Department of Pharmacy and Pharmacology[1], Slotervaart Hospital, Amsterdam; Central Committee on the Treatment of Heroin Addicts[2], Utrecht; Department of Psychiatry[3], Academic Medical Centre, University of Amsterdam; Department of Pharmacology and Anatomy[4], Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Faculty of Pharmaceutical Sciences[5], Utrecht University,Utrecht, The Netherlands

Volatilisation of diacetylmorphine: *In vitro* simulation of 'chasing the dragon'

M. G. KLOUS[1], W. C. LEE[1], W. VAN DEN BRINK[2,3], J. M. VAN REE[2,4], J. H. BEIJNEN[1,5]

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Mrs Marjolein G. Klous, PharmD PhD, Slotervaart Hospital, Dept. Pharmacy and Pharmacology, P.O. Box 90440, 1006 BK Amsterdam, The Netherlands
apmlk@slz.nl

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In preparation for a trial on co-prescription of heroin to chronic treatment-resistant addicts, a pharmaceutical dosage form for smokable heroin was developed. During development of this product (a mixture of diacetylmorphine and caffeine), *in vitro* experiments were performed simulating 'chasing the dragon': the technique used by addicts for inhalation of heroin after volatilisation. Samples were heated on aluminium foil using a heating device and the vapours were collected and analysed using a HPLC-UV method. The recovery of diacetylmorphine and caffeine in vapours was studied after volatilisation of different powder mixtures at temperatures between 200 and 350 °C. Furthermore, the volatilisation set-up was combined with an Andersen sampler to determine the sizes of aerosol particles. Only small differences in recovery of diacetylmorphine and caffeine were found between temperatures and between powder mixtures: 46–62% of diacetylmorphine from the sample was recovered in vapour and 65–83% of caffeine. The only degradation product detected in vapour was 6-acetylmorphine (4.1–7.1%). In the temperature range studied, temperature mainly influenced the volatilisation rate. Mass median aerodynamic diameters of aerosols from diacetylmorphine-containing samples ranged from 1.8–4.1 μm; 45–60% of each sample was recovered as aerosol particles <5 μm. Volatilising pharmaceutical smokable heroin resulted in sufficient amounts of diacetylmorphine in vapour and in particles suitable for effective deposition in the lungs.

1. Introduction

Heroin (3,6-diacetylmorphine) is a well-known drug of abuse that is usually administered intravenously. However, smoking heroin has gained popularity since it was first described in Shanghai in the 1920s (Strang et al. 1997). After some refinement the use of an inhalation procedure called 'chasing the dragon' spread to South East Asia, India and some parts of Europe in 1960–1980 (Strang et al. 1997). In this procedure, addicts heat heroin powder on a piece of aluminium foil with a cigarette lighter until it melts and evaporates. The fumes are subsequently inhaled through a straw in the mouth.

A clinical trial was performed in the Netherlands to evaluate the effect of medical co-prescription of heroin and methadone on mental and physical health and social functioning of chronic, treatment-resistant, heroin-dependent patients (Van den Brink et al. 2003). Since in the Netherlands 75–85% of the heroin addicts use heroin by 'chasing the dragon' (Hendriks et al. 2001), two separate study protocols were developed; in one trial patients received injectable heroin, in the other they were prescribed pharmaceutical heroin to be inhaled after volatilisation. For the latter, we developed a dosage form: diacetylmorphine for inhalation, which consisted of a mixture of 75% w/w diacetylmorphine base and 25% w/w caffeine anhydrate (Klous et al. 2004a, 2004b). Diacetylmorphine base was preferred to diacetylmorphine hydrochloride, since the base has a lower melting point (173 °C) than the hydrochloride salt (243–244 °C) (The Merck Index 1996) and because of its relative insensitivity to degradation (Huizer 1987). Caffeine was added as it was suggested to increase the recovery of diacetylmorphine base and hydrochloride after volatilisation and to reduce degradation upon heating (Huizer 1987). Furthermore, it is commonly used as a diluent in street heroin (de la Fuente et al. 1996; Huizer 1987; Kaa and Bent 1986; Risser et al. 2000) and has never been associated with any adverse events as far as we know. It was therefore considered to be relatively safe to use as an excipient in pharmaceutical heroin for inhalation.

In this study, we describe a standardised method for *in vitro* simulation of the process of 'chasing the dragon'. This method was used to study the recovery of diacetylmorphine and caffeine from samples of diacetylmorphine base mixed with varying proportions of caffeine anhydrate at different temperatures. Furthermore, since in preparations for inhalation aerosol properties are important for

Table 1: Recovery results after complete volatilisation of pure diacetylmorphine base and pure caffeine anhydrate at different temperatures (°C)

Temperature	Caffeine			Diacetylmorphine base		
	250	300	350	250	300	350
Recovery (%)						
Condensate	65.0 (5.9)	66.2 (2.3)	72.1 (11.7)	55.2 (1.9)	48.5 (9.6)	45.1 (8.9)
Residue	1.4 (0.6)	0.0 (−)	0.1 (0.2)	0.9 (0.6)	8.7 (9.8)	2.4 (1.6)
Overall	66.4 (6.3)	66.2 (2.3)	72.2 (11.8)	56.1 (2.1)	57.2 (10.2)	47.5 (9.6)
Residue size (%)	2.9 (0.4)	0.0 (0.0)	0.1 (0.9)	11.4 (1.4)	16.5 (14.9)	7.5 (1.7)

Recoveries (as unchanged diacetylmorphine or caffeine) in condensate, in residue and overall are given as mean% w/w of sample mass, with standard deviation between parentheses. Residue sizes are given expressed as% w/w of sample mass

lung penetration and bioavailability, particle-sizing experiments were performed on the aerosols that were formed after volatilisation of diacetylmorphine, caffeine, and mixtures thereof.

