calculated theoretical permeability coefficient and theoretical flux value (32.637 μg/cm^2/h) predicted high percutaneous absorption. This was further validated by the experimentally determined permeability coefficients and flux values (62.73 ± 12.14 μg/cm^2/h), demonstrating proficient transdermal delivery of 4-benzylpiperidine.

1. Introduction

Cocaine-use disorder is a significant and insidious public health problem, with 1.5 million Americans reporting current cocaine use in 2014 [14]. Despite evidence for sustained prevalence, clinical harm, demand for treatment along with the decades of research, currently there are no FDA-approved pharmacotherapies to treat cocaine-use disorder [57–59]. Previous attempts to develop a medication for cocaine-use disorder have focused largely on substitute agonist approaches. Substitute-agonist therapies mimic key aspects of the abused drug to reduce craving and withdrawal and promote abstinence. The goal of such agonist-based pharmacotherapies is to use a medication that has similar pharmacological effects to that of the abused drug, while providing slower onset over abused drug to reduce abuse liability, and prolong the duration of action to promote compliance [12]. Research over the last decade has suggested that this substitute agonist-based strategy may be useful in treating cocaine-use disorders [15,47].

For other highly abused insidious drugs such as heroin, substitute agonist therapy as a maintenance strategy has been successful for addiction treatment [20,36]. FDA-approved substitute-agonist therapies for substance-use disorders include methadone, buprenorphine, varenicline, and transdermal and buccal formulations of nicotine. It was the relative success of these medications for treatment of substance-use that stimulated initial research on potential of agonist medications to treat cocaine dependence [32]. Strengths of this approach include the clinical success of these agents, better compliance, reduced withdrawal and craving, and excellent efficacy profiles in preclinical models. Weaknesses include the risk of toxic drug interactions during relapse and diversion for abuse. These weaknesses of conventional dosage forms can be mitigated through transdermal formulation of the substitute agonist. Transdermal formulation provides slow and sustained drug delivery. Slow drug onset can reduce abuse potential and long duration of action can reduce the frequency of required treatment leading to better compliance and reduce problematic neuroadaptations to the severe oscillations in drug levels that often occur with drug abuse. Further, transdermal formulation can be an abuse deterrent as it is harder and more time consuming to extract the effects of the drug over a pill or tablet [42].

Cocaine is a nonselective reuptake inhibitor of three monoamine transporters: dopamine, serotonin and norepinephrine [24] and [43].

Abbreviations: HPC, hydroxyl propyl cellulose; RP-HPLC, reverse phase high performance liquid chromatography; LVR, Linear viscoelastic region; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; Kp, permeability coefficient; PBS, phosphate buffered saline; PG, propylene glycol; SD, standard deviation

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The behavioral effects of cocaine associated with its abuse liability have been attributed primarily to its actions at the dopamine transporter (DAT) [44] which has been confirmed in rodent, nonhuman primate, and human studies. Positive correlations between the *in vitro* potency of cocaine analogs at DAT binding and their *in vivo* potency in producing locomotor-stimulant effects in rodents [7] and [21] as well as cocaine-like behavioral effects in squirrel monkeys [4,24,54] has been established.

4-benzylpiperidine is a phenethylamine substrate-based dopamine/norepinephrine (DA/NE) releaser. Although there are many targets for cocaine-use disorder that have been identified, substitute agonists that function as substrate-based DA/NE releasers have demonstrated promising efficacy in preclinical models and double-blind placebo controlled clinical trials ([32]; [12]. Researchers have previously demonstrated the efficacy of DA/NE selective substrate-based releasers [2,3,34,35] to decrease cocaine vs. food choice in nonhuman primates. This is a highly reproducible finding across DA/NE selective releasers, with phenmetrazine, phendimetrazine, and 4-benzylpiperidine all shown to be effective in cocaine vs. food choice during 7-day continuous treatment experiments [33]. 4-benzylpiperidine has shown to be effective in preclinical models as a substitute agonist for cocaine-use disorder but has a rapid onset of action, producing its peak effects within 10 min of administration, and a short duration of action of 10–30 min. The value of an agonist medication lies in its ability to target pharmacological receptors to produce effects for a long duration of time with slower onset; thereby reducing cravings for cocaine consumption while ensuring lower toxicity than produced by cocaine use. Transdermal drug delivery sustains the duration of action of 4-benzylpiperidine and promotes the agonist properties just mentioned. The small molecular weight (175), moderate lipophilicity (log P 2.924) and low melting point (6–7 °C) of 4-benzylpiperidine make it an excellent candidate for transdermal drug delivery [40]. Considering its distinguished preclinical efficacy in human-relevant animal models and the therapeutic benefits of transdermal delivery of substitute agonists for cocaine-use disorder, in the present study our aim was to investigate the *in vitro* transdermal delivery of 4-benzylpiperidine over dermatomed human skin. The study was further extended to include the formulation, rheological evaluation and transdermal delivery of a hydroxyl propyl cellulose based gel of 4-benzylpiperidine. This is the first of its kind study that reports the transdermal delivery of 4-benzylpiperidine over dermatomed human skin.

