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Pharmaceutical heroin for inhalation: Thermal analysis and recovery experiments after volatilisation

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Abstract

Pharmaceutical heroin for inhalation was developed for a clinical trial on co-prescription of heroin and methadone to chronic treatment-resistant heroin addicts. Diacetylmorphine base was selected as the active pharmaceutical ingredient for this product with caffeine anhydrate added as an excipient. Differential scanning calorimetry and thermogravimetric analysis showed that addition of caffeine resulted in a lower melting temperature and a higher volatilisation rate for the mixture than for diacetylmorphine base alone. Recovery experiments showed that $40.8 \pm 5.3\%$ of diacetylmorphine base could be found in smoke condensate after volatilisation of diacetylmorphine–caffeine tablets. All of the caffeine from each tablet was recovered unchanged in the fumes, while 85.6% of the diacetylmorphine from each tablet was recovered, either unchanged in the fumes or as non-volatilised residue. Recovery was found to be reproducible and only small differences were found between the tablet types. The experimental set-up was found to efficiently collect the vapours resulting from heating the powder. Under the tested experimental conditions, no evidence was found that degradation products of diacetylmorphine or caffeine, other than 6-acetylmorphine (5.9%) had volatilised, even though a decomposed residue was present after heating diacetylmorphine–caffeine samples. Diacetylmorphine–caffeine was found to be a suitable basis for pharmaceutical heroin to be used by 'chasing the dragon'.

Keywords: Heroin; Diacetylmorphine; Smoking; Inhalation; Thermal analysis

1. Introduction

Heroin is a well-known drug of abuse, that is usually administered intravenously, but smoking heroin has gained popularity since it was first described in Shanghai in the 1920s [1]. After some refinement, the use of a smoking procedure called 'chasing the dragon' spread to South East Asia, India and some parts of Europe in 1960–1980 [1]. In this procedure, drug users 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.

A clinical trial was conducted 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. Since in The Netherlands, 75–85% of the heroin addicts use heroin by 'chasing the dragon' [2], two separate study protocols were developed, one trial testing the efficacy of the prescription of an inhalable form of heroin and another trial testing the efficacy of the prescription of injectable heroin. In preparation for the first trial, an inhalable form of

Abbreviations: DAM, diacetylmorphine base; DSC, differential scanning calorimetry; HCl, hydrochloride; HPLC–UV, high-performance liquid chromatography with ultraviolet detection; TGA, thermogravimetric analysis

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pharmaceutical heroin was developed, containing diacetylmorphine base and caffeine anhydrate in tablets, obtained via direct compression. The formulation of this product was restricted by the unpredictable (adverse) effects that excipients could have when the product was heated and the resulting vapours inhaled. Therefore, no excipients (except for caffeine) were added. Caffeine was considered acceptable, because it is commonly found in street heroin samples [3–6] and has been shown to improve the volatilisation of heroin [7]. It was considered important for patient compliance to offer a product that could be used without interfering too much with the habits and rituals the subjects had developed over the years. Alternative dosage forms, like orally, nasally or rectally administered heroin were therefore not considered. In this article, pharmaceutical heroin to be used via the procedure of 'chasing the dragon' is referred to as diacetylmorphine for inhalation after volatilisation.

The primary goal for the development of diacetylmorphine for inhalation after volatilisation was to ascertain that its use would result in an acceptable and reproducible level of diacetylmorphine in the inhaled fumes. Furthermore, thermal analysis was used to gain insight in the volatilisation process that occurs when using heroin in the abovementioned way. Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) analyses were used to study melting and volatilisation of diacetylmorphine base and the hydrochloride salt in the absence and presence of different proportions of caffeine. A simple in vitro model for the procedure of 'chasing the dragon' was developed and used to study the recovery of diacetylmorphine from the pharmaceutical product after volatilisation.