2. Investigations and results

2.1. Volatilisation of pure drug substance samples

The results of the complete volatilisation of drug substance samples are given in Table 1. Most of the caffeine from the pure drug substance samples was recovered unchanged from the collected fumes ($68.2 \pm 7.8\%$ w/w ($n = 12$)), only very little (0–1.4%) was left in the sample holder. No carbonisation of these samples was observed, nor were unidentified peaks in the chromatograms from the condenser, or from the aluminium foil, which means that 31.8% w/w of the sample was unaccounted for.
Diacetylmorphine recoveries in the fumes emitted from diacetylmorphine base were lower, $52.9 \pm 8.8\%$ ($n = 12$) (Table 1). No significant differences were found between the three temperatures tested for either drug substance, but a trend of decreasing diacetylmorphine recoveries in condensate with increasing temperature was observed (Table 1). Even though diacetylmorphine base samples left carbonised residues after volatilisation and unidentified peaks were present in residue chromatograms, no signs of decomposition were detected in the chromatograms of the corresponding condensate samples. The major degradation product found in both condensate and residue samples after volatilisation of diacetylmorphine base was 6-acetylmorphine: 3.5–5.2% w/w (relative to diacetylmorphine in the sample, corrected for molecular weight) in condensate and 0.3–0.6% in residue. No morphine was detected in condensate or residue chromatograms. Mean overall recovery of a diacetylmorphine base sample as diacetylmorphine or 6-acetylmorphine in vapours or as residue weight was found to be $64.2 \pm 11.4\%$ w/w, indicating that 35.8% of the sample was not accounted for.

2.2. Volatilisation of diacetylmorphine/caffeine mixture samples

The results of the volatilisation experiments with diacetylmorphine/caffeine mixtures are given in Fig. 1. Mean diacetylmorphine recovery from the mixture samples was not significantly different between the two temperatures tested: $55.0 \pm 8.2\%$ w/w at 250 °C and $56.2 \pm 6.7\%$ at 300 °C. The same was true for 6-acetylmorphine recovery ($5.6 \pm 1.3\%$ and $5.9 \pm 1.5\%$) and caffeine ($76.0 \pm 9.4\%$ and $76.9 \pm 6.0\%$, respectively). Some significant differences, however, were found between temperatures for specific mixture samples: diacetylmorphine recovery in condensate from 25% diacetylmorphine mixture samples was higher ($p = 0.043$) at 250 °C ($60.0 \pm 4.9\%$, $n = 4$) than at 300 °C ($49.0 \pm 6.7\%$, $n = 4$), while the opposite was found for 50% diacetylmorphine mixtures ($p < 0.035$, 250 °C: $45.6 \pm 2.7\%$, $n = 4$; 300 °C: $57.4 \pm 8.4\%$, $n = 3$) (Fig. 1). These differences were not reflected in the respective caffeine and 6-acetylmorphine recoveries (Fig. 1), or in diacetylmorphine, 6-acetylmorphine or caffeine recoveries from 75% diacetylmorphine mixtures (Fig. 1). There was no difference in recovery of these substances from 75% mixtures between temperatures of 250 °C and above, even though 6-acetylmorphine recovery showed a slight increase with temperature (Fig. 2). The mean recovery of 6-acetylmorphine from the 75% diacetylmorphine samples ($4.8 \pm 0.4\%$, $n = 8$) was significantly ($p < 0.002$)

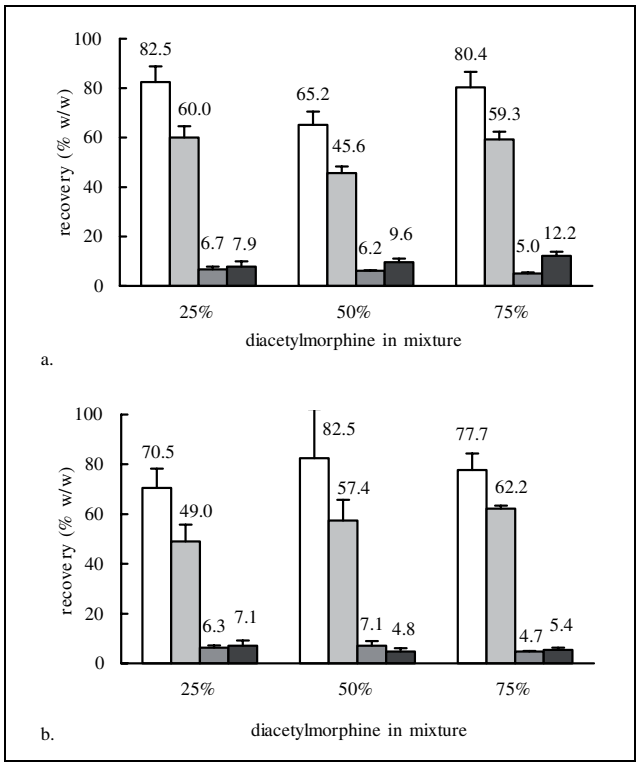

Fig. 1: Results of volatilisation of three different diacetylmorphine/caffeine mixtures (25%, 50%, 75%) at 250 °C (a) and 300 °C (b). Mean recoveries are given (% w/w) with error bars indicating standard deviations. Caffeine recovery (white bars) is given relative to the amount of caffeine in the powder sample; diacetylmorphine (light gray bars), 6-acetylmorphine (dark grey) and residue size (black) are given relative to the amount of diacetylmorphine in the sample (6-acetylmorphine % w/w corrected for molecular weight)

