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ORIGINAL ARTICLE

Bioavailability of Δ^9-tetrahydrocannabinol following intranasal administration of a mucoadhesive gel spray delivery system in conscious rabbits

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Abstract

Background: The purpose of this study was to investigate the potential of the intranasal route for systemic delivery of solubilized Δ^9-tetrahydrocannabinol (THC). A further aim was to investigate the effect of nasally administered chitosan-based nasal bioadhesive gel on THC bioavailability as a formulation strategy to decrease normal mucociliary drug clearance. *Method*: The THC formulations were administered intranasally and compared to intravenous administration utilizing conscious rabbits. *Results*: After nasal administration, the THC nasal solution afforded a C_{max} value of 20 ± 3 ng/mL at 20 minutes. Interestingly, the THC loaded in chitosan gel formulation followed almost the same profile at early time points and subsequently afforded a higher C_{max} value of 31 ± 4 ng/mL (T_{max} = 45 minutes). The absolute bioavailability of THC after nasal delivery was studied to compare plasma THC concentrations after nasal administration with those after intravenous injection. Absolute bioavailability values were 13.3 ± 7.8% and 15.4 ± 6.5% for the THC nasal solution and gel formulations, respectively. *Conclusion*: The results of the present study suggest that intranasal administration of THC in solution or in a chitosan-based nasal gel formulation could be an attractive modality for delivery of THC systemically.

Key words: Chitosan, gel, LC–MS, nasal, pharmacokinetic, Δ^9-tetrahydrocannabenol

Introduction

Over the past few years, Δ^9-tetrahydrocannabinol (THC) (Figure 1) has been recognized as a useful treatment for various medical conditions, such as nausea and vomiting associated with chemotherapy, and for appetite stimulation of AIDS patients suffering from anorexia[1,2]. Furthermore, THC exhibits other biological activities, which lend themselves to possible additional therapeutic applications in conditions such as migraine headaches, spasticity, anxiety, multiple sclerosis[3–5], pain[6], and Parkinson's disease[7].

The main challenge for the medicinal use of cannabinoids, including THC, is the development of a safe and effective method of administration[8]. Despite the promising clinical potential of THC, an effective clinical dosage form has not been developed to date. Currently, the only practical cannabinoid dosage form available in the United States is the soft gelatin capsule formulation (Marinol®). The oral use of this dosage form is, however, limited by substantial first-pass metabolism of THC[9,10] and the fact that severely nauseated patients may not be able to keep the capsules in the stomach long enough for the drug to be absorbed and to take effect.

Systemic drug delivery through the nasal mucosa is a useful method to avoid hepatic first-pass metabolism[11–13]. Furthermore, the nasal mucosa is well suited for the absorption of drugs as it has a large epithelial surface area available because of numerous microvilli. The nasal absorption of lipophilic compounds such as THC involves concentration gradient-dependent permeation of epithelial cell membranes via the trans-cellular route. Thus, nasal absorption is possible if the lipophilic compound can be dissolved in the dosage form. Substantial solubilization formulation efforts were reported to enhance the nasal absorption of lipophilic compounds utilizing complexing agents (i.e., cyclodextrins) and cosolvents[14–16].

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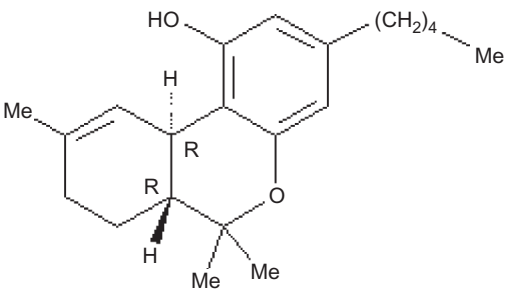

Figure 1. Structure of Δ^9-tetrahydrocannabinol.

