

Review

# Development of pharmaceutical heroin preparations for medical co-prescription to opioid dependent patients

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## Abstract

Presently, there is a considerable interest in heroin-assisted treatment: co-prescription of heroin to certain subgroups of chronic, treatment-resistant, opioid dependent patients. In 2002, nine countries had planned (Australia, Belgium, Canada, France, Spain) or ongoing (Germany, The Netherlands, Switzerland, United Kingdom) clinical trials on this subject. These trials (and the routine heroin-assisted treatment programs that might result) will need pharmaceutical heroin (diacetylmorphine) to prescribe to the patients. Research into the development of pharmaceutical forms of heroin for prescription to addicts can benefit from the large amount of knowledge that already exists regarding this substance. Therefore, in this paper we review the physicochemical and pharmaceutical properties of diacetylmorphine and the clinically investigated routes of administration, as well as routes of administration utilised on the street in the context of developing pharmaceutical heroin formulations for prescription to addicts. Patient acceptability of the formulation is essential, because heroin-assisted treatment is aimed at treatment-resistant addicts, who often have to be encouraged to participate (or to maintain participation) in a treatment program. This means that the most suitable products would have pharmacokinetic profiles mimicking that of diacetylmorphine for injection, with rapid peak concentrations of diacetylmorphine and 6-acetylmorphine, ensuring the ‘rush effect’ and the sustained presence of morphine(-6-glucuronide) creating the prolonged euphoria. Diacetylmorphine for inhalation after volatilisation (via ‘chasing the dragon’) seems to be a suitable candidate, while intranasal and oral diacetylmorphine are currently thought to be unsuitable. However, oral and intranasal delivery systems might be improved and become suitable for use by heroin dependent patients.

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**Keywords:** Heroin; Prescription; Addiction; Pharmaceutical technology

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## 1. Introduction

Heroin (3,6-diacetylmorphine, diamorphine) is a di-ester of morphine that was introduced into medicine by Bayer in 1898, as a cough suppressant to assist breathing in patients with severe lung disease (Sneader, 1998). It was known to be twice as potent a cough suppressant as morphine, but its analgesic potency (two to three times that of morphine (Moffat et al., 1986)) was only recognised decades later, when it had been banned from prescription in many countries due to its addictive properties (Sneader, 1998). Heroin is now considered a drug of abuse that it is included in the United Nations list of Narcotic drugs under international control (International Narcotics Control Board, 2004). However, heroin was not banned from medical practice completely, the drug and its preparations are still included in the British Pharmacopoeia today (British Pharmacopoeia, 2004).

Nowadays, addiction has been accepted as a psychiatric disorder and several pharmacological treatments have been developed to treat addiction to opioids. In the last decade, attention has also turned to heroin-assisted treatment: co-prescription of heroin to certain subgroups of chronic, treatment-resistant, opioid dependent patients. In 2002, nine countries had planned (Australia, Belgium, Canada, France, Spain) or ongoing (Germany, The Netherlands, Switzerland, United Kingdom) clinical trials (Fischer et al., 2002; March et al., 2004). Most heroin-assisted treatment programs involve methadone with co-prescribed injectable heroin, although heroin tablets (UK, Spain) and cigarettes (UK, Switzerland) are also used. Street heroin is most commonly injected, snorted or smoked. The first route of administration poses little problems in heroin-assisted treatment programs, because parenteral use of diacetylmorphine is well established in the UK. However, it has proven more difficult to provide addicts that are used to snorting or smoking their street heroin with a suitable pharmaceutical alternative. In addition, alternative dosage forms could prove useful, even in countries where these routes of administration are unpopular compared to injecting, because they could be used by patients who wish to change their route of administration in order to avoid the risks associated with injecting or because of damaged veins. For the same reasons, non-injectable pharmaceutical dosage forms of diacetylmor-

phine could be stimulated in heroin-assisted treatment programs.

Research into the development of pharmaceutical forms of diacetylmorphine for prescription to addicts can benefit from the large amount of knowledge that already exists regarding this substance. Therefore, in this paper we review the physicochemical and pharmaceutical properties of diacetylmorphine and the clinically investigated routes of administration as well as routes of administration utilised on the street in the context of developing pharmaceutical heroin for prescription to addicts.