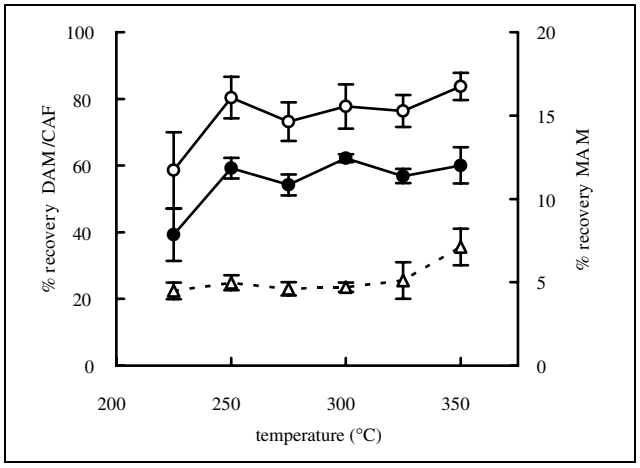

Fig. 2: Mean recoveries of diacetylmorphine (DAM, closed bullets), caffeine (CAF, open bullets) and 6-acetylmorphine (MAM, open triangles, right y-axis) after complete volatilisation of 75% diacetylmorphine mixtures at different temperatures (recoveries given as% w/w of the original amount in the sample, 6-acetylmorphine as% w/w of diacetylmorphine in the sample, corrected for molecular weight; error bars indicate standard deviations)

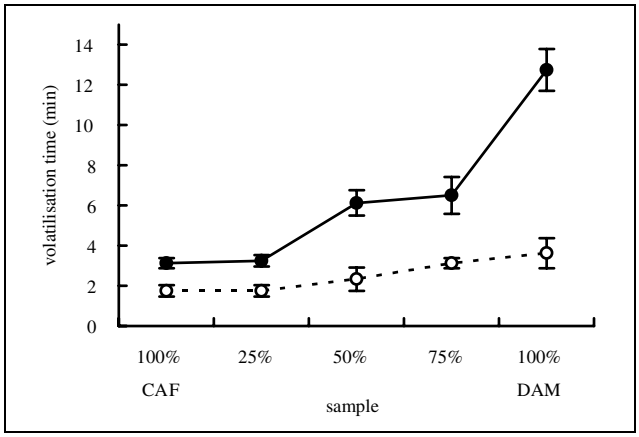

Fig. 3: Mean time needed for complete volatilisation for different sample types. The solid line represents the volatilisation time at 250 °C, the dashed line at 300 °C; error bars indicate standard deviation

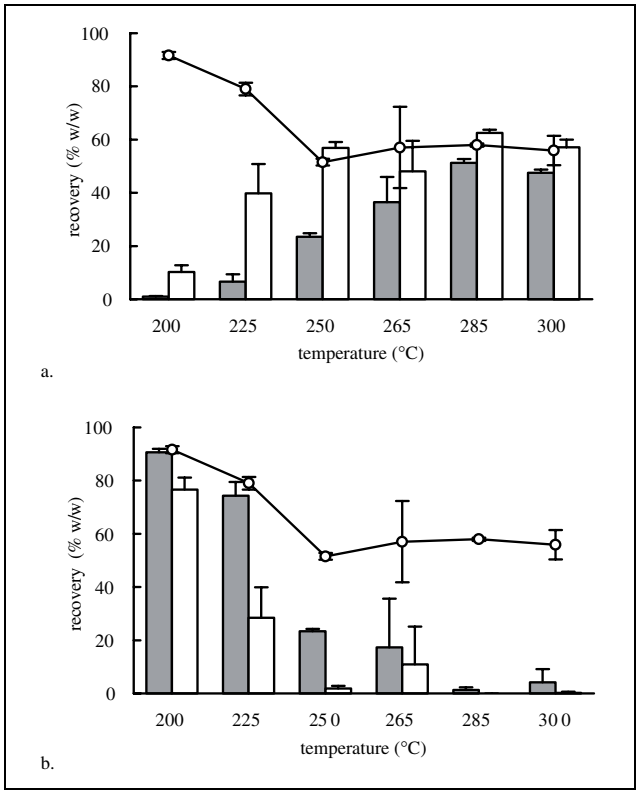

Fig. 4: Mean recoveries of diacetylmorphine and caffeine from a 75% diacetylmorphine mixture samples after heating them for 3 min at different temperatures. Bars represent recoveries in condensate (a.) and residue (b.): grey: diacetylmorphine, white: caffeine; the solid line represents overall recovery of the sample (as diacetylmorphine, 6-acetylmorphine or caffeine in condensate or residue)

lower than from the other two mixtures (50%: $6.6 \pm 1.2\%$, $n = 7$; 25%: $5.9 \pm 1.2\%$, $n = 8$) (Fig. 1). Overall, 62.9–80.3% of the mixture samples' weight was accounted for as diacetylmorphine, caffeine, or 6-acetylmorphine in condensate or as residue mass left on the aluminium foil. No morphine or any unknown extra peaks were detected in condensate chromatograms from volatilisation of diacetylmorphine/caffeine mixtures. Thus, 19.7–37.1% of the mixture samples was unaccounted for.

The ratio (w/w) of diacetylmorphine/caffeine had changed from 3 in the 75% diacetylmorphine powder mixture to 2.2 ± 0.2 in the condensate. Similarly, a decrease in the diacetylmorphine/caffeine ratio was observed with the 50% and 25% diacetylmorphine mixtures, from 1 and 0.33 in the powder mixture to 0.70 and 0.24 in the condensate, respectively. In residues, left after complete volatilisation of 75% diacetylmorphine mixtures, no caffeine was recovered and the amount of diacetylmorphine base that remained decreased when the temperature increased (2.9%, 1.8%, 1.0%, and 0.1% at 225 °C, 250 °C, 275 °C, and 300 °C, respectively).

The volatilisation rate of 75% diacetylmorphine mixture samples was found to depend on temperature: complete volatilisation took 25–34 min at 200–225 °C, 4.5–7.5 min at 250–275 °C and 2.5–3.1 min above 300 °C. Furthermore, complete volatilisation was shown to take more time when a sample consisted of a larger proportion of diacetylmorphine (Fig. 3).