In an effort to enhance the solubility of THC, water-soluble prodrugs of THC have been investigated for nasal drug delivery[17]. Furthermore, a readily dissolved formulation of THC and cannabidiol (Sativex®) mixed with ethanol and propylene glycol has been developed for sublingual delivery. This formulation was recently approved in Canada for the relief of neuropathic pain. However, some side effects were reported such as bad taste, high intersubject variability, and irritation at the site of administration[6]. The same cosolvent approach was also reported to enhance the nasal delivery of THC in anesthetized rats[18].

In the current study, we focused our studies on the potential of the nasal route for systemic delivery of solubilized THC. Furthermore, a formulation strategy to decrease normal mucociliary drug clearance was tested utilizing a chitosan-based nasal bioadhesive gel in conscious rabbits. Chitosan is a natural linear cationic polysaccharide obtained by deacetylation of chitin and is considered to be a biologically safe, nontoxic, biocompatible, and biodegradable polysaccharide[19]. The majority of the investigations published so far on the use of mucoadhesive gel formulations in animal experiments utilize anesthetized subjects. In a conscious animal or human, mucociliary clearance would be more active and the absolute bioavailability might be somewhat lower than values determined when the subjects are under anesthesia. To our knowledge, this is the first reported study to investigate the nasal absorption in a conscious, nonanesthetized animal model for a lipophilic drug such as THC and to further determine the effect of a bioadhesive gel on the nasal absorption of such drug.

Materials and methods

Materials

THC, acetic acid, propylene glycol, and polyethylene glycol 400 were obtained from Sigma-Aldrich Chemical Co. (Milwaukee, WI, USA). Medium molecular weight chitosan was obtained from Fluka (Buchs, Switzerland). Acetic acid, purified water USP, ammonium formate, and high-performance liquid chromatography (HPLC) grade solvents were obtained from Fisher Scientific (Pittsburgh, PE, USA). Water for HPLC was passed through a reverse osmosis system (Milli-Q® Reagent Water System) before use. Isoflourane gas for anesthesia was provided by Ohmeda VMC Anesthesia (Madison, WI, USA). Siliconized microcentrifuge tubes, vials, and tips were purchased from Fisher Scientific (Fair Lawn, NJ, USA). Saline (0.9%, injectable) was purchased from Baxter Healthcare Corporation (Deerfield, IL, USA). All chemicals, reagents, and solvents were of the highest grade available and were used as provided.

Nasal gel preparation

Chitosan 2% (w/v) was dissolved in 2% (v/v) acetic acid in distilled water to form the gel base. About 400 μL of THC (100 mg/mL ethanol) and 10% (v/v) polyethylene glycol 400 were added to 1.6 mL of the chitosan gel while mixing at 1000 rpm for 15 minutes. The final pH of the gel formulation and the volume were adjusted to pH 5.0 and 2 mL, respectively. A control aqueous THC formulation that contained all the above ingredients except the chitosan gel was also prepared.

THC solutions

THC solutions for intranasal and intravenous administration were prepared utilizing 400 μL of THC (100 mg/mL ethanol) and 10% (v/v) polyethylene glycol 400, which were added to 1.6 mL mixture solution of ethanol, sterile water, and propylene glycol (50:20:30).

In vitro drug release studies

Mucus secretion from a healthy mucosal layer has been reported to be slightly acidic and to have a weak ionic strength[20]. Thus, the in vitro release studies were carried out with phosphate buffer, 0.1 M, pH 6.0, maintained at 37 ± 0.5°C, in an effort to simulate the physical properties of the mucus in the nasal cavity. A membraneless dissolution method was used for the THC in vitro release studies[21]. The chitosan gel formulation containing THC was incubated in 2 mL of release medium layered over the surface of the gel. To maintain sink conditions, 2 mL of hexane was placed on top of the buffer layer to continuously extract the THC from the release medium. At assigned time points, the hexane layer was removed, and a fresh 2 mL volume of hexane was layered on top of the release medium. An aliquot part (100 μL) of the resulting supernatant was directly transferred to autosampler vials, evaporated to dryness with nitrogen gas at ambient temperature, and analyzed by HPLC-mass spectrometry (MS) after appropriate dilution with the HPLC mobile phase.