## 2. Properties of diacetylmorphine

### 2.1. Physicochemical properties

Diacetylmorphine is a morphine ester, its synthesis involves replacement of the two hydroxyl groups at the 3 and 6 position of the morphine molecule by acetyl groups. A base form exists, but the hydrochloride monohydrate salt is much more common in pharmaceutical dosage forms. Diacetylmorphine is a lipophilic substance with a partition coefficient ( $P(\text{octanol/water})=52$ ) between that of morphine ( $P=6$ ) and fentanyl ( $P=955$ ). As the  $pK_a$  of diacetylmorphine (7.6 (Moffat et al., 1986)) is close to physiological pH, a large proportion is present in the lipophilic non-ionised form, favouring absorption, while it also has excellent water solubility in the ionised form. The melting point of diacetylmorphine base (173 °C (The Merck Index, 1996)) is lower than that of the hydrochloride salt (243–244 °C (The Merck Index, 1996), 229–233 °C (British Pharmacopoeia, 1990; Hays et al., 1973; Moffat et al., 1986)), favouring its use in smoking or ‘chasing the dragon’ (see Section 3.3).

Since researchers and patients will tend to compare safety, efficacy and toxicity of pharmaceutical heroin for prescription to addicts with that of street heroin, it is important to address the properties of the latter. Street heroin varies in chemical composition: generally about 35–45% of a sample of brown heroin is identified as diacetylmorphine (hydrochloride) (Darke et al., 1999; de la Fuente et al., 1996; Huizer et al., 1977; Huizer, 1983; Kaa and Bent, 1986), while white heroin

is usually much purer, with diacetylmorphine hydrochloride contents up to 85–95% (de la Fuente et al., 1996; Huizer, 1992). Substances present in street heroin besides diacetylmorphine (hydrochloride) can be divided into manufacturing impurities, diluents and adulterants. The first category consists of morphine, codeine, papaverine, noscapine, acetylmorphine, acetylcodeine, etc.; active substances originating from the opium or morphine that was used in the synthesis of heroin and intermediates from the acetylation process. The second category comprises mainly sugars that are used as inert bulking agents. Thirdly, adulterants can be active drugs (paracetamol, caffeine, phenobarbitone, methaqualone, procaine, strychnine, quinine, piracetam), which, like heroin, have a bitter taste or that may mimic some of its effects (Darke et al., 1999; de la Fuente et al., 1996; Huizer et al., 1977; Huizer, 1983; Kaa and Bent, 1986; Risser et al., 2000). The efficacy and toxicity of street heroin is influenced by the presence of impurities, diluents and adulterants. For example, in ‘chasing the dragon’, heating a sample containing noscapine hydrochloride could result in formation of cotarnine, which is reported to give highly toxic fumes (Huizer, 1987).

## 2.2. Pharmacokinetics and pharmacodynamics

Diacetylmorphine lipophilicity combined with its near-physiological  $pK_a$  results in rapid absorption into the systemic circulation after administration and in rapid distribution into the tissues. These topics (absorption and distribution) will be discussed in more detail in the sections on the different routes of administration.

Diacetylmorphine has a very short half-life in the circulation, due to rapid conversion to 6-acetylmorphine and morphine by esterase enzymes that are present in the blood (plasma and erythrocytes), the liver and the brain (Kamendulis et al., 1996; Lockridge et al., 1980; Salmon et al., 1999). Both substances are conjugated in the liver into 6-acetylmorphine-3-glucuronide and morphine-3- and -6-glucuronide, respectively. These hydrophilic compounds are subsequently excreted in urine (Elliott et al., 1971; Mo and Way, 1966; Yeh et al., 1977). Results of pharmacokinetic studies will be discussed with each route of administration.