The influence of temperature on the volatilisation process was also illustrated by the results from the experiment with a fixed heating time (Fig. 4). It is obvious from these graphs that heating the sample for 3 min at 200 °C results in volatilisation of only a small amount of caffeine and almost no diacetylmorphine (Fig. 4a), while heating for 3 min above 285 °C results in maximum recovery of both components in vapour and a negligible recovery in residue (Fig. 4b). A difference in volatilisation rate for both components of the residue can also be observed, since heating the sample for 3 min at temperatures below 250 °C results in higher recoveries of caffeine in condensate than diacetylmorphine (Fig. 4). Fig. 4 also shows a decrease in overall recovery with temperature: after 3 min at 200 °C 91.6% was recovered as diacetylmorphine, 6-acetylmorphine, or caffeine in condensate or residue, while above 250 °C mean overall recovery was $55.6 \pm 2.8\%$.

Analysis of the residues left in the aluminium sample holders after volatilisation of 50% and 75% diacetylmorphine mixtures show a decreasing proportion of caffeine in time for both mixtures (Fig. 5). Furthermore, the graphs show signs of increasing degradation in the residue when volatilisation times increase: the proportion of 6-acetylmorphine in the sample increases (especially in the 75% samples), as well as the 'unidentified' proportion of the residue (not diacetylmorphine, 6-acetylmorphine, or caffeine).

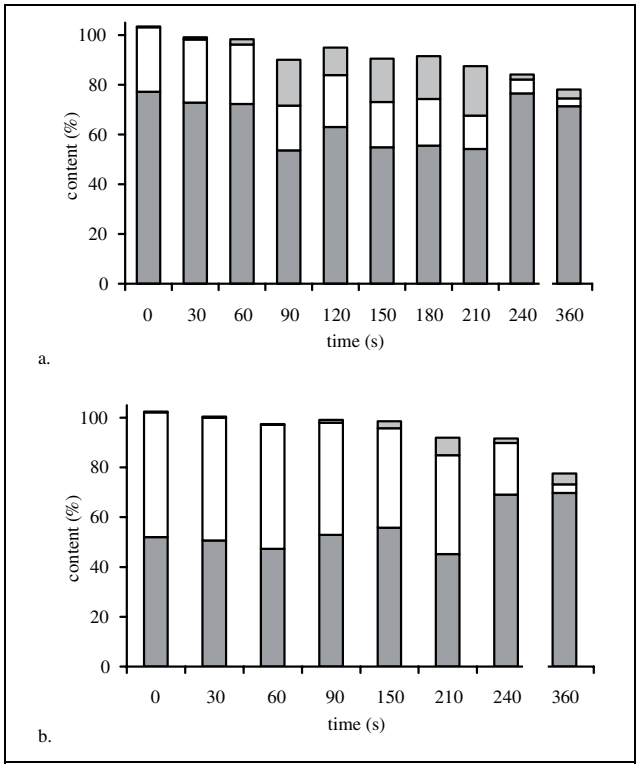

Fig. 5: Composition of the foil residue versus sample heating time (at 250 °C). Proportions (% w/w) of diacetylmorphine (dark grey), caffeine (white) and 6-acetylmorphine (light grey) are given found in residues left after volatilising (a) 75% and (b) 50% diacetylmorphine mixtures

2.3. Particle size

The results of the particle size determinations are shown in Table 2. When diacetylmorphine base and caffeine anhydrate were volatilised at 300 °C, the resulting aerosols showed very different particle sizes (MMAD 2.4 ± 0.2 μm and 6.2 ± 0.5 μm, respectively). Mixture samples containing 75% diacetylmorphine showed similar MMAD values (2.8 μm) as for diacetylmorphine base at 300 °C; samples with larger proportions of caffeine showed larger MMAD values. Furthermore, samples with more caffeine showed slightly more impaction in the inductor port of the Andersen sampler, reflecting the situation *in vivo*, where larger particles would be expected to deposit in the mouth and throat (for which the inductor port is a model). Within the diacetylmorphine/caffeine mixture samples, there were only small differences between $MMAD_{diacetylmorphine}$ and $MMAD_{caffeine}$. 6-Acetylmorphine seemed to be consistently more abundant in the smaller particles of the mixture aerosols, as indicated by the small $MMAD_{6\text{-}acetylmorphine}$ values (Table 2).

Temperature seemed to affect the particle size of the aerosol from the 75% mixture: volatilisation at 250 °C yielded smaller aerosol particles (MMAD 1.8 μm) than at 300 °C or 350 °C (MMAD 2.8 and 3.8 μm, respectively). Geometric standard deviations did not show much variation between samples or between temperatures. The results from the 75% sample that was heated at 300 °C intermittently were similar (MMAD 2.2 μm) to the aerosol from the sample that was continuously heated at 250 °C (1.8 μm).

The aerosol recovery (% w/w of sample mass recovered in Andersen sampler and inductor port) of the caffeine samples was 88.9% (Table 2), indicating that the particle sizing experimental set-up was able to efficiently collect the vapours arising after volatilisation. The other sample types show lower aerosol recoveries (59.0–81.7%). The fine particle fraction (% sample mass recovered as aerosol particles <5 μm) ranged from 41.4–59.9% w/w; no correlation with sample composition was observed, but increasing temperatures did result in much lower fine particle fractions for 75% mixture samples. The best results were obtained after volatilisation of a 75% mixture sample at 250 °C: 59.9% of the sample was recovered as aerosol particles <5 μm. This fraction of the aerosol was found to consist mainly of unchanged diacetylmorphine (61.3% w/w) with 7.6% 6-acetylmorphine and 31.1% caffeine. Similar aerosol compositions were observed after volatilisation of a 75% mixture via intermittent heating at 300 °C. Higher volatilisation temperatures resulted in larger proportions of 6-acetylmorphine in this fraction of the aerosol.