2. Materials and methods

2.1. Chemicals

Diacetylmorphine base and diacetylmorphine hydrochloride (HCl) (British Pharmacopoeia Quality) were manufactured specifically for the clinical trial and obtained through the Central Committee on the Treatment of Heroin Addicts. Caffeine anhydrate was purchased from Bufa (Uitgeest, The Netherlands), 6-acetylmorphine hydrochloride from Sigma–Aldrich Co. Ltd. (Zwijndrecht, The Netherlands). Potassium dihydrogen phosphate, phosphoric acid 85% and hydrochloric acid 25% (w/w) were analytical grade and originated from Merck (Amsterdam, The Netherlands). Acetonitrile was HPLC grade and came from Biosolve (Amsterdam, The Netherlands).

2.2. Differential scanning calorimetry

DSC measurements were performed on a DSC Q1000 v.2.5 Differential Scanning Calorimeter (TA Instruments Inc., New Castle, DE, USA). Samples were punched out of a powder bed and weighed into aluminium pans (diameter: 5 mm, TA Instruments) that were hermetically sealed. An empty pan was used as a reference and indium was used for temperature and heat calibration. Thermal Advantage^{TM} Software (Version 1.3.0.179 for Q-Series^{TM}, TA Instruments) was used for data acquisition and Universal Analysis 2000^{TM} Software (Version 3.0G, TA Instruments Inc.) was used for data analysis. Simple heating experiments were performed, measuring heat flow at a temperature of 50 °C, rising to 300 °C at a rate of 10 °C/min. Additional experiments concerned repeated cycles of heating (10 °C/min) and cooling (50 °C/min was the maximum rate). Diacetylmorphine base, diacetylmorphine HCl and caffeine anhydrate were tested, as well as 11 different physical mixtures of diacetylmorphine base and a 1:1 mixture of diacetylmorphine HCl and caffeine. The mixtures were prepared by weighing the two components and mixing them by stirring with a spatula and shaking the powder in its container.

Additional visual information on the heating process was obtained by performing experiments, using the same temperature ramp as in the DSC measurements, in a melting point apparatus (Büchi B-540, Mettler-Toledo, Tiel, The Netherlands).

2.3. Thermogravimetric analysis

A TGA 51 apparatus (TA Instruments, New Castle, DE, USA) was used for thermogravimetric analysis of diacetylmorphine base and diacetylmorphine–caffeine mixtures. It measures the decrease of sample weight in time, at a set temperature (under a nitrogen flow). Calciumoxalate monohydrate was used for calibration. Samples (10–20 mg) were brought into platinum pans and put in the oven at 30 °C. Temperature rose at 10 °C/min to the set temperature, which was then kept constant until sample weight was minimal. The experiment was performed under a constant nitrogen flow. The volatilisation time was derived from the resulting thermogravimetric curves.

2.4. Recovery of diacetylmorphine for inhalation after volatilisation

Tablets of diacetylmorphine for inhalation after volatilisation from test batches were used for the recovery experiments. The tablets contained 25, 50 or 100 mg of diacetylmorphine base and 100 mg of caffeine anhydrate without other additives and they were manufactured via direct compression. Samples were heated in a porcelain crucible, placed in a brass block on a heating device (IKAMAG RCT Basic, IKA-Werke GmbH, Staufen, Germany). The resulting fumes were collected in a reflux condenser, fitted with a funnel that covered the sample on one side and a water pump on the other side (Fig. 1). To prevent loss of vapours into the pump, a cotton plug was placed in the top of the condenser.

The heating device was set at a temperature of 300 °C and the brass block and crucible were pre-heated for 30 min before the tablet was inserted. Samples were heated to achieve

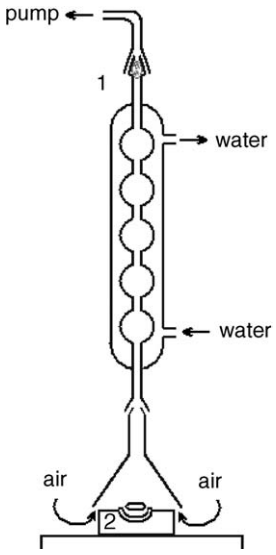

Fig. 1. Schematic of the set-up of the recovery experiment, showing (top to bottom): outlet to pump, (1) location of the cotton plug, reflux condenser, funnel, brass block surrounding the crucible (2), top of the heating device. Arrows indicate the direction of the flow of water and air.