Animals

Male New Zealand albino rabbits weighing 4.04.5 kg (Myrtle's Rabbitry Inc., Thompson Station, TN, USA) were used. The animal work was conducted at the University of Kentucky Chandler Medical Center, Division of Laboratory Animal Resources (DLAR). All research and testing activities related to this work were reviewed

and approved by the Institutional Animal Care and Use Committee (IACUC) prior to the initiation of this research and during its execution.

In vivo nasal bioavailability studies

Rabbits were acclimated for 2 weeks before the study. Following introduction of anesthesia (isoflourane gas), a catheter was placed in the marginal ear vein of the animals for blood sample collection.

A comparative determination of the blood levels of THC delivered both intravenously and nasally was carried out in a random cross-over design. Two weeks were allowed between treatments. Prior to intranasal administration, the test formulations were bottled in a 5 mL nasal spray bottle (Pfeiffer Corp., Radolfzell, Germany), which consisted of a quantitative spray pump (0.1 mL/spray). Each spray device was primed by activating the pump 10 times. The nasal formulations were administered by pumping a single spray into each nostril while the rabbit's head was held in an upright position, such that a total dose of 1 mg/kg was administered. The actuator tip was inserted about 1 cm into the nostril and forehead of the rabbit and the rabbit was kept in the upright position for 2 minutes after drug administration to prevent leakage of the nasal formulation out of the nostril. The spray devices were weighed before and after dosing to confirm that the required volume had been delivered. To determine the absolute bioavailability of the nasal dose, rabbits received 1 mg/kg THC intravenously injected into the marginal ear vein cannula followed by a 0.2 mL flush with 10% (v/v) heparin/normal saline solution to keep the cannula patent.

Animals were conscious throughout the duration of the experiment and were held in rabbit restrainers during blood sampling. All the blood samples were collected from a 2–3 mm longitudinal venosection catheter of the marginal ear vein. This enabled easy and repeated sampling after washing out the blood clot. Blood samples (about 0.5 mL) were collected at baseline, before THC dose administration; and subsequently at 5, 10, 20, 45, 60, 120, and 180 minutes post dose administration. Blood samples were collected by allowing the blood to drip freely from the marginal ear vein catheter into pre-heparinized tubes. Plasma (200 μL) was separated by centrifugation at 500 × *g* for 10 minutes, and was frozen at −20°C in polypropylene tubes until the time of analysis.

Sample preparation

Hexane (0.5 mL) was added to 200 μL of plasma sample in 2 mL polypropylene test tubes. The samples were vortexed for 60 seconds and centrifuged at 3578 × *g* for 10 minutes. An aliquot part (100 μL) of the resulting supernatant was directly transferred to autosampler vials, evaporated to dryness with nitrogen gas at ambient temperature, and then reconstituted in 100 μL HPLC mobile phase. Aliquot parts (5 μL) of this final solution were then injected onto the HPLC-MS system.

HPLC-MS analysis

Chromatography was performed on a Supelco (C_{18}, 4.6 mm × 50 mm) column with a mobile phase consisting 90% methanol and 10% 30 mM ammonium formate. The flow rate was set at 0.3 mL/min. The LC–MS system consisted of a Waters 2690 HPLC pump (Waters, Milford, MA, USA), a Waters 2695 autosampler, and a Micromass® ZQ™ Mass Spectrometer (Waters) which utilized electrospray ionization detection. Selected ion monitoring of THC was performed in the positive mode for the most abundant ion (m/z = 315.2), M+ = 304 m/z (dwell time 0.8 seconds). Capillary voltage was 4 kV, and cone voltage was 38 V. The source block and desolvation temperatures were set at 110°C and 350°C, respectively. Cone and desolvation gas flow were set at 50 and 500 L/h, respectively. Calibration curves were constructed using a linear regression of the drug peak area versus nominal drug concentrations. MS control and spectral processing were performed using MassLynx™ software, version 4.0 (Waters).

