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### Abstract:

What is currently needed for optimal use of medicinal cannabinoids is a feasible, nonsmoked, rapid-onset delivery system. Cannabis "vaporization" is a technique aimed at suppressing irritating respiratory toxins by heating cannabis to a temperature where active cannabinoid vapors form, but below the point of combustion where smoke and associated toxins are produced. The goal of this study was to evaluate the performance of the Volcano vaporizer in terms of reproducible delivery of the bioactive cannabinoid tetrahydrocannabinol (THC) by using pure cannabinoid preparations, so that it could be used in a clinical trial. By changing parameters such as temperature setting, type of evaporation sample and balloon volume, the vaporization of THC was systematically improved to its maximum, while preventing the formation of breakdown products of THC, such as cannabiol or delta-8-THC. Inter- and intra-device variability was tested as well as relationship between loaded- and delivered dose. It was found that an average of about 54% of loaded THC was delivered into the balloon of the vaporizer, in a reproducible manner. When the vaporizer was used for clinical administration of inhaled THC, it was found that on average 35% of inhaled THC was directly exhaled again. Our results show that with the Volcano a safe and effective cannabinoid delivery system seems to be available to patients. The final pulmonary uptake of THC is comparable to the smoking of cannabis, while avoiding the respiratory disadvantages of smoking. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 95:1308-1317, 2006

**Keywords:** delta-9-tetrahydrocannabinol; cannabis; vaporizer; aerosol; pulmonary drug delivery; formulation vehicle; controlled delivery

### Introduction

Cannabis (*Cannabis sativa* L.) has a long history as a recreational drug and as part of traditional medicine in many cultures of the world. Nowadays, cannabis is used medically by patients suffering from diseases varying from cancer and HIV/AIDS to multiple sclerosis, frequently in the form of unprescribed self-medication.<sup>1, 2</sup>

Marinol®, an oral form of the main psychoactive constituent of cannabis, delta-9-tetrahydrocannabinol (THC), has been developed for some indications. However, oral THC is notoriously unreliable in its effects.<sup>3</sup> Drawbacks of Marinol® include its slow onset of action, large variability in bioavailability, and extensive first pass metabolism. Moreover, there is the inconvenience of taking oral medication in case of nausea or vomiting. Therefore, for many patients the demand for more effective cannabinoid-based medications persists. For this group of patients cannabis smoking is a more convenient method of administration, allowing self-titration of the desired effects. However, inhalation of toxic compounds during cannabis smoking poses a serious hazard. This risk is not thought to be due to cannabinoids, but rather to noxious pyrolytic byproducts.<sup>4, 5</sup> Consequently, the shortcomings of smoked cannabis have been widely viewed as a major obstacle for approval of crude cannabis as a medicine by public health authorities.<sup>6</sup>

Cannabis "vaporization" or "volatilization" is a technique aimed at suppressing irritating respiratory toxins by heating cannabis to a temperature where active cannabinoid vapors are formed, but below the point of combustion where pyrolytic toxic compounds are made. Vaporization offers patients who use medicinal cannabis the advantages of the pulmonary routes of administration, that is: rapid delivery into the bloodstream, ease of self-titration, and concomitant minimizing the risk of over- and under-dosing, while avoiding the respiratory disadvantages of smoking.

In an series of studies the vaporizing of cannabis samples was systematically tested to show its advantage over smoking. When a variety of smoking devices (including water pipes) were compared, specifically examining THC and solid smoke tars, it was found that only vaporizers were capable of achieving reductions in tar relative to THC when compared to direct smoking of cannabis.<sup>7, 8</sup>

A follow-up study tested a vaporizer that was found to deliver THC while completely eliminating three specific toxins (naphthalene, benzene, and toluene) in the solid phase of the vapor.<sup>9</sup> The study also detected a > 56% reduction in tars and a qualitative reduction in carbon monoxide, but did not test for any other chemicals.<sup>10</sup> In a more recent study,<sup>11</sup> GC-mass-spectrometry was used to analyze the gas phase of vaporized cannabis for a wide range of toxins, particularly concentrating on the highly carcinogenic polynuclear aromatic hydrocarbons (PAHs). The vaporizer that was used was the Volcano.<sup>® 12</sup>