complete volatilisation, which was defined as the moment that no more fumes arise from the heated samples. Complete volatilisation was achieved within 7 min for tablets containing 25 or 50 mg diacetylmorphine base and within 15 min for tablets with 100 mg diacetylmorphine. The water pump and condenser were started 5 min prior to the start of the experiment and stopped 5 min after the end. After volatilisation, the condenser, the funnel and cotton plug were rinsed with 80 mL 0.1N HCl. The rinse fluid was collected, sonicated using an ultrasonic bath, filtered, diluted to 100 mL with 0.1N HCl and diluted further with mobile phase for injection into the HPLC system. The experiment was repeated three to four times per tablet type. Tablet and crucible were weighed before and after the experiment, so that the size of the residue could be determined.

2.5. High-performance liquid chromatography

The recovery of diacetylmorphine, caffeine and degradation product 6-acetylmorphine in the vapour condensate after heating diacetylmorphine–caffeine tablets was determined using a HPLC–UV method. The system consisted of a Zorbax SB-C_{18} analytical column (75 mm × 4.6 mm i.d., particle size 3.5 μm; Rockland Technologies Inc., Newport, DE, USA), connected to a P1000 pump (Spectra Physics, San Jose, USA), a Model U6K injection system and a Model 441 Absorbance detector (Waters Associates, Milford, MA, USA). A DataJet integrator (Thermo Separation Products, Fremont, CA, USA) calculated the peak areas. The flow was 1.0 mL/min, the injection volume was 10 μL and the detection wavelength was set at 214 nm. The mobile phase consisted of KH_2PO_4 buffer (0.05 M, pH 3)–acetonitrile (85:15, v/v). Samples were quantified using calibration curves of diacetylmorphine, caffeine and 6-acetylmorphine. Standard solutions were prepared by dissolving diacetylmorphine base, 6-acetylmorphine and caffeine in 0.1N HCl and diluting to concentrations ranging from 30–125, 0.5–50 and 15–85 μg/mL, respectively.

3. Results

3.1. Differential scanning calorimetry

The thermogram for diacetylmorphine HCl showed two endotherms on heating (50–300 and 10 °C/min, Fig. 2A) at ±172 and 210–220 °C that are probably attributable to solid transitions, degradation and/or dehydration processes. At 150.4–154.3 °C, a glass transition occurred (see insert in Fig. 2). An exothermic signal with an onset temperature of 252 °C occurred, where the melting point was expected (243–244 °C [8]. This signal most likely represents a combination of melting, boiling and decomposition. A sample that was heated from 20–255 °C at 10 °C/min (followed by rapid cooling) did show a melting endotherm at 243.4 °C (Fig. 2B), indicating that melting, boiling and decomposition occur in a narrow temperature range and could be competitive processes. When diacetylmorphine HCl samples were reheated, none of the thermal events reappeared, except the exothermic degradation signal. When the 20–300 °C at 10 °C/min temperature gradient was used to heat a sample of diacetylmorphine HCl in the melting point apparatus, discolouration was observed when sample temperature exceeded 180 °C. Melting was observed at 247 °C, soon followed by signs of boiling and extensive degradation.

The DSC thermogram for the diacetylmorphine HCl–caffeine mixture (1:1, w/w) showed a large endotherm at 160.8 °C and a small one at 204.1 °C (Fig. 2C). An exothermic process occurred above 250 °C, but less pronounced than in the diacetylmorphine HCl samples. A heating cycle experiment conducted with the mixture