3. Discussion

In this paper, we describe an experimental set-up for *in vitro* experiments simulating heroin smoking via 'chasing the dragon'. The sample was heated in an aluminium foil

Table 2: Results of aerosol particle size measurements

Sample	100% CAF	25% DAM	50% DAM	75% DAM			100% DAM	
Temperature (°C)	300	300	300	250	300	350	300[a]	300
MMAD (μm)	6.2	3.4	4.1	1.8	2.8	3.8	2.2	2.5
GSD	2.9	3.2	2.8	2.9	2.8	2.6	2.8	2.5
$MMAD_{diacetylmorphine}$		2.6	4.0	1.7	2.9	4.1	2.1	2.5
$MMAD_{caffeine}$		3.8	4.2	2.2	2.8	3.7	2.3	
$MMAD_{6\text{-}acetylmorphine}$		1.3	2.6	1.3	2.3	3.3	1.8	2.3
Aerosol recovery (%)[b]	88.9	81.7	80.6	72.3	63.2	63.4	64.2	59.0
Recovery in inductor port (%)[b]	7.1	6.6	9.2	0.9	3.7	5.0	3.1	3.0
Fine particle fraction (%)[c]	41.4	51.2	46.5	59.9	45.2	35.4	50.8	46.5
Aerosol <4.7 μm content (%)[d]								
Diacetylmorphine		29.1	43.2	61.3	55.2	49.7	62.6	88.7
6-Acetylmorphine		2.8	3.4	7.6	10.6	10.3	7.6	11.3
Caffeine	100	68.1	54.0	31.1	34.2	40.0	29.7	

For each experiment, temperature, particle size parameters and recovery parameters are given. DAM = diacetylmorphine base; CAF = caffeine anhydrate; MMAD = mass median aerodynamic diameter; GSD = geometric standard deviation. [a] heated intermittently; [b] Aerosol recovery (mass in inductor port and in Andersen sampler) and recovery in inductor port are given as% w/w of sample mass; [c] Fine particle fraction = fraction (% w/w) of sample mass recovered as aerosol particles <5 μm; [d] Aerosol <4.7 μm contents are given as % w/w of total mass of aerosol <4.7 μm

sample holder, for accurate simulation of street practice. But for standardisation purposes, a heating device was preferred to the cigarette lighter used by addicts. Combining the excellent heat conducting properties of the aluminium foil sample holder with the heating device enabled us to subject the samples to exactly the desired temperature (set accurately using an infrared thermometer) and made temperature easy to control. This was considered important, as varying results of volatilisation studies in the literature often might be explained by different volatilisation temperatures.

Our results for the recovery of diacetylmorphine in vapour after volatilisation of diacetylmorphine base (45.1–55.2%) resembled those found in a study in which a cigarette lighter was used to (intermittently) heat the samples: 57–69% (Huizer 1987). Volatilisation temperature could account for the small difference between the outcomes, assuming that intermittent use of a lighter (maximum temperature about 600 °C (Huizer 1987)) results in average volatilisation temperatures below 300 °C. Similarly, larger recoveries were found in a Swiss study (70% diacetylmorphine base), because in this case the cigarette lighter reportedly only heated the samples to 250 °C (Brenneisen and Hasler 2002). Different volatilisation temperatures could not explain the recovery of 69% of a diacetylmorphine base sample after heating it (at 300 °C) in a quartz furnace (Cook and Jeffcoat 1990). However, it was not clear if complete volatilisation was attempted nor if this value indicated overall recovery or recovery in vapour only. The largest recovery of unchanged diacetylmorphine base in vapour (89%) was found after heating 3–11 mg using a diacetylmorphine coated wire coil at 200 °C (Jenkins et al. 1994). However, although elegant, this set-up did not mimic 'chasing the dragon', nor would it be suitable for administration of diacetylmorphine to addicts in the quantities they need (100–300 mg), which is the purpose of the product studied here. The influence of temperature was limited in the temperature range studied in our volatilisation experiments. Increasing volatilisation temperature seemed to slightly (but non-significantly) decrease the recovery of diacetylmorphine in vapour from samples of diacetylmorphine base, and a slight increase in 6-acetylmorphine recovery from 75% mixture samples was observed when temperature increased (Fig. 2). Diacetylmorphine/caffeine mixtures showed little change in recovery of diacetylmorphine on changes of temperature (Fig. 2); some statistically significant differences were found for 25 and 50% mixtures, the first showed a higher recovery at 250 than at 300 °C, the other a lower diacetylmorphine recovery (Fig. 1).

It has been suggested that the presence of caffeine in a sample will protect diacetylmorphine from degradation when volatilised (Huizer 1987). Experiments on intermittent heating of 50% mixtures of diacetylmorphine base or hydrochloride with caffeine yielded higher diacetylmorphine recoveries with caffeine (76% and 36%) than without (62% and 17%, respectively). Caffeine recovery was found to decrease when less volatile substances were admixed (Huizer 1987). This could be explained thermodynamically: sublimation and volatilisation of caffeine utilise part of the energy supplied by the heat source and 'divert' it from volatilisation and degradation of diacetylmorphine in the sample. In our mixture experiments, where samples were heated continuously rather than intermittently (Huizer 1987), no protective effect was observed. It is possible that continuous heating leads to an excessive supply of heat to the volatilising sample, masking a possible protective effect of caffeine. However, we considered continuous heating of the samples necessary in order to standardise the heating process, which Huizer admitted was as important as it was variable (Huizer 1987).

The only result suggesting a protective effect of caffeine was the finding that 75% diacetylmorphine mixture residues soon contain a larger proportion of 6-acetylmorphine than 50% diacetylmorphine mixtures (Fig. 5). However, since overall residue sizes decreased in time and the foil residue compositions in Fig. 5 are relative figures, the absolute amount of 6-acetylmorphine in residue would have decreased during the time needed for complete volatilisation. Moreover, proportions of analytes in residue samples do not necessarily predict proportions in vapour: no difference in 6-acetylmorphine recovery in vapour was found between 75% and 50% diacetylmorphine/caffeine mixtures after complete volatilisation (Fig. 1).