It consists of a heater, a ventilator, a filling chamber, a valve, and a balloon. During operation the balloon is inflated with hot air and cannabinoid vapors. Using cannabis plant material as the sample, vapors were found to consist overwhelmingly of cannabinoids, while the combusted control contained over one hundred additional chemicals, including several known PAHs.

Although a large variety of vaporizing devices is available on the market, the Volcano is one of the few devices that have been tested scientifically to some extent. It is a herbal vaporizer, intended for the vaporization of whole cannabis plant materials (i.e., flowertops), but numerous unexplored variables could affect the efficiency and output of vaporization. These parameters are variations in temperature; differences in specimen density, weight, content of water and essential oils, and consistency of material in the filling chamber; differences in the variety and potency of cannabis used; and use of different preparations such as crude flowertops, hashish, hash oil, etc. Because of the paucity of data it has so far been difficult to show that the Volcano vaporizer can be used as a reliable tool for the reproducible administration of THC or other cannabinoids. A solution to this would be in the use of pure cannabinoid preparations of known concentration to guarantee an exact and reproducible loading of cannabinoids.

In this study the Volcano vaporizer was evaluated as a novel method for the administration of THC. Pure cannabinoid preparations were used in order to obtain quantitative results in terms of efficiency and reproducibility of THC delivery into the balloon of the Volcano. By changing parameters such as temperature setting, type of evaporating sample, and balloon volume, the vaporization of THC was systematically improved to its maximum yield, while preventing the formation of degradation products. Factors that resulted in loss of THC by condensation, that is, storage time of the balloon and used of the filling chamber, were evaluated. The inter-device reproducibility of THC vaporization under optimized conditions was determined. Finally, the results of this study were used for the clinical administration of THC by vaporizing. The amount of exhaled THC was determined and compared to the dose, which was inhaled through the Volcano.

Our results indicate that the Volcano is a convenient device of the administration of THC by inhalation.

## **Materials and methods**

### **Materials**

All organic solvents were HPLC or analytical grade, and were purchased from J.T. Baker (Deventer, The Netherlands). Anthracene (min. 99% purity) was purchased from Aldrich (St. Louis, MO). Deuteriated chloroform (CDCl<sub>3</sub>) was from Eurisotop, Gif-sur-Yvette, France. Glass fiber filters (Cambridge type, borosilicate glass, 92 mm diameter) and tightly fitting filter holders for vapour extraction were obtained from Borgwaldt Technik GmbH (Hamburg, Germany). Cannabis plant material (female flowertops) was medical grade and obtained from Bedrocan BV (VGeendam, The Netherlands). It had a water content of about 8%, a THCA content of about 12% and virtually no free THC.

Purified THC and THCA (purity <98%) were produced and quantified as reported earlier.<sup>13, 14</sup> THC was of pharmaceutical grade. The cannabinoids were stored as ethanolic solutions at -20°C at a concentration of 50mg/mL.

### **The Volcano Device**

The Volcano<sup>®</sup> was obtained from Storz & Bickel GmbH & Co. (Tuttlingen, Germany) and was used according to the manual as provided by the manufacturer. It is a vaporizer or evaporator that can evaporate the active substances or aromas from plant material by using a hot air flow (Fig. 1). Depending on the type of filling chamber used, whole plant material or liquid samples (e.g., aromatic oil, extract, or pure compounds in solution) can be used. Evaporated compounds are collected in a