Diacetylmorphine is assumed to pass the blood–brain barrier rapidly due to its lipophilicity, resulting in an almost instant effect (Oldendorf et al., 1972). Even though the mechanism by which opioids produce euphoria is not entirely clear,  $\mu$ -receptors in the brain seem to be involved, as well as dopaminergic neurons (Goodman and Gilman, 1996; Van Ree et al., 1999). However, as binding to  $\mu$ -receptors requires a free phenolic hydroxyl (3-OH) group in the morphinan structure, it is likely that diacetylmorphine does not bind to these receptors and actually acts as a pro-drug for 6-acetylmorphine (Goodman and Gilman, 1996; Inturrisi et al., 1983; Selley et al., 2001). 6-Acetylmorphine was found to be more potent at the  $\mu$ -receptor than morphine (Inturrisi et al., 1983; Selley et al., 2001), but both could be considered active metabolites of diacetylmorphine (Goodman and Gilman, 1996; Inturrisi et

al., 1983; Inturrisi et al., 1984; Selley et al., 2001; Umans and Inturrisi, 1981). This explains why the maximum concentrations of diacetylmorphine and 6-acetylmorphine in plasma seem to be related to the almost instant ‘high’ effect (‘rush’) that occurs when addicts inject or inhale heroin. However, the exact relationship between plasma concentrations and effect remains a difficult issue to investigate. Peak plasma concentrations ( $C_{max}$ ) of diacetylmorphine are difficult to determine exactly, because of its rapid absorption and very short half-life in plasma. The values of  $C_{max}$  that are reported in literature should therefore be considered highly variable, apparent  $C_{max}$  values that are determined largely by the sampling schedule used and patient characteristics. Exposures to 6-acetylmorphine and morphine (glucuronides) are likely to be less variable and are preferred for the study of pharmacokinetic–pharmacodynamic relationships.

## 3. Routes of administration

### 3.1. Clinical use

Clinically, diacetylmorphine is mostly used parenterally: in the UK, diacetylmorphine hydrochloride is licensed for intravenous, intramuscular, or subcutaneous use in the treatment of moderate to severe pain (Kendall and Latter, 2003), but epidural administration of diacetylmorphine for post-operative or cancer pain has also been described extensively (Gopinathan et al., 2000; Hallworth et al., 1999; Morgan, 1989; O’Doherty et al., 2001; Sanders, 2002). For oral administration of diacetylmorphine, tablets containing diacetylmorphine hydrochloride or the so-called Brompton mixture (Poochikian and Cradock, 1980) are available in the UK and/or Canada. Oral diacetylmorphine is considered to be 1.5 times more potent than morphine sulphate, due to better absorption in the gastrointestinal tract (Aherne et al., 1979; Inturrisi et al., 1984; Twycross, 1977). It is however not surprising that its pharmacological effects are no different from morphine (when the potency difference was accounted for) (Sawynok, 1986), since first-pass metabolism was found to completely convert diacetylmorphine into morphine after absorption (Inturrisi et al., 1984).

Several studies were published on alternative methods for administration of diacetylmorphine. Even though lipophilic opioids showed better absorption in the mouth after sublingual administration, absorption of diacetylmorphine was not better than that of morphine, with a bioavailability of only 9% compared to intramuscular administration (Weinberg et al., 1988). However, diacetylmorphine lipophilicity did improve its bioavailability when inhaled (nebulised) compared to morphine (Masters et al., 1988). Intranasal administration of diacetylmorphine (as nasal spray or drops) was found to be effective and well tolerated in many studies (Hallett et al., 2000; Kendall et al., 2001; Kendall and Latter, 2003; Ward et al., 2002; Wilson et al., 1997). The lipophilic nature of diacetylmorphine could also explain its effect when applied

dermally (as a gel) for suppression of pressure ulcer pain (Flock, 2003) or intravesically for relief of bladder spasm (McCoubrie and Jeffrey, 2003).

### 3.2. Injecting heroin

Intravenous injection is the most widely used mode of administration of heroin as a drug of abuse: in many EU countries, 60–80% of the heroin users in treatment predominantly injected the drug (data 1990–2001 (EMCDDA, 2003)). However, the proportion of injectors varies considerably between countries and has changed over time, with levels of injection falling in almost all countries during the 1990s, although there is some evidence of more recent increases. Intravenous use of heroin is uncommon in Portugal and The Netherlands (10–15%) and has shown a large decrease ( $\pm 60$  to  $\pm 25\%$ ) in Spain. In 2002, about half of the heroin users in the EU predominantly injected (EMCDDA, 2003).