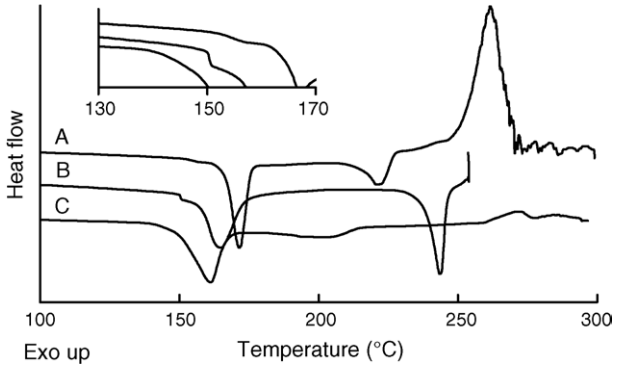

Fig. 2. DSC thermograms of: (A) diacetylmorphine hydrochloride (temperature range: 50–300 °C, heating rate 10 °C/min); (B) diacetylmorphine hydrochloride (50–255 °C, 10 °C/min, followed by rapid cooling); (C) 1:1 mixture of caffeine and diacetylmorphine hydrochloride (50–300 °C, 10 °C/min). The insert shows the glass transitions in curve A and B.

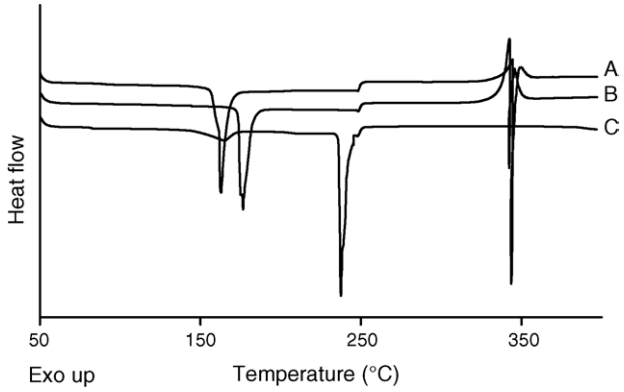

Fig. 3. DSC thermograms of a physical mixture (3:1) of diacetylmorphine base and caffeine anhydrate (A), diacetylmorphine base (B) and caffeine anhydrate (C) (heating rate 20 °C/min, 50–250 °C; 10 °C/min, 250–400 °C). The baseline shift at 250 °C was caused by a programmed change in heating rate.

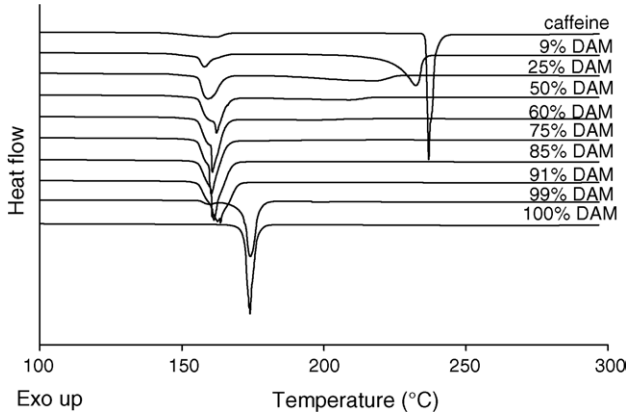

Fig. 4. DSC thermograms of physical mixtures of diacetylmorphine base and caffeine anhydrate (temperature range: 50–300 °C, heating rate 10 °C/min), showing (from left to right): the melting signal of the eutectic mixture, the melting signal for (excess) diacetylmorphine base (DAM) and the melting signal for the (excess) caffeine anhydrate.

showed a re-crystallisation exotherm at 174.3 °C during cooling, but only a small ±200 °C endotherm reappeared in the second heating cycle. Visual observation of the heated diacetylmorphine HCl–caffeine mixture showed similar behaviour of discolouration and boiling and a lower melting temperature (215–224 °C) than for diacetylmorphine HCl.

DSC thermograms of diacetylmorphine base and caffeine (heated 50–300 °C at 10 °C/min) showed sharp melting endotherms at the expected temperatures (174.4 and 236.6 °C, respectively, Fig. 3B and C). In the thermogram for caffeine anhydrate there was also a small endotherm at 161.4 °C that did not reappear on reheating, indicating that it might represent an irreversible process, like dehydration or a solid transition (β → α modification [9]). When samples were heated to 350 or 400 °C, diacetylmorphine base (as well as the 3:1 diacetylmorphine–caffeine mixture) showed a mixed endothermic and exothermic process with an onset temperature of 335 °C, possibly representing boiling or evaporation (Fig. 3A and B). Caffeine samples did not show any thermal events between 250–400 °C (Fig. 3C).