detachable plastic balloon, which can be removed and fitted with a mouthpiece for inhalation. Volume of the balloon can be varied. Unless otherwise stated, a balloon length of 55 cm (around 8L) was used, as recommended by the manufacturer. The temperature control ranges from setting 1-9, corresponding to temperatures of 130-226°C (see tab. 1). Before each new set of experiments the whole device was thoroughly cleaned with ethanol. At the start of each evaporation the Volcano was preheated until the indicator light showed that the target temperature was reached. The balloon, connected to the filling chamber, was immediately placed onto the Volcano and the ventilation was started. When the balloon was completely inflated, ventilation was stopped and the content of the balloon was processed for analysis within 5min, unless stated otherwise. All laboratory experiments were carried out in a standard laboratory fume hood under constant ventilation with an ambient room temperature of about 22°C and a humidity of 40-60%. The air was not conditioned (e.g., by HEPA filters).

### **Use of the Liquid Pad**

The pure cannabinoids THC or THCA were used as ethanolic solutions. For these liquid samples an adapted filling chamber was used, containing a removable disc made of tightly packed stainless steel wire mesh (liquid pad), obtained from the manufacturer of the Volcano. For each experiment the appropriate amount of the cannabinoid was dissolved in a final volume of 200 µl of ethanol for application onto the liquid pad and ethanol was allowed to evaporate for 10 min under ambient conditions. A new liquid pad was used for each experiment.

### **Extraction of THC from the Vapor and the Liquid Pad**

Cannabinoids were recovered from the vapor phase inside the balloon by condensation onto glass fiber filters, designed to capture particles <0.1 microns. Vapor was slowly aspirated through the glass-fiber filter which was then extracted twice with 15mL mL of methanol/chloroform (9:1, v/v) under ultrasonication. After evaporating the extraction solvent, samples were reconstituted in 5mL of ethanol for analysis by HPLC or NMR. These ethanolic samples will be further referred to as vapor extracts. Residual THC on the liquid pad was recovered by extracting the liquid pad twice using methanol/chloroform (9:1, v/v) under ultrasonication. Extracts were further handled as described above for the vapor extracts. Recovery was determined by spiking filters or liquid pads with THC (2 mg) and performing the described extraction procedure.

To assess the efficiency of condensation of cannabinoids onto the glass fiber filter, a wash bottle filled with ethanol was placed after the filter. The escaping gases were bubbled through this liquid which was thereafter analyzed by HPLC to measure untrapped cannabinoids.

### **Quantitative <sup>1</sup>H-Nuclear Magnetic Resonance Spectroscopy (NMR)**

Quantitative of THC in the extracts was done by quantitative <sup>1</sup>H-NMR using a Bruker 300 MHz NMR apparatus as described by Hazekamp et al.<sup>14</sup>

In short, an exact volume of the sample was mixed with 1.0 mg of anthracene as internal standard for quantification. The sample was then evaporated to dryness under vacuum and reconstituted in chloroform (deuteriated) for <sup>1</sup>H-NMR analysis.

### **High Pressure Liquid Chromatography (HPLC)**

HPLC was used for both qualitative and quantitative analysis of the obtained extracts. The HPLC profiles were acquired on a Waters (Milford, MA) HPLC system consisting of a 626 pump, a 717 plus autosampler, and a 2996 diode array detector (DAD), controlled by Waters Millennium 3.2 software. Full spectra were recorded in the range of 200-400 nm. The analytical column was a Vydac (Hesperia, CA) C<sub>18</sub>, type 218MS54 (4.6 x 250 mm, 5 µm), with a Waters Bondapak C<sub>18</sub> (2 x 20 mm, 50 µm) guard column. The mobile phase consisted of a mixture of methanol-water containing 25mM of formic acid gradient mode; methanol: water in ratios from 65:35 to 100:0 over 25 min, then isocratic to 28 min. The column was reequilibrated under initial conditions for 4 min. Flow-rate was 1.5 mL/min and total runtime was 32 min. All determinations were carried out at ambient temperature. The main neutral and acidic cannabinoids were well separated with this method.<sup>15</sup> Analyzed concentrations were well above the limit of quantification of the used method.