Another positive effect of addition of caffeine to a sample was the increase in volatilisation rate of diacetylmorphine/caffeine mixtures (Fig. 3). This could be explained by an increase in vapour pressure of the mixture, increasing its volatility (caffeine vapour pressure: 9×10^{-4} Torr at 25 °C; diacetylmorphine base: 6×10^{-8} Torr at 25 °C) (Meng et al. 1997). Moreover, it is known that caffeine has a sublimation temperature (178 °C) below its melting temperature (238 °C) (The Merck Index 1996). These properties could cause a distillation effect in diacetylmorphine/caffeine mixtures, resulting in a decreasing proportion of caffeine in the sample (residue) and an increasing proportion of caffeine in the vapours. This is illustrated by our findings in the experiments with a fixed heating time (Fig. 4): a larger proportion of caffeine volatilises from the 75% mixture in 3 min, especially at lower temperatures. The analysis of the composition of the foil residues shows a decrease in the proportion of caffeine in time, consistent with this hypothesis (Fig. 5). This distillation effect could cause the beneficial effect of caffeine on onset and rate of volatilisation of diacetylmorphine to decrease during the time needed for volatilisation, but this does not seem very likely, since thermal analysis has shown that the eutectic mixture contains only 6–10% caffeine (and 90–94% diacetylmorphine) (Klous et al. 2005).

The most obvious (visual) difference between diacetylmorphine and caffeine during volatilisation seems to be the extent of degradation of the sample: none was observed for caffeine, while carbonised residues and detection of 6-acetylmorphine in the vapour were clear indications of degradation of diacetylmorphine samples. Apparently, degradation of diacetylmorphine to 6-acetylmorphine occurs readily on heating, similar to the process of hydrolysis in aqueous solutions (Poochikian et al. 1983). However, there is no evidence for the next step of hydrolysis of diacetylmorphine occurring on heating: no morphine was detected in condensate or in residue samples. Apparently, the rate of carbonisation and pyrolysis of diacetylmorphine (and 6-acetylmorphine) is higher than the rate of conversion to morphine. Carbonisation and pyrolysis could account for part of the loss of sample that was observed in the volatilisation experiments (mean loss: 31.8% of caffeine samples, 35.8% of diacetylmorphine samples and 19.7–37.1% of mixture samples). Diacetylmorphine could have decomposed to substances that escaped the vapour collection system (gases) or that could not be detected by our HPLC-UV system. However, the HPLC-UV system was designed to enable detection of compounds in a wide polarity range (gradient 3–80% acetonitrile) and used an aspecific detection wavelength (214 nm), it is therefore not

very likely that degradation products would escape detection, unless they were present in very small quantities.

The particle sizing experiments showed that volatilisation of diacetylmorphine (mixture) samples using our standardised *in vitro* set-up resulted in aerosols with small MMADs: 1.8–3.8 μm, small enough to reach the primary, secondary and terminal bronchi (product information Andersen sampler). The fine particle fraction of these samples was found to be 35.4–59.9% w/w, indicating that approximately half of the volatilised sample was recovered as aerosol particles <5 μm that are able to penetrate to the tracheobronchial area of the lungs and beyond (product information Andersen sampler). The experiment with a 75% mixture sample heated at 250 °C resulted in the largest fine particle fraction (59.9%), which contained 61.3% diacetylmorphine and 7.6% w/w 6-acetylmorphine. Furthermore, it can be derived from the log-normal distributions of the aerosol particles that 16% w/w of the particles from a diacetylmorphine base aerosol will be smaller than (MMAD/GSD = 2.4/2.5 =) 0.96 μm, small enough to reach the alveoli. That is even true for the diacetylmorphine sample with the largest MMAD (50% diacetylmorphine), since 16% is smaller than 1.5 μm. Addition of caffeine to diacetylmorphine did not seem to influence deposition of diacetylmorphine samples negatively, even though caffeine samples showed a relatively large MMAD (6.2 μm) and a relatively small fine particle fraction (41.4%). In summary, our *in vitro* simulation of 'chasing the dragon' indicates that inhalation of diacetylmorphine after volatilisation could deliver a sufficiently large dose of diacetylmorphine to the airways for rapid absorption (Table 2). The experimental set-up was considered to be a reasonably accurate simulation, even though the (prescribed) air flow rate (28.3 l/min) in these experiments was not powerful enough to trap all of the vapours in the Andersen sampler and continuous heating was used instead of intermittent heating. *In vivo*, it is also impossible for addicts to inhale all of the vapours they generate, and there is no reason to assume that the Andersen sampler 'inhaled' a non-representative proportion of the vapours. The bioavailability found for diacetylmorphine for inhalation used via 'chasing the dragon' by addicts (52.2%, (Rook 2003)) was similar to the fine particle fraction found in our *in vitro* studies, which supports the validity of the simulation set-up.

Our results are similar to earlier (*in vitro*) findings for cocaine: powdered cocaine base smoked from a glass pipe was found to result in airborne cocaine particles with MMAD of 2.05–2.87 μm (GSD 1.68–2.22) (Snyder et al. 1988). These findings add to the explanation of the success of heroin and cocaine as smokable drugs of abuse. The obvious pharmaceutical alternative, an aerosol generated from an aqueous solution, was tested in Switzerland: 50, 100 or 200 mg/mL aqueous solutions of diacetylmorphine HCl were nebulised using different types of nebulisers (jet-nebulisers Pari IS-2 and Pari LC-Plus, and ultrasonic nebuliser Omron U1) (Speich 1998). The particle size was found to depend on the nebuliser, and ranged from MMAD 2.4–2.6 μm to between 3.9–4.1 μm and 7.6–21.5 μm, respectively. However, this method was not found to be suitable for administering diacetylmorphine to addicts: inhalation of an effective dose of 240 mg (= 3.1 mL = 536 mg) took a patient in a pilot study 95 min and caused nausea and retching, due to the extreme bitterness of the solution (Speich 1998).