2. Materials and methods

2.1. Materials

4-Benzylpiperidine (99% purity) was obtained from Sigma Aldrich (St. Louis, MO, USA). Acetonitrile and Phosphate Buffered Saline (PBS) were purchased from Fisher Scientific (NJ, USA). Hydroxy propyl cellulose (HPC) (Klucel HF Pharm HPC) was procured from Ashland (Covington, KY, USA). EpiDerm™ skin irritation kit (OECD TG 439) was purchased from Mattek Corporation (Ashland, MA, U.S.A). De-ionized water was used to prepare all solutions required in this study and for HPLC analysis.

2.2. Methods

2.2.1. Permeability coefficient determination

Theoretical permeability coefficient was calculated using the Guy Potts Eq. (1);

$$\text{Log Kp} = -2.7 + 1.7*\log\ \text{P} - 0.0061*\text{MW} \quad (1)$$

Where Kp is the permeability coefficient, P is the octanol-water partition coefficient and MW is the molecular weight [39]. Theoretical maximum drug flux (Jmax) across the skin was calculated from Kp × saturation solubility (intrinsic solubility) of drug in water [31].

The experimental permeability coefficient was calculated by using Eq. (2);

$$\text{Kp} = \text{J/C X A} \quad (2)$$

Where J is the flux at steady state (mg/h), Kp is the permeability coefficient (cm/h), C is the concentration in the donor (μg/cm^3), and A is the diffusion area (cm^2) of the drug, which in our study was constant (0.64 cm^2). The steady state flux (J) was determined from the slope of the linear portion of the average cumulative amount versus time plot. The time required to reach steady state (lag time) was determined by extrapolating the linear portion of permeation *vs.* the time curve to the time axis [9,13].

2.2.2. Formulation of 4-benzylpiperidine gels

4-benzylpiperidine gels were formulated using three different concentrations (1.5%, 2%, 4%) of gelling agent (hydroxyl propyl cellulose). 4-benzylpiperidine was initially dissolved in propylene glycol (PG) and then dissolved in water. Hydroxyl propyl cellulose powder was slowly added to the vortex of agitated water containing drug in PG at room temperature (< 35 °C). Addition of hydroxyl propyl cellulose powder was slow enough to not form lumps but was completed before any appreciable viscosity buildup was achieved in the solution. The rate of agitation was then reduced, but continued until a gel consistency was formed [18]. All gels contained 2 g of drug in 20 g of gel. The composition of the three gels is presented in Table 1.

2.2.3. Rheological assessment

The gels were subjected to rheological analysis using a rheometer (Rheoplus/32 V3.62, Anton Paar Germany GmbH, Germany) to assess the flow properties and structural stability to determine the gel composition with the optimal properties. This was achieved by performing rotational and oscillatory tests of the gels at 32 °C using a parallel-plate spindle (PP 25/S) with the diameter of 24.99 mm and a gap of 100 μm maintained between the plates. For all the tests, enough gel to cover the lower plate was applied, and when the parallel plate spindle touches the gel with zero gap the excess gel is wiped off. Between each gel assessment, the plate was cleaned with 75% ethanol and wiped dry [41,52].

2.2.3.1. Flow curves. All the gels were subjected to shear at an increasing rate of 0–100 s^{-1} and the viscosity versus the resulting shear rate rheograms were plotted. The data obtained was then fit in to the Herschel–Bulkley model: $\tau = \tau y + K\gamma n$ by the rheoplus software in built in the rheometer. In the Herschel–Bulkley model, τ represents shear stress (Pa), τy the yield stress (Pa), K the flow consistency index (Pa.sn), γ the shear rate (0–100 s^{-1}) and n the flow behavior index [41]. The values of shear stress, yield stress, flow consistency index and flow behavior index were recorded for all the gels.

2.2.3.2. Amplitude sweep. The gels were subjected to an increasing strain of 1–100% at a constant angular frequency (10 rad/s). The resulting storage modulus (G′) and loss modulus (G″) rheograms versus the increasing strain (1–100%) were plotted on logarithmic scale. The linear viscoelastic region (LVR) of the gels was recorded and used to choose the strain value to be applied for the subsequent frequency sweep and thixotropy oscillation tests.

Table 1
Compositions of 4-benzylpiperidine gels with varying amounts of hydroxyl propyl cellulose (HPC).

Ingredients	1.5% HPC gel (g)	2% HPC gel (g)	4% HPC gel (g)
HPC	0.3	0.4	0.8
Water	5	5	5
Drug	2	2	2
PG	12.7	12.6	12.2