## **Evaluation of Temperature Control**

Temperature control was evaluated at setting 1, 3, 5, 7, and 9 (see Table 1). Time needed to reach target temperature, and accuracy and stability of target temperature were determined using an electronic thermometer (response time; 250 ms). Temperature was measured in the middle of the filling chamber, on top of the liquid pad, and each measurement was started by switching on the airflow directly after the indicator light of the heater had switched off. Inter-device variability for the same parameters was tested for four different Volcano devices. All experiments were repeated three times.

## **Optimization of Vaporizing Parameters**

- (a) Temperature: Cannabis plant material, and pure cannabinoids THCA and THC were vaporized at temperature settings 1, 3, 5, 7, and 9 in order to determine the delivery into the balloon as well as the formation of degradation products. Vapor extracts were qualitatively analyzed by HPLC for detection of degradation products, while quantitative analysis by NMR was used for determination of delivery.
- (b) Heating time: In order to determine the minimal time that is needed to reach maximal evaporation of THC, the following experiment was performed: THC (2 mg) was applied onto the liquid pad and the ventilation was activated for a duration ranging from 10 to 300s, without balloon attached to the device so THC could evaporate freely. Subsequently, residual THC was extracted from the liquid pads and extracts were quantitatively analyzed by NMR.

## **Relationship Between Loaded Dose and Delivery**

The relationship between quantity of THC loaded onto the filling chamber and delivery into the balloon was determined in the range of 2-8 mg of THC. Vapor extracts were analyzed by NMR and HPLC, and each experiment was performed threefold.

## **Inter-Device Variability**

Using the optimized parameters as determined in this study, four Volcano devices were finally evaluated for inter-device variability in THC delivery. Samples of 4 mg of THC were used for vaporizing and each Volcano was tested on five occasions. Vapor extracts were analyzed by NMR.

## **Condensation of THC onto the Balloon and Filling Chamber**

The effect of storage time of the balloons on condensation of THC was determined by storage of the balloon at room temperature for a duration of up to 180 min after vaporizing (2 mg THC). The vapor extract was then collected for analysis. Each experiment was performed threefold. Throughout this study balloons were always processed within 5 min after vaporizing. Therefore, it was determined more exactly how much THC was lost due to condensation onto the walls of the balloon after 5 min of storage by carefully cutting the balloon (n=5) into pieces and extracting twice with ethanol under ultrasonication.

In order to determine the amount of THC that condensed onto the filling chamber (excluding liquid pad) and valve, after some experiments these parts were extracted twice with ethanol under ultrasonication. Finally, extracts were concentrated and THC was quantified by NMR.

## **Clinical Application of the Volcano**

At the Centre for Human Drug Research (CHDR, Leiden, The Netherlands) a methodology study was performed to study the effects of THC administration using the Volcano vaporizer. The study was approved by the Medical Ethical Committee of Leiden University, The Netherlands. Preliminary results of this study were published recently,<sup>16</sup> and full results will be published in the near future. In short, during two separate occasions subjects received a rising dose of 2, 4, 6, and 8 mg THC (loading dose in filling chamber) or placebo (ethanol only) administered via the volcano, using the optimized parameters as determined in this study. Administrations were given with 1.5 h intervals. The balloon (8 L) had to be inhaled through the mouth within 3 min and breath was held for 10 s after each inhalation. Following each inhalation, subjects were asked to exhale through a filter of the same type as used for vapor extraction. Filters were subsequently extracted as mentioned before and the quantity of exhaled THC was determined by NMR. Because of time restraints, no further evaluation of lung function (e.g., FEV1) could be performed.