Summarising, volatilisation experiments showed little influence of the amount of caffeine in the mixture on the recovery of diacetylmorphine in vapour, or on degradation of diacetylmorphine to 6-acetylmorphine. Moreover, particle sizing experiments showed that adding more than 50% caffeine yielded larger aerosol particles and would result in larger deposition of caffeine in the lungs, as 54–68% of aerosol particles <5 μm consisted of caffeine. Since patients in the trial on co-prescription of heroin use diacetylmorphine doses up to 1000 mg per day, the use of 25% or 50% diacetylmorphine mixtures as medication would result in deposition of the equivalent of 5–9 cups of coffee in the lungs (at ±80 mg caffeine per cup). The 75% diacetylmorphine/caffeine mixtures seemed to profit from beneficial effects of caffeine as an excipient (facilitating volatilisation and possibly protecting diacetylmorphine when it is heated intermittently by 'chasing the dragon'), without the disadvantage of co-depositing large doses of caffeine in the lungs. Therefore, a mixture of 75% w/w diacetylmorphine with 25% w/w caffeine was preferred for the pharmaceutical product 'diacetylmorphine for inhalation after volatilisation'. This product has been used successfully in a Dutch clinical trial on medical co-prescription of heroin and methadone (Van den Brink et al. 2003) and further pharmaceutical development studies were performed in preparation for market authorisation (Klous et al. 2004a, 2004b).

In conclusion, volatilisation of 25, 50 and 75% diacetylmorphine/caffeine mixtures at 250 and 300 °C resulted in about 45.6–62.2% recovery of unchanged diacetylmorphine in the collected vapours. In the temperature range studied (200–350 °C), the main effect of increasing volatilisation temperature was an increasing volatilisation rate. Degradation of diacetylmorphine upon volatilisation was limited to conversion of 4.1–7.1% to 6-acetylmorphine. Particle sizes of aerosols from volatilised diacetylmorphine base and diacetylmorphine/caffeine mixtures were found to be very suitable for effective deposition of the active substance in the lungs: MMAD values ranged from 1.8–4.1 μm, and 45–60% of each sample was recovered as aerosol particles <5 μm. Samples with more caffeine showed larger particle sizes and increasing volatilisation temperature also increased particle sizes. The 75% diacetylmorphine/25% caffeine mixture was preferred for the pharmaceutical development of diacetylmorphine for inhalation after volatilisation, since sufficient recoveries of unchanged diacetylmorphine in vapour were obtained, combined with little degradation to 6-acetylmorphine and acceptable amounts of caffeine co-depositing in the lungs.

4. Experimental

4.1. Chemicals

Diacetylmorphine base was manufactured specifically for the clinical trial and obtained through the Central Committee on the Treatment of Heroin Addicts. Caffeine anhydrate and morphine hydrochloride were purchased from Bufa (Uitgeest, The Netherlands), and 6-acetylmorphine hydrochloride was obtained from Sigma Aldrich Co. Ltd. (Zwijndrecht, The Netherlands).

4.2. Analysis

A high performance liquid chromatography system with diode array detection (HPLC-DAD) was used to quantitate the recoveries of diacetylmorphine, caffeine, and degradation products of diacetylmorphine, in condensates and residues obtained from the *in vitro* volatilisation procedure. The system consisted of an 1100 Series binary HPLC pump, Model G1312A (Agilent Technologies, Amstelveen, The Netherlands), a SpectraSERIES Model AS3000 automatic sample injection device, equipped with a 100 μL sample loop (Thermo Separation Products, Breda, The Netherlands), and a photodiode array detector Model Waters™ 996 (Waters Chromatography B.V., Etten-Leur, The Netherlands). Chromatograms were processed using Chromeleon® software (Dionex Corporation, Sunnyvale, CA, USA). In the

liquid chromatography system, separation was achieved using a Zorbax Bonus RP analytical column (4.6 mm ID × 15 cm, particle size 5 μm, Rockland Technologies Inc., Newport, DE, USA), protected by a Chromguard RP column (10 × 3 mm ID, Chrompack, Middelburg, The Netherlands). The mobile phase consisted of a 5 mM ammonium acetate buffer pH 5.7, mixed with acetonitrile according to a programmed gradient: 0–2 min 3% acetonitrile, 2–2.6 min a linear rise from 3–13%, 2.6–8 min 13–15.5%, 8–15 min 15.5–80%, 15.1–24 min 3% acetonitrile. Quantification of diacetylmorphine, caffeine, 6-acetylmorphine, and morphine was performed using 6-point calibration curve in the following respective concentration ranges: 1–50 μg/mL, 1–40 μg/mL, 0.5–5 μg/mL and 1–10 μg/mL.

4.3. In vitro volatilisation

The powder samples were heated in sample holders, shaped from aluminium foil (∅ 3 cm, height 0.5–1.5 cm, flat bottom), which were placed on a heating device (IKA Werke RH Basic, Staufen, Germany). The desired temperatures were set using an infrared thermometer (Fluke Model 65, Fluke Corporation Europe, Eindhoven, The Netherlands) to check the exact surface temperature the sample was exposed to. Fumes emitted from the volatilising sample were directed through a 40 cm ball condenser, fitted with a funnel (∅ 9 cm) above the sample and with a vacuum pump (Type N022 AT18, KNF Neuberger, Vleuten, The Netherlands) on the other side (Fig. 6). To prevent the fumes being sucked into the pump, a cotton plug was placed in the top of the condenser. Condenser temperature was kept at −5 °C by a cooling bath (Haake GH Fisons D8, Karlsruhe, Germany), filled with coolant (1 : 1 ethylene glycol:water). The sample was weighed accurately into the tared sample holder, to enable determination of the size of the residue by weighing it again after the experiment.