The pharmacokinetics of injected heroin probably account for much of its popularity: intravenous injection of diacetylmorphine rapidly results in peak plasma concentrations of diacetylmorphine ( $T_{\max}$  1.1–2.8 min) and 6-acetylmorphine ( $T_{\max}$  0.7–2.7 min) (Gyr et al., 2000; Rentsch et al., 2001; Rook, 2003) that are often associated with the ‘rush’ effect. Both substances are hydrolysed rapidly, resulting in short half-lives, 1.3–3.8 min for diacetylmorphine (Gyr et al., 2000; Jenkins et al., 1994; Rentsch et al., 2001; Rook, 2003) and 9.3–49 min for 6-acetylmorphine (Gyr et al., 2000; Jenkins et al., 1994; Rook, 2003). Morphine peak concentrations generally occur after 3.6–7.8 min and it is detectable in plasma for much longer ( $T_{1/2}$  109–287 min) (Gyr et al., 2000; Rentsch et al., 2001; Rook, 2003). The same is true for the active conjugate, morphine-6-glucuronide ( $T_{\max}$  1 h,  $T_{1/2}$  4 h) (Rook, 2003).

Intravenous drug use is considered the most harmful route of administration, for its many possible complications; most of which result from the bad quality of the product (impurities, adulterants, diluents, contamination with microorganisms (Dancer et al., 2002; McLachlan-Troup et al., 2001; McLauchlin et al., 2002; Moustoukas et al., 1983)) and from problems with the administration paraphernalia (contaminated needles, syringes, or acid solution (Strang et al., 1997a, 2001)). Problems of infection are the most common, for example, hepatitis or HIV infection, abscesses, collapsed veins, necrosis, sepsis and endocarditis. However, many of these complications could be prevented, if pharmaceutical quality diacetylmorphine for intravenous administration would be used. This leaves the increased risk of overdose that is associated with intravenous drug use as the most important disadvantage.

### 3.3. Smoking heroin

The term ‘heroin smoking’ is often used, but its exact meaning is not always clear, as two major types of heroin smoking can be distinguished: ‘chasing the dragon’ or smok-

ing cigarettes containing heroin (‘ack ack’ for example). For reasons of clarity, in this paper the first will be termed ‘inhalation after volatilisation’, since smoking implies the use of cigarettes or burning, while ‘chasing the dragon’ (performed correctly) involves only volatilisation and inhalation of the vapours. The first description of heroin inhalation after volatilisation (Shanghai, in the 1920s) involved heating heroin pills in porcelain jars and inhaling the fumes through a bamboo tube (Strang et al., 1997b). This procedure was refined into what is now known as ‘chasing the dragon’: heating heroin on aluminium foil using a cigarette lighter and inhaling the fumes by mouth through a straw or tube. Movement of the melted substance over the surface of the foil and careful application of heat are attempts to obtain optimal control over the volatilisation process and to minimise charring. Over the years, ‘chasing the dragon’ has spread from South East Asia to several countries in Europe (The Netherlands in the 1970s, UK in the 1980s and Spain and Switzerland in the 1990s) (Strang et al., 1997b) and it is still gaining in popularity (EMCDDA, 2003); in 2001, about 45% of the European addicts in treatment predominantly smoked heroin in this way (EMCDDA, 2003).

Inhalation of diacetylmorphine has several advantages over intravenous administration. Inhalation of a given dose takes more time, which leads to increased control and less risk of overdose compared to injection of a bolus dose. In addition, the onset of intoxication will lead to respiratory depression, which in turn automatically leads to a reduction of the heroin intake and the prevention of a serious overdose. It is a non-invasive route of administration with a much lower risk of infection and better social acceptability in some cultures. Furthermore, toxicity due to systemic exposure to impurities and adulterants present in street heroin is less likely, since many will not be inhalable and therefore not be available for absorption in the airways. On the other hand, heating may cause degradation of diacetylmorphine (hydrochloride) and the additives present in street heroin may also be susceptible to degradation and/or pyrolysis, which could lead to formation of volatile, toxic substances (Huizer, 1987). Such substances have been suggested as a cause for the occurrence of spongiform leuko-encephalopathy, a serious and rare, but recurrent toxicity that has been attributed to inhalation of heroin vapour, even though some reports of this toxicity involved injected heroin overdose (Rizzuto et al., 1997) and snorted heroin (Zuckerman et al., 1996). It was first recognised in The Netherlands, where 47 cases were reported in 1981 (Wolters et al., 1982) and since then reports from other parts of the world (Europe (Celius and Andersson, 1996; Hungerbühler and Waespe, 1990; Schiffer et al., 1985), the US/Canada (Hill et al., 2000; Kriegstein et al., 1997; Kriegstein et al., 1999)) have been published. The estimated mortality rate of 25% associated with spongiform leukoencephalopathy (Wolters et al., 1982) has attracted much attention to this complication that should however be considered very rare: less than 100 cases were reported in 18 years (Hill et al., 2000), while inhalation of heroin vapours was already quite common among