## **RESULTS**

### **Trapping and Recovery of THC for Analysis**

Since no trace of THC could be found in the ethanol fraction of the wash bottle inserted after the filter, it was concluded that THC was completely trapped onto the use type of filter. Recovery of THC was found to be 99.3 (1.1)% from the filter and 83.0 (2.5)% from the liquid pad. All measurements were corrected for these values

### **Accuracy of the Temperature Setting**

At all tested temperature settings it was found that temperature reached a first plateau after about 30 s. After that temperatures remained relatively stable for some time, but kept below accepted limits (target temperature 4°C, as claimed by the manufacturer) for all tested settings. Results can be seen in Figure 2a. However, after about 45-60 s, depending on the setting, the heating element was activated again by the temperature sensor, and about 20 s later temperatures increased by a few degrees bringing the temperature within specified limits. It must be concluded that the liquid pad and the filling chamber need some time to heat up to the target temperature.

### **Reproducibility of the Vaporizer**

When four different Volcano devices were evaluated under equal conditions to evaluate inter-device variability (Fig.2b), some small differences in heating profile were found. Only temperature setting 9 was evaluated here after it had been shown to be the optimal temperature for THC delivery. Although two devices reached target temperature (accepted variation 4°C) already after 30 s, the two others needed 60 s or more to do so. For devices the temperature increased above the maximum limit of target temperature in the 90 s duration of our experiment. In conclusion each individual Volcano device shows little variability during sequential uses (intra-device variability), although small differences do exist between different devices (inter-device variability).

### **Optimizing of Vaporizing Parameters with Different Substrates**

THCA: Under the influence of heat THCA can be converted into THC by decarboxylation. Indeed, when THCA was used it was observed that this conversion increased with temperature and maximum delivery of THC was about 33% at the highest temperature setting (Fig. 3). However, conversion was not complete and THCA was present in the vapor extracts at a level of about 5.5 (1.3) % relative to THC.

Crude flower tops: The use of plant material (200 mg at 12% THCA) resulted in a maximum THC delivery of only 29% (Fig. 3). In fresh cannabis plant materials THC is present in the form of its acidic precursor THCA and the use of plant material resulted in an incomplete decarboxylation with about 3.8% residual THCA present in the vapor. Besides THC, several other cannabinoids as well as a range of other plant components were detected. Therefore, the use of cannabis plant material in the Volcano should not be recommended for the administration and study of THC alone.

Pure THC: Evaporation of THC was shown to increase with temperature with a maximal delivery of about 53% at setting 9 (Fig. 3), while no degradation products (delta-8-THC ( $\Delta^8$ -THC), cannabinoid (CBN), or other unknown peaks in the HPLC-chromatogram) were observed at any setting. Therefore, using the Volcano device, it was concluded that the highest delivery yield was achieved with an ethanolic solution of pure THC. When liquid pads were extracted after vaporizing it showed a very low amount of residual THC, indicating a very high yield of evaporation, at the highest temperature setting. This strongly suggests that nondelivered THC doses not remain on the liquid pad, but is probably lost by condensation after initial evaporation.

Minimum time was determined for the maximal evaporation of THC from the liquid pad by measuring residual THC after vaporizing. Figure 4 shows that the amount of residual THC rapidly decreases between 20 and 40 s after starting of the vaporizing. This corresponds with the observation that in the same time-period the (near) target temperature of the Volcano is reached (Fig. 2a and b). After 45 s most of the THC is evaporated and just a small fraction of THC can be found in the liquid pad extract, indicating that vaporizing time should be at least 45 s. In a preliminary test when using a temperature setting of 9 with a balloon volume of 4 L (filling time around 30 s), a low THC delivery (only 30% for 8 mg of THC) with a high dose variability (relative SD 22%) was observed indicating that the maximum delivery yield was not yet reached.

It was observed that the maximal evaporation of THC is reached after 120 s, (Fig. 4). Since the Volcano is blowing air at a constant rate of about 9 L per min, this corresponds to a balloon volume of about 18 L. However, by empirical testing in our laboratory (data not shown) it was found that a maximum volume of about 8 L could be inhaled within 3 min when following the protocol of the clinical trial. Therefore, a balloon volume of 8 L (filling time of about 55 s) was selected for further study. Under these conditions, only about 5% THC remained on the liquid pad.