Pharmacokinetic analysis

Plasma concentration–time profiles of THC after intravenous and intranasal delivery were evaluated by a non-compartmental model (WinNonlin Professional, version 5.2, Pharsight Corporation, Mountain view, CA, USA). The maximum plasma concentration of THC (C_{max}) and the time required to reach the maximum concentration (T_{max}) were obtained directly from the actual plasma profiles. The area under the curve between 0 and 180 minutes was calculated by the linear trapezoidal method. The 0 minute concentration for the i.v. administration studies was extrapolated by the WinNonlin program. Pharmacokinetic parameters, such as terminal elimination half-life ($t_{1/2}$), the elimination rate constants (k_e), and area under the curve from 0 minute to infinity ($AUC_{0min-\infty}$), were also determined using the WinNonlin program.

The percent absolute bioavailability (F, %) of the nasal formulation was calculated from Equation (1):

$$F = \frac{AUC_{IN}}{AUC_{IV}} \times \frac{DOSE_{IV}}{DOSE_{IN}} \times 100, \quad (1)$$

where AUC_{IN} is the area under the curve from 0 minutes to infinity ($AUC_{0min-\infty}$) for either intranasal gel or the drug solution administration and AUC_{IV} is the area under the curve from 0 minutes to infinity ($AUC_{0min-\infty}$) for i.v. administration. $DOSE_{IN}$ and $DOSE_{IV}$ are the corresponding doses for the nasal and intravenous administration, respectively.

Statistical analysis

Pairs of groups were compared by Student's t-test. Differences between groups were considered significant at $P < 0.05$. Values for all measurements are expressed as means ± SD.

Results

The in vitro release profile of THC from the chitosan gel formulation is shown in Figure 2. The time taken for the release of 50% of the drug in the formulation ($t_{50\%}$) was within 62 minutes, which was well fitted to first-order kinetics ($r > 0.99$). The rate constant of release was obtained by plotting the logarithm of remaining drug percent versus time and was found to be 0.01 minute^{-1} (Figure 3).

The LC–MS method was developed and validated over the THC concentration range 1–4000 ng/mL, and found to be satisfactory for the determination of THC in rabbit plasma. The limit of quantification was established at 1 ng/mL.

To investigate the feasibility of the nasal route for systemic delivery of THC, the pharmacokinetics of the compound was compared following intranasal and intravenous dosing in rabbits. Figure 4 illustrates the mean plasma concentration versus time curves for THC obtained after i.v. injection, nasal gel administration, and nasal solution administration, at a dose of 1 mg/kg in rabbits. The representative kinetic values were determined for each rabbit using a noncompartmental i.v. bolus model with first-order elimination. The values (mean ± SD) for k_e and $t_{1/2}$ were 0.01 ± 0.00 minute^{-1} and 133.9 ± 39.9 minutes, respectively.

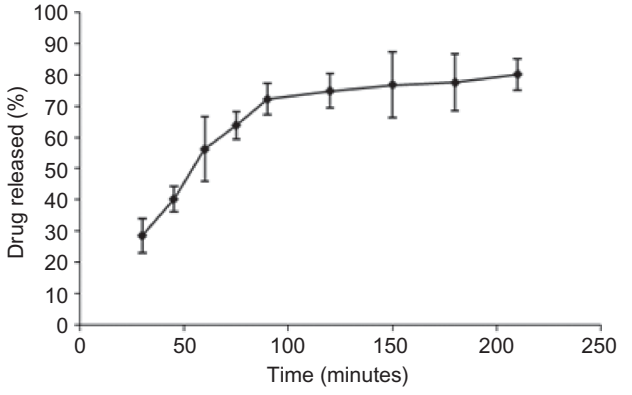

Figure 2. In vitro release profile of THC from the mucoadhesive chitosan gel formulation.