addicts during that period, especially in Asia, where it was reported only once (Chang et al., 1997). The cause for this condition was thought to be a toxin present in street heroin, but it was not identified, nor was the condition reproducible in animals exposed to heroin pyrolysate from suspect street heroin samples (Wolters et al., 1982).

Heroin smoking was reported to have negative consequences for the pulmonary function of patients: chronic heroin smoking was related to an impaired lung function and a higher prevalence of dyspnoea (Buster et al., 2002). However, almost all patients in this study also had a history of smoking tobacco, which caused part of the impairment of the lung function. Therefore, the authors concluded that further research is needed to quantify the separate effects of heroin smoking and tobacco smoking (Buster et al., 2002).

### 3.4. Snorting heroin

Intranasal use of opioids was the most common route of administration in the United States before 1930 (when intravenous use of heroin became popular) and snorting heroin made a comeback in the US around 1990 (Cone et al., 1993). It is not very common in Europe, about 4% of the addicts in treatment use their heroin intranasally (EMCDDA, 2003). Sniffing heroin is thought to be a phase of involvement with heroin, in which the habit is developed and after which a transition to other modes of administration is often made (Casriel et al., 1988). The pharmacokinetic profile of intranasal administration is similar to the intramuscular route, with a relative potency of 50%. Even though lower blood concentrations and a slower onset of action are achieved compared to the intravenous route, adequate efficiency combined with reduced fear of infection and a non-invasive nature could make intranasal administration an attractive alternative for injection of heroin (Cone, 1998).

## 4. Pharmaceutical heroin for prescription to addicts

A growing number of (European) countries are developing programs for (the study of) heroin-assisted treatment for addicts (Germany, The Netherlands, Spain, Switzerland). Main goals are usually related to harm reduction by providing addicts with pure medication, hygienic circumstances, medical supervision and (compulsory) psycho-education and psychosocial support (EMCDDA, 2003; Fischer et al., 2002). Suitable forms of pharmaceutical heroin are obviously needed for such programs, but surprisingly little has been published on this subject. Injectable and smokable forms of diacetylmorphine were expected to be required most frequently in heroin-assisted treatment programs, considering the patterns in the routes of administration of heroin. In the EU, most of the addicts in treatment inject ( $\pm 45\%$ ) or smoke ( $\pm 45\%$ ) heroin and  $\pm 10\%$  uses the oral route (EMCDDA, 2003). In the UK, licensed doctors prescribe diacetylmorphine to addicts in ampoules (92%), tablets

(32%), reefers (marijuana cigarettes, 16%), powder (11%) or as a solution (5%), which were dispensed for unsupervised consumption at home, usually daily (Metrebian et al., 2002). In a pilot study in Switzerland, prescription of intravenous, oral, or smoked diacetylmorphine was possible; 77% of the patients preferred injection (Brehmer and Iten, 2001).

An important requirement for pharmaceutical heroin would be its acceptability to clients, since heroin-assisted treatment is usually only an option for treatment-resistant addicts that have to be encouraged to participate in a treatment program. Furthermore, pharmaceutical heroin would have to comply with the usual requirements of efficacy, safety and quality of pharmaceutical products. With regard to acceptability to clients, rapid delivery of unchanged diacetylmorphine and/or 6-acetylmorphine to the circulation seems to be an important pharmacokinetic requirement for diacetylmorphine for prescription to addicts. Addicts dissatisfied with using methadone or morphine replacement therapy report missing the 'rush' effect that is generally associated with the rate of achieving high diacetylmorphine or 6-acetylmorphine peak concentrations. Fast and sufficient delivery of diacetylmorphine and/or 6-acetylmorphine to the circulation is a prerequisite to ensure rapid absorption into the brain, where 6-acetylmorphine activity is superior to that of morphine (Inturrisi et al., 1983; Selley et al., 2001).