### **Relationship between Loaded Dose and Delivery under Optimal Conditions**

With a Volcano operating under the aforementioned optimized conditions (temperature setting 9, balloon volume 8 L) the delivery was determined with an increasing amount of THC ranging from 2 to 8 mg. It is shown in Figure 5 that the delivery was proportional to the loaded dose of THC; a linear curve was obtained with a regression coefficient ( $R^2$ -value) of 0.99. From the slope of the line, a mean delivery yield of 57.8 (6.9)% could be calculated.

Four available devices were then tested under conditions as mentioned above using a sample of 4 mg of THC. Differences in delivery between the Volcano devices were relatively small. Average delivery of all four Volcanos was 53.9 (8.1) % and this value was taken as the average delivery for further considerations.

### **Condensation onto Balloon and Filling Chambers**

Loss of THC during experiments could partially be accounted for by incomplete evaporation and condensation onto parts of the Volcano vaporizer. Prolonged storage of the balloon at room temperature after vaporizing led to a steadily increasing loss of THC by condensation up to the point that after 180 min almost no THC could be detected anymore in vapor extracts (Fig. 6). However, if the balloon was extracted within 5 min after vaporizing, less than 2% of the total dose was recovered from the inner surface of the balloon. Condensation of THC onto the other parts of the Volcano setup was found to be of significant importance. Visual inspection of the filling chamber shows the presence of a condensate mostly on the inside of the filling chamber just above the liquid pad. Extraction of the filling chamber together with the valve, but excluding the liquid pad, showed that an average of 23.6 (14.1) % of the loaded THC had condensed onto these parts of the Volcano, and could therefore account for a large part of the nondelivered THC.

### **Clinical Study and Loss by Exhalation**

The clinical trial was finished without any serious complaints by the test subjects. Some mild complaints included irritation of the throat and lungs, and coughing. However, these effects were also observed during inhalation of placebo and therefore could be an effect of residual ethanol. The development of significant physiologic changes after inhalation of vaporized THC indicates that THC can be effectively administered by this route.

Interestingly, it was shown that a large proportion of inhaled THC was not absorbed by the lungs. The total amount of THC used for evaporation was 20 mg of THC for each subject (Rising dose of 2, 4, 6,

and 8mg resulting in a total dose of 20 mg). Taking into account the average delivery yield of 53.9% as found in this study, only an average of 10.8 mg of THC was totally inhaled from the balloon. The amount of THC recovered from exhaled breath ranged from 2.5 to 4.4 mg, which means that up to 30% -40% of inhaled THC was not absorbed by the lungs. The variability of THC in exhaled breath (relative SD 5.4%) is comparable to the variability in delivery of THC by the Volcano. Taking this into account it could be concluded that absorption of THC by the lungs is probably very similar between different subjects.

## DISSCUSSION AND CONCLUSION

The Volcano® vaporizer was validated for the efficient and reproducible delivery of delta-9-THC, and was found to be able to deliver an average amount of about 54% of applied dose of THC into the balloon for inhalation. THC recoveries from smoke was found to range from 34% to 69% in a variety of studies using different types of smoking procedures.<sup>19-20</sup> Because the plant material is not burned in the Volcano, no significant harmful cancer causing combustion products are expected and the noxious intake, when compared to smoking, is greatly reduced.<sup>10, 11</sup> Using the Volcano device for pulmonary administration of THC, a delivery is reached that is comparable to smoking, but without the presence of degradation products or harmful byproducts in significant amounts.