DSC analysis of the physical mixtures of diacetylmorphine base and caffeine showed that a eutectic mixture was formed, that melted at 159.8 ± 0.96 °C (Fig. 4). The excess component melting in the mixtures took place at a temperature that was lower than the melting temperature of the pure substance and melting temperature decreased with the proportion in excess. From the thermograms of several mixtures of diacetylmorphine base and caffeine (Fig. 4), a phase diagram was constructed (Fig. 5). It shows that the eutectic mixture contains 90–94% diacetylmorphine base; other mixtures of diacetylmorphine and caffeine need temperatures above 160 °C for complete melting.

Experiments using heat–cool cycles showed identical behaviour for caffeine anhydrate samples when it was reheated or reheated twice (Table 1). Furthermore, the melting endotherm observed during heating was compensated during the cooling phase by a re-crystallisation exotherm at 231.5 °C (102.2 J/g). On reheating diacetylmorphine base and the 50 and 75% diacetylmorphine base–caffeine mixtures however, melting temperature and associated heat of fusion values (Table 1) decreased, especially, in the second heating cycle. Re-crystallisation exotherms occurred in the first cooling phase (at 99 °C) for some diacetylmorphine base samples, but most diacetylmorphine base and mixture samples exhibited some degree of super-cooling, only re-crystallising in the following heating phase (at 82–101 °C). Heats of fusion of the re-crystallisation exotherm(s) did not equal those of the melting endotherms, possibly indicating some degree of contamination of the sample with degradation products.

3.2. Thermogravimetric analysis

TGA experiments were started at a temperature of 165 °C, slightly higher than the melting point of the eutectic in

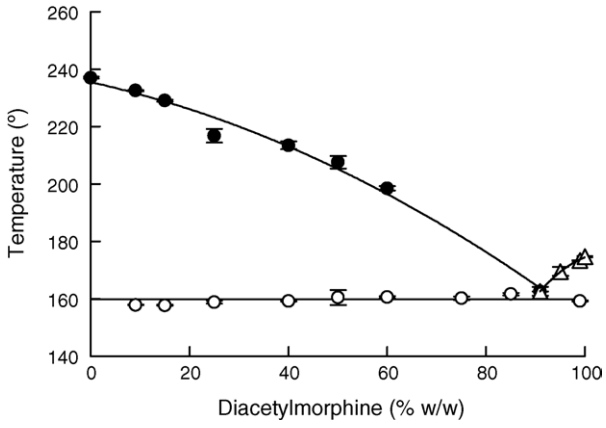

Fig. 5. Phase diagram, obtained from the results of the DSC experiments: (◯) mean temperature of the eutectic signal; (●) mean temperature of the excess caffeine signal; (△) mean temperature of the excess diacetylmorphine signal; error bars indicate standard deviations.

Table 1
Repeated DSC heat cycle experiments on diacetylmorphine base, caffeine anhydrate and mixture samples (3:1 and 1:1, w/w diacetylmorphine and caffeine)

	Heat cycle					
	1		2		3	
	Melting temperature (°C)	Heat of fusion (J/g)	Melting temperature (°C)	Heat of fusion (J/g)	Melting temperature (°C)	Heat of fusion (J/g)
Diacetylmorphine base	174.5	89.3	169.7	78.8	167.0	80.8
Caffeine	237.0	99.8	238.5	99.1	237.7	97.6
3:1 Mixture	160.1	85.6	154.0	72.6	151.1	74.2
1:1 Mixture	158.3	67.2	152.0	45.9	150.7	43.3

Melting temperatures are given for each heat cycles (1–3) with the corresponding heat of fusion; temperature range: 50–300 °C; heating rate: 10 °C/min; cooling rate: 50 °C/min.