Diacetylmorphine base and caffeine were volatilised at 250 °C, 300 °C and 350 °C. Three different mixtures of diacetylmorphine base and caffeine (containing 25%, 50%, and 75% diacetylmorphine) were tested at 250 °C and 300 °C, while the 75% diacetylmorphine mixture was also tested at 225 °C, 275 °C, 325 °C and 350 °C. Volatilisation was said to be complete when the sample was heated until no more fumes were emitted. The heating process was easily controllable, since the thin aluminium sample holder allowed the heating process to start directly after placing it onto the preheated device and to stop instantly after its removal. This enabled us to test the 75% diacetylmorphine base/caffeine mixture using a fixed heating time (3 min) and variable temperature (200 °C, 225 °C, 250 °C, 265 °C, 285 °C, 300 °C). Each experiment was repeated four times. In order to determine the composition of the foil residue, samples (±30 mg) of 50% and 75% diacetylmorphine mixtures were heated at 250 °C for 0, 30, 60, 90, etc. to 360 s.

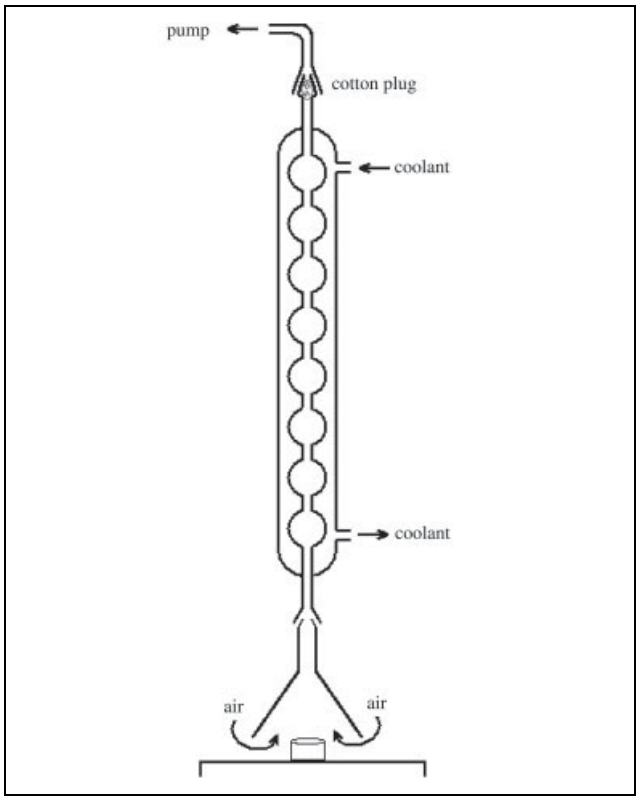

Fig. 6: Experimental set-up for *in vitro* volatilisation of samples van diacetylmorphine and caffeine. From top to bottom: air outlet towards vacuum pump, cotton plug, ball condenser (40 cm) with inlet and outlet for coolant (−5 °C), funnel (∅ 9 cm), aluminium sample holder on a heating device

After volatilisation of the sample, the condenser, the funnel, and the cotton plug were rinsed with 1 : 1 v/v mixture of 5 mM ammonium acetate buffer pH4 and acetonitrile. The rinsing fluid was collected and diluted to 100.0 mL. The aluminium sample holder was sonicated for 15 min in 25 mL of the abovementioned solvent that was diluted to 50.0 mL after removal of the sample holder. The condensate and residue samples were diluted with 5 mM ammonium acetate buffer pH 5.7 before analysis. Diacetylmorphine and caffeine recoveries in vapour (condensate) or residue were calculated relative to the respective amounts present in the powder sample (percentage w/w). 6-Acetylmorphine recovery was calculated relative to the amount of diacetylmorphine present in the original sample, using a correction for the difference in molecular weight.

4.4. Particle size

The particle size of the aerosols, generated after *in vitro* volatilisation of (mixtures of) diacetylmorphine and caffeine powder samples were determined using an eight-stage Andersen sizing sampler (apparatus D, (EDQM 2002)). This sampler consists of eight aluminium stages, each designed to collect airborne particles in a specific size range (<0.4 μm, 0.4–0.7 μm, 0.7–1.1 μm, 1.1–2.1 μm, 2.1–3.2 μm, 3.2–4.7 μm, 4.7–5.8 μm and 5.8–9.0 μm). Separation of particles is achieved via the principle of inertial impaction. The Andersen sampler was fitted with an inductor port (EDQM 2002), that was positioned ±1.5 cm above and directly next to the sample holder to minimise the loss of vapours. Glass fibre filters (grade 934 AH, ∅ 82 mm, 1.5 μm, Whatman via VWR International, Amsterdam, The Netherlands) were placed on the collection plates on each stage of the Andersen sampler in order to limit particle bounce. The powder samples were volatilised in the aluminium sample holders on the heating device, as described under 4.3. A Becker pump, attached to the sizing sampler, was set to generate a 28.3 L/min air flow rate at the induction port, sucking the vapours into the sizing sampler.

After complete volatilisation of the 100–150 mg powder samples, the inductor port, the eight stages, and the final filter were analysed using the abovementioned HPLC method with UV detection (λ = 214 nm). Each of these components was washed and diluted with a mixture of 15% v/v acetonitrile and 85% v/v 5 mM ammonium acetate buffer pH 4 before injecting 20 μL in the HPLC-system. The resulting data (analyte mass on each of the stages) were used to determine the mass median aerodynamic diameter (MMAD, in μm) and geometric standard deviation (GSD), via a log-probability plot of the cumulative mass fraction per stage versus the cut-off diameter of each stage (EDQM 2002). Furthermore, this plot was used to calculate the fine particle fraction: the fraction of the sample mass (% w/w) that was recovered as aerosol particles <5 μm. Concentration data from the lower 6 stages of the Andersen sampler were used to calculate the composition of the aerosol particles <4.7 μm (in% w/w).

Diacetylmorphine base, caffeine anhydrate, and 75% diacetylmorphine mixture samples were volatilised at 300 °C (in duplicate), as well as a 25% and a 50% diacetylmorphine mixture. Temperature effects were tested in 75% mixtures, volatilised at 250 °C, 300 °C and 350 °C. This mixture was also volatilised via intermittent (20 s on, 10 s off) heating at 300 °C.

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