Loading the Volcano with Cannabis plant material or pure THCA resulted in a residual amount of THCA in the vapor in the order 5% relative to THC. Not much is known about biological effects or metabolism of THCA, and therefore the use of THCA as sample for intended clinical administration of pure THC should be avoided. Older studies at least indicate that THCA is not psychoactive in monkeys.<sup>22</sup> Although in our study cannabis plant material was used only for comparative reasons, it is clear that a variety of cannabinoids and other compounds such as terpenoids are present in the vapor. With pure THC as the loading sample, temperature setting and balloon volume were optimized for a maximal, reproducible delivery of THC without formation of detectable amounts of degradation products. Using the highest temperature setting together with a balloon volume of 8 L was found to yield optimal results. Balloon volumes over 8L were not tested because of restraints in the clinical trial protocol. The target temperature of the Volcano was found to be not completely accurate and stable. Possibly this is a contributing factor to the relative variability in the delivery of THC, which was about 15% at setting 9. However, this is reasonable when compared found in smoking studies of cannabis plant material.<sup>19</sup> Accuracy of temperature control therefore does not seem to be of crucial importance under these conditions, although a more accurate temperature control might result in an even lower variability in THC delivery.

In the range of 2-8 mg of THC, the delivery was found to be linear with the amount of THC used. Prolonged storage of the balloon before inhalation resulted in an increasing loss of THC by condensation inside the balloon and after 3 h almost no THC could be recovered from the vapor in the balloon. However, if the content was extracted within 5 min after vaporization not more than 2% of THC present was lost. Vaporized THC was visible inside the balloon as a thin gray mist which was absent in placebo balloons, so during the clinical trial balloons had to be blinded with a black plastic cover.

During the clinical administration, it was found that about 35% of total THC was exhaled directly after inhalation and was therefore not absorbed by the lungs. When the efficiency of delivery during vaporizing and incomplete absorption by the lungs is considered, the final administration dose equaled about 6-8 mg of THC of the total amount of 20 mg loaded. The subjective effect upon the subjects seemed to be in accordance with such a dose as described in other papers.<sup>17, 18</sup> So it seems that a final uptake of 30-40% was reached (relative to loaded amount of THC), which is comparable to the efficiency reached by smoking of cannabis.

It has been shown that the administration of THC by aerosol is capable of producing the full constellation of cannabinoid effects in mice. These effects were CB1-receptor mediated, as shown by the use of selective Cb1 antagonists,<sup>23</sup> which confirms that the pulmonary administration of cannabinoids certainly has a clinical potential. Several studies have been performed using an aerosol for the administration of THC.<sup>23-26</sup> But because cannabinoids are almost completely insoluble in water this requires the use of solubilizers that are to be inhaled together with THC, which frequently results in irritation of the lungs and coughing. Moreover part of an administered aerosol can be swallowed and thereby administered orally, complicating the effects, kinetics, and metabolism of the administered compound. This has already been shown for aerosol administration of radiolabeled isoproterenol.<sup>27</sup>

Using the Volcano vaporizer seems to eliminate at least part of the problems associated with the use of an aerosol for the delivery of THC or other cannabinoids. It is likely that the Volcano also produces an aerosol, that is, droplets of various sizes in a gas phase made up of vapor and air. However, in an artificial lung model the majority of vaporized THC could reach the deepest compartment (personal communication with Volcano manufacturer) indicating that the exhaust blown from the Volcano consists for a large part of very fine droplets and vapor. Nonetheless, the composition of an aerosol is partially dependent on the ambient conditions such as humidity and presence of nuclei for condensation. So although our results were found to be reproducible with a relatively low variability, these factors must be taken into consideration for further development of the Volcano.

What is currently needed for optimal use of medicinal cannabinoids is a feasible, nonsmoked, rapid-onset delivery system. With the Volcano a safe and effective cannabinoid delivery system seems to be available to patients. Although our current study has concentrated on the delivery of THC, it should be noted that other cannabinoids might also have a role to play for some indications. In several medical studies, the effect of THC or dronabinol alone could not match the effect of a total cannabis preparation, indicating there might be other active cannabinoids needed for a full range of effects.<sup>28</sup> As an example, a combination of THC with CBD is now under clinical investigation for the treatment of chronic pain conditions.<sup>29</sup> The next step in the evaluation of the Volcano vaporizer should therefore include the study of mixtures of pure cannabinoids.

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