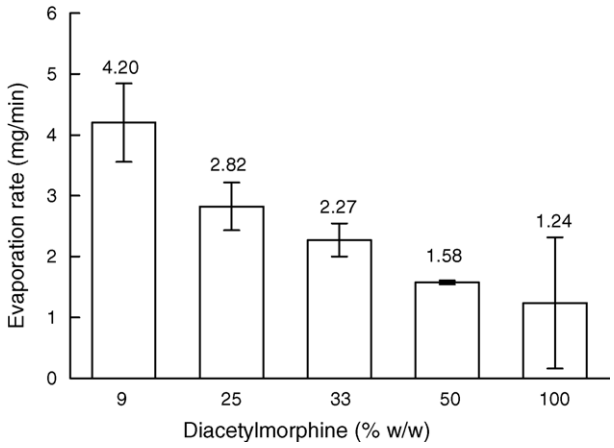

Fig. 6. Results of TGA experiments on different diacetylmorphine–caffeine mixtures. The bars represent the mean volatilisation rate (at 230–275 °C) with error bars indicating the standard deviation.

the diacetylmorphine–caffeine mixtures found in the DSC experiments. However, since at temperatures below 205 °C complete volatilisation took 1 h or more, experiments were conducted at 230, 250 and 275 °C. The resulting thermograms were used to determine the volatilisation rate and the onset temperature for volatilisation. Mean volatilisation rate (slope of the thermogram) was found to depend on the proportion of caffeine in the mixture (Fig. 6), increasing proportions of caffeine increased the volatilisation rate. No correlation between volatilisation rate and temperature was found. Onset temperature for volatilisation was higher for diacetylmorphine base (184.0 ± 7.8 °C) than for the different diacetylmorphine base–caffeine mixtures (155.0 ± 4.4 °C), which is consistent with the difference in melting point found in the DSC experiments (Table 1). Volatilisation seems to start at slightly lower temperatures than melting of the eutectic mixture in mixture samples, while for pure diacetylmorphine base the onset temperature for volatilisation is higher than the melting temperature.

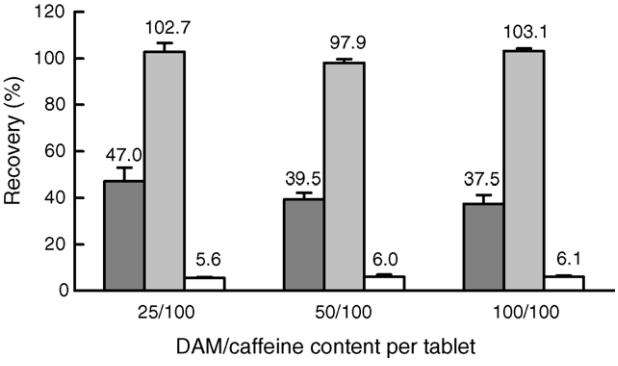

Fig. 7. Results of recovery experiments. Mean percentages are given (error bars: standard deviation) for recoveries in condensate as well as for the size of the foil residue. Recovered caffeine (%, w/w, dark grey bars) is given relative to the total amount of caffeine in the tablet; diacetylmorphine (light grey bars) and 6-acetylmorphine (white bars) are given as percentages (%, w/w) of the amount of diacetylmorphine in the sample.

3.3. Recovery of diacetylmorphine for inhalation after volatilisation

Volatilisation of diacetylmorphine–caffeine tablets was not complete; a small residue remained in the crucible after fumes had ceased to arise from the sample at the end of the experiment. The recovery of diacetylmorphine from the tablets in the fumes collected by the condenser system was found to be 40.8 ± 5.3% versus 101.1 ± 3.2% for caffeine (Fig. 7). Since all of the caffeine was recovered in the condenser system, the residue in the crucible was assumed to have originated from diacetylmorphine in the tablet. The size of the residue was therefore expressed as a percentage (%, w/w) of the amount of diacetylmorphine in the tablet, similar to the 6-acetylmorphine that was found in the condensate in small quantities (5.9 ± 0.6%, w/w) (Fig. 7). Overall, 83.5–88.4% (w/w) of diacetylmorphine from the tablet was recovered as volatilised diacetylmorphine and 6-acetylmorphine (in mg) or as residue in the crucible. Mean diacetylmorphine recovery from a 25/100 mg diacetylmorphine–caffeine tablet was slightly higher (47.0 ± 5.2%) than the recovery from a 50/100 mg tablet (39.5 ± 2.4%, $p = 0.046$) and a 100/100 mg tablet (37.5 ± 3.9%, $p = 0.038$); similarly, the mean residue (30.8 ± 3.4%) was significantly smaller (42.9 ± 4.9%, $p = 0.024$ and 41.4 ± 2.5%, $p = 0.005$, respectively).