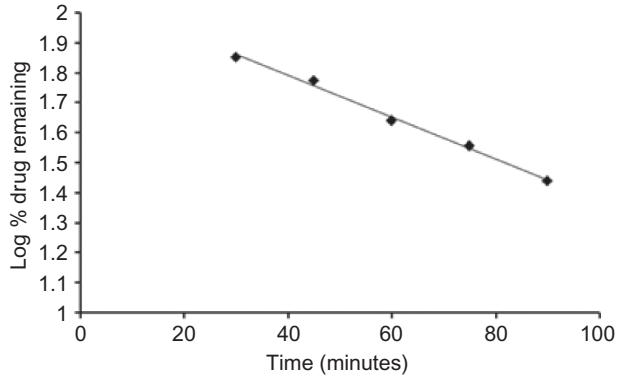

Figure 3. In vitro release profile of THC from the mucoadhesive chitosan gel formulation, plotted in first-order kinetic model.

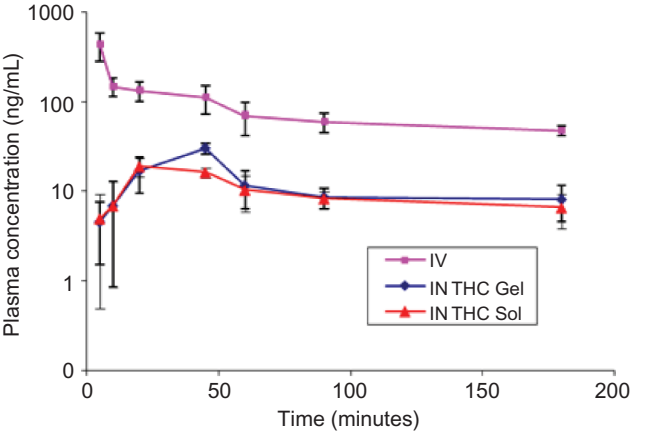

Figure 4. Mean plasma THC concentration versus time curves after nasal (IN) and intravenous (IV) delivery (1 mg/kg dose) to rabbits ($n = 3$). All values show the mean ± SD.

The pharmacokinetic parameters C_{max}, T_{max}, $AUC_{0min-\infty}$, and the F values for THC after i.v., intranasal gel administration, and intranasal solution administration are summarized in Table 1.

Discussion

Intranasal delivery could be especially important in the management of crisis situations such as severe nausea and vomiting[13,22]; intranasal administration of THC was the focus of this current research by utilizing fully dissolved THC in either solution or a gel formulation.

The mean absolute bioavailability values for THC after nasal administration of THC in solution or in gel formulation did not show any significant statistical difference ($P > 0.05$). However, both values are close to the THC absolute bioavailability value of 16.0 ± 7.5% that was obtained after sublingual administration of a solid THC/β-cyclodextrin complex to rabbits[23]. After nasal administration, the THC in chitosan gel formulation was absorbed less rapidly (T_{max} = 45 minutes) than THC solution (T_{max} = 20 minutes).

After nasal administration, the THC solution reached a C_{max} value of 20 ± 3 ng/mL at 20 minutes. Interestingly, the THC loaded in chitosan gel formulation followed almost the same profile at early time points and subsequently afforded a higher C_{max} value of 31 ± 4 ng/mL (T_{max} = 45 minutes). The absolute bioavailability of the THC solution after nasal delivery was determined from plasma THC concentration in comparison to plasma concentrations obtained after intravenous injection; the value was 13.3 ± 7.8%. Utilizing intranasal delivery, a drug is absorbed directly into the systemic circulation, by-passing the problems that occur with oral administration. Solubilized THC in ethanolic solution given

Table 1. Pharmacokinetic parameters of THC after intravenous and nasal administration of THC gel or solution formulation at 1 mg/kg dose in rabbits (mean ± SD, $n = 3$).