### 4.1. Diacetylmorphine for injection

The safety and efficacy of diacetylmorphine for injection were established for the marketed forms (UK) of this product: ampoules of lyophilised diacetylmorphine hydrochloride. Especially the ampoules containing larger doses (100, 500 mg) would be suitable for prescription of injectable heroin to addicts. Development of new (multi-dose) formulations with larger doses is relatively simple, using the existing knowledge on manufacturing and stability (Klous et al., 2004c; Poochikian et al., 1983) and the quality control guidelines from the British Pharmacopoeia for the bulk substance and the final product (British Pharmacopoeia, 2004). Heroin-assisted treatment programs for addicts in Switzerland use specially manufactured multi-dose 10 g ampoules of lyophilised diacetylmorphine hydrochloride for administration of average dosages of 500–700 mg per day (Bundeli, 1999; Uchtenhagen et al., 1996). The Dutch Heroin trial uses multi-dose vials containing 3 g of lyophilised diacetylmorphine hydrochloride for maximum 400 mg per gift and maximum 1000 mg per day dosages (Van den Brink et al., 2003).

### 4.2. Diacetylmorphine for inhalation

Inhalation is gaining popularity as a route of administration for systemically acting drugs, because the large tissue area of the airways provides a quick and non-invasive route for delivery of drugs to the general circulation. Furthermore, blood flow from the lungs is directed straight to the brain, which makes a fast onset of action possible for centrally

acting drugs. Lipophilicity of the inhaled compound is likely to be important for absorption, which is illustrated by studies on morphine aerosols (Chrubasik et al., 1987, 1988; Cohen and Dawson, 2002; Dershwitz et al., 2000; Masood and Thomas, 1996; Masters et al., 1988; Ward et al., 1997) and a fentanyl aerosol (Alexander-Williams and Rowbotham, 1998). Nebulised morphine bioavailability was lower (5.5% Masood and Thomas (1996) and 17% Chrubasik et al. (1988)) than bioavailability of morphine from dose aerosols (59% Dershwitz et al. (2000), 100% Ward et al. (1997)). Since diacetylmorphine is more lipophilic than morphine, its bioavailability after inhalation can be expected to be similar or better than found for morphine.

When different methods for inhalation of diacetylmorphine are compared, it is important to remember what goals should be achieved. Obviously, maximum amounts of unchanged diacetylmorphine from the dosage form should be made available for inhalation. Furthermore, for addicts, an efficient method for inhalation should achieve two goals: quick appearance of large enough peak concentrations of diacetylmorphine and 6-acetylmorphine for the ‘rush’ effect and sufficient exposures to the other metabolites for prolonged euphoria (Gyr et al., 2000). The results of several in vitro and in vivo studies into the efficiency of using heroin via inhalation are summarised in Tables 1 and 2; they will be discussed in detail in the following three paragraphs.

#### 4.2.1. Smoking

Development of pharmaceutical heroin for smoking has an inherent safety problem, since smoking is known to be unsafe, due to inhalation of harmful substances like tar and carbon monoxide. Efficacy of smokable diacetylmorphine will also suffer from the ‘burning’ aspect of this mode of administration. This is illustrated by a comparison of ‘chasing the dragon’ and a procedure called ‘ack ack’, in which cigarettes dipped in street heroin is smoked: bioavailability (determined via total morphine in urine) of ‘chasing’ was higher (26%) than that of ‘ack ack’ (14%) (Mo and Way, 1966). Degradation and burning of heroin smoked via cigarettes are likely to be more extensive, since much higher temperatures are involved. The technique of ‘chasing the dragon’ is aimed at applying just enough heat for volatilisation and preventing burning. Furthermore, in this study street heroin containing diacetylmorphine base was used for ‘chasing the dragon’, while ‘ack ack’ involved dipping a cigarette in street heroin containing diacetylmorphine hydrochloride, which is known to be less suitable for smoking (Huizer, 1987; Mo and Way, 1966).