4. Discussion

Diacetylmorphine is available as the free base and as the hydrochloride salt. The latter is theoretically less suitable for inhalation after volatilisation, since it has a higher melting point (243–244 °C) than the free base (173 °C) [8]. Furthermore, diacetylmorphine HCl was found to be more sensitive to degradation on heating [7]. Our DSC experiments supported this; diacetylmorphine HCl thermograms showed extensive degradation, large exothermic signals appeared at relatively low temperatures in the first heating cycle and none of the non-degradation-associated signals reappeared on reheating. Diacetylmorphine base samples also showed signs of degradation: a small decrease in melting temperature and melting energy on reheating, discolouration on heating and exothermic signals suggesting decomposition. However, this seemed to occur at higher temperatures (335 °C versus 240–250 °C) and to a lesser extent than observed for diacetylmorphine HCl.

Addition of caffeine has been suggested to increase the recovery of diacetylmorphine HCl and diacetylmorphine base after volatilisation and to reduce degradation upon heating [7]. DSC experiments with caffeine indeed showed more stable thermal behaviour on heating and reheating than diacetylmorphine base and diacetylmorphine HCl. The main effects of the addition of caffeine to diacetylmorphine base seemed to be the formation of a eutectic mixture with a 14 °C lower melting point and increasing volatilisation rates for mixtures with larger proportions of caffeine. DSC thermograms for diacetylmorphine base and mixtures of diacetylmorphine base and caffeine did not show obvious differences in the events associated with degradation. However, it is likely that a lower melting point and an earlier onset of volatilisation benefit the stability of diacetylmorphine during heating. This might explain why the recovery experiments showed slightly larger diacetylmorphine recoveries as well as slightly smaller residues for the 25/100 mg diacetylmorphine–caffeine tablets than for the tablet types with smaller proportions of caffeine. Furthermore, the increased recovery of diacetylmorphine from mixtures with caffeine might be due to an increased volatility of the mixture: the vapour pressure of diacetylmorphine for inhalation after volatilisation would be expected to increase after addition of caffeine (vapour pressure 9×10^{-4} Torr at 25 °C) to diacetylmorphine base (vapour pressure 5×10^{-8} Torr at 25 °C)[10].

Caffeine is commonly used as a diluent in street heroin [3,5–7] and has never been associated with any adverse effects. It was therefore considered to be relatively safe to use as an excipient in pharmaceutical heroin for inhalation. Unlike some of the other diluents found in street heroin, caffeine does not exhibit strong pharmacological effects that could interfere in the evaluation of the effect of diacetylmorphine. Having considered the arguments mentioned above, it was decided to continue the development of a dosage form for diacetylmorphine for inhalation after volatilisation with a combination of diacetylmorphine base and caffeine.

In the process of ‘chasing the dragon’ or smoking heroin, temperature is a very important variable, influencing recovery of the unchanged drug in smoke and thereby influencing bioavailability. An in vitro test on tobacco cigarettes containing diacetylmorphine HCl found 12–19% recovery as unchanged heroin [11]. Similarly, in vitro recovery from woodruff cigarettes containing diacetylmorphine base was reported as 5–14%, expressed as total opiates [12]. These results could be explained by extensive degradation caused by the high temperature occurring at the tip of a cigarette (400–700 °C). This suggestion was supported by findings of Cook and Jeffcoat [13] that showed rapidly decreasing recoveries with increasing temperatures after pyrolysis of diacetylmorphine HCl (from 89% at 200 °C to 8% at 300 °C) and diacetylmorphine base (±70% at 2–300 °C, 30% and decreasing from 400 °C upward). A pharmacokinetic study using a computer-controlled smoking device to administer diacetylmorphine base to human volunteers [14] showed much better results. The device volatilised small doses (0–10 mg) at a temperature of ±200 °C, which were then inhaled as a single puff. In the smoke condensate 89% heroin was found.