Route	Formulation	C_{max} (ng/mL)	T_{max} (minutes)	$AUC_{0min-\infty}$ (ng/mL/min)	F (%)	Volume of distribution (mL/kg)	Clearance (mL/min/kg)
Intravenous	THC solution	1475 ± 1230[a]	0[a]	26,062 ± 6043	100	6059 ± 1593	39.8 ± 9
Nasal	THC chitosan gel	31 ± 4	45	3759 ± 776	15.2 ± 6.2	9037 ± 4287	41.5 ± 8.7
Nasal	THC solution	20 ± 3	20	3452 ± 1109	13.6 ± 4.7	1,0314 ± 3115	41.8 ± 11

[a]Extrapolated value.

orally to rabbits was reported to have a bioavailability value of 1.3 ± 1.4%[23]. In the current study, the increase in THC bioavailability after nasal administration of the THC formulations is most probably because of the avoidance of first-pass metabolism.

The nasal absorption of THC from the gel formulation, in conscious rabbits, was evaluated in comparison with absorption of THC from the nasal solution. The absolute bioavailability values for THC were 15.4 ± 6.5% and 13.3 ± 7.8%, for the THC nasal gel and solution formulations, respectively. This small difference in bioavailability may be related because of one or more factors, such as an increase in the mucosal lipid fluidity or direct loosening up of the tight junctions of the nasal epithelia. Furthermore, chitosan acts as a mucoadhesive material by binding strongly to negatively charged biological surfaces such as mucous membranes. The hypothesis behind the use of chitin was that chitosan gel would intensify the contact between the drug and the nasal absorption mucosa, thus leading to an increased THC concentration at the absorption site. The formulation containing chitosan gel slightly increased the bioavailability as compared to the solution formulation, although the difference did not reach statistical significance ($P > 0.05$). This might be attributed to the lipophilic physicochemical properties of THC that hindered a statistically significant enhancement in the compound nasal absorption even with the aid of a mucoadhesive gel.

One of the major factors which affect the release of drug from a gel matrix formulation is dilution by biological fluids. This can be a challenge in nasal drug delivery because of the small volume of aqueous mucous and relatively short residence time of drug at the absorption site. Mucoadhesive gels such as chitosan enhance the bioavailability of some drugs after nasal administration. However, in the case of THC no statistical difference in bioavailability between the nasal gel and the nasal solution formulations was observed. This might be related to the lipophilic character of THC and its poor water solubility which causes drug absorption from the nasal cavity to the systemic circulation to be the rate-limiting step rather than the release from the nasal gel formulation being the rate-limiting step. The lipophilicity of THC could influence epithelial permeation, especially in the presence of epithelial mucus and other secretions which are polar in nature.

After nasal administration, the THC in chitosan gel formulation was absorbed less rapidly (T_{max} = 45 minutes) than the THC nasal solution (T_{max} = 20 minutes). Thus, the effective nasal absorption of THC from the gel formulation is dependent on fast dissolution and release from the chitosan gel matrix. Furthermore, the mucociliary clearance can play a major factor. The majority of the investigations published thus far on the use of mucoadhesive gel formulations in animal experiments utilize anesthetized subjects with very few exceptions. In a conscious animal or human, mucociliary clearance is more active and the absolute bioavailability might be somewhat lower than values obtained when the subjects are under anesthesia. The slow absorption of THC from the nasal cavity when the gel formulation is administered can be attributed to the high viscosity of the formulation together with the extreme lipophilic nature of THC, which might interfere with the permeation of the drug through nasal epithelium. In our rabbit model, conscious animals were used, because of the fact that anesthesia could impair the mucociliary clearance to some extent and allow the formulation to remain in contact with the nasal mucosa for a longer period of time than would be normally expected without anesthesia.

Conclusion

The results of the present study suggest that intranasal administration of THC in a solubilized form or in a mucoadhesive chitosan gel formulation could be an attractive modality for the delivery of THC systemically. Thus, the clinical efficacy and safety of this intranasal delivery system needs to be further investigated.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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