These findings suggest that heating diacetylmorphine at lower temperatures (closer to its melting temperature) is beneficial and will produce more unchanged drug in the smoke. The technique heroin users on the street apply also shows several aspects that could be considered to aim to control the temperature of the drug. The substance is generally heated intermittently and the resulting liquid is moved around to prevent it becoming too hot and char. The ideal method for volatilising diacetylmorphine might have to incorporate several of the abovementioned parameters to optimise the temperature of the sample.

For this reason, our recovery experiments were conducted at the lowest possible temperature (±300 °C) that could ensure a reasonable volatilisation time for the relatively large amount of diacetylmorphine. The results show a reasonable 40.8% recovery, which was, however, less than reported by others [13,14]. This could be explained by the different volatilisation temperatures used, as well as increased degradation in our samples due to overheating part of the sample by continuously heating the tablets. Using a powder instead of a compressed sample could prevent large temperature differences within the sample.

There was no evidence, however, for the presence of potential degradation products of diacetylmorphine or caffeine (besides 6-acetylmorphine) in the vapours collected after complete volatilisation of diacetylmorphine for inhalation after volatilisation. All of the caffeine from the tablets was recovered unchanged in the vapours, indicating that: (a) the method used to collect the vapours was quite efficient in collecting volatilised solids and (b) caffeine did not degrade upon heating and volatilisation. Furthermore, only 11.6–16.5% (w/w) of diacetylmorphine from the tablets was unaccounted for after volatilisation, the rest was recovered as volatilised diacetylmorphine and 6-acetylmorphine or as residue in the crucible. The diacetylmorphine not accounted

for could have decomposed to substances that escaped the fume collection system (gases) or that could not be detected by our HPLC–UV system. There was no evidence for any formation of toxic products vaporising in significant quantities, especially not from the excipient, caffeine anhydrate. However, it is possible that products of degradation and pyrolysis of diacetylmorphine were missed in the analysis of the fumes. Therefore, formation of these (possibly toxic) products in the volatilisation process cannot be completely ruled out and requires further investigation.

As mentioned above, 6-acetylmorphine was the only degradation product in the chromatograms of the condensate from the recovery experiments of diacetylmorphine for inhalation after volatilisation. This is consistent with findings in condensate from diacetylmorphine base heated with a computer-controlled smoking device [14] and from other in vitro experiments imitating 'chasing the dragon' [7]. The latter also identified *N*-6-diacetylnormorphine and *N*-3,6-triacetylnormorphine in the fumes. Cook and Brine showed that heating diacetylmorphine base for 10 min at 250 °C produced all of the aforementioned pyrolysis products and 3,4-diacetoxyphenanthrene [15].

As can easily be predicted from the ester structure of diacetylmorphine, 6-acetylmorphine has also been found an important metabolite in vivo, produced under the influence of esterases [16–18]. In in vitro and animal studies, 6-acetylmorphine was found to be pharmacologically active [19–21] and it is even considered to be the active metabolite responsible for the actions of heroin [22]. Detection of 6-acetylmorphine as a degradation product of diacetylmorphine for inhalation after volatilisation was, therefore, not considered a safety problem.

5. Conclusion

Diacetylmorphine base in combination with caffeine was found to be a suitable basis for a pharmaceutical dosage form for heroin to be inhaled after volatilisation ('chasing the dragon'). Thermal analysis showed these substances, as well as their mixtures, to have better thermal stability than diacetylmorphine hydrochloride. Recovery experiments showed that $40.8 \pm 5.3\%$ of diacetylmorphine base could be found in smoke condensate after volatilisation of diacetylmorphine for inhalation after volatilisation. All of the caffeine and 85.6% of the diacetylmorphine from each tablet was recovered, either unchanged in the fumes or as non-volatilised residue. Under the tested experimental conditions, no degradation of caffeine was observed and only small amounts of one degradation product (6-acetylmorphine) of diacetylmorphine appeared to volatilise with the main components. However, further research into possible toxic degradation products is necessary to ensure safe use of diacetylmorphine for inhalation after volatilisation.

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