Despite the disadvantages of smoking diacetylmorphine mentioned above, a Swiss study into pharmaceutical smokable heroin for prescription to addicts was performed (Stalder, 1997). These cigarettes have also been dispensed to addicts in heroin-assisted treatment, because no better alternative was available (Uchtenhagen et al., 1996). Special impregnated woodruff cigarettes (without nicotine) were developed that contained 100 mg diacetylmorphine base (from a 200 mg/mL

Table 1  
Comparison of DAM inhalation techniques

Study	Rook (2003)	Rook (2003)	Rook (2003)	Mo and Way (1966)	Mo and Way (1966)	Stalder (1997)	Jenkins et al. (1994)	Speich (1998)	Hendriks et al. (2001)	Speich (1998)
Method	Chasing	Chasing	Chasing	Chasing	Cigarette <sup>a</sup>	Cigarette <sup>b</sup>	Device <sup>c</sup>	Device <sup>d</sup>	Device <sup>e</sup>	Nebulisation
Number of patients	9	74	66–450	35	14	2	2	2	5	1
Dose	200–300	66–450	A1	150–450	225–600	100 (*500)	10.5	100–300	50	536
Heroin type	A1	A1	A1	D1	D2	B	B	A2	A3	C
Temperature (°C)					>500	>500	200	275	300	Amb.
In vitro recovery (%)	52	68	53	68	19	2	89	53	41	45
Bioavailability (%)		38		38	21		12–324	37	38–45	58
Diacetylmorphine										
$C_{max}$ (µmol/L)	1.85					1.27	0.551	0.52		0.91
$T_{max}$ (min)						2.2	1–5	9.5		5.6/30.7
AUC (h µmol/L)	0.47					0.08	0.041	0.14		0.73
$T_{1/2}$ (min)	3.2		7.6			2.5	3.3	4.3		
Morphine AUC (h µmol/L)	3.65					1.59*		1.06		2.17

Heroin types: A, diacetylmorphine base/caffeine anhydrate (A1, 3:1 powder; A2, 2:1 tablets; A3, 1:2 tablets); B, diacetylmorphine base; C, diacetylmorphine hydrochloride, 173 mg/mL in aqua bidest; D, street heroin (D1, 64% pure diacetylmorphine base; D2, 92% pure diacetylmorphine hydrochloride).

<sup>a</sup> Tobacco.

<sup>b</sup> Woodruff.

<sup>c</sup> Computer controlled heating device with nichrome wire coil.

<sup>d</sup> TAS-oven heating device.

<sup>e</sup> Laboratory heating device with brass/aluminium sample holder.

\* The total dose of 5 cigarettes (500 mg) was used to calculate morphine AUC.

Table 2  
Results of in vitro experiments on the recovery of heroin (% unchanged) after volatilisation

Sample	Temperature (°C)	Recovery (%)	Study	
Diacetylmorphine hydrochloride	200	28	Jenkins et al. (1994)	
	200–300	10	Cook and Jeffcoat (1990)	
	–	17	Huizer (1987)	
	With caffeine (1:1)	–	36	Huizer (1987)
With barbital (1:1)	–	33	Huizer (1987)	
Diacetylmorphine base	200	89	Jenkins et al. (1994)	
	200–300	65	Cook and Jeffcoat (1990)	
	>400	<30	Cook and Jeffcoat (1990)	
	–	62	Huizer (1987)	
	With caffeine (1:1)	–	76	Huizer (1987)
	With methaqualone (1:1)	–	55	Huizer (1987)

solution in dichloromethane). They showed low recoveries of diacetylmorphine and 6-acetylmorphine in an in vitro smoking experiment: 2.2% and 5.5%, respectively (Stalder, 1997).

In vivo pharmacokinetic studies were performed: two female addicts smoked five cigarettes each, which resulted in surprisingly high AUCs for diacetylmorphine, and 6-acetylmorphine (0.08 and 0.07 h  $\mu\text{mol/L}$ , respectively) (Table 1). This might be explained by the fact that the Swiss researchers collected five plasma samples in the first 5 min after the start of smoking (Stalder, 1997). In the other studies on diacetylmorphine inhalation (Table 1), fewer samples from this period were available, resulting in underestimation of the AUCs of diacetylmorphine and 6-acetylmorphine. Exposures to morphine (1.6 h  $\mu\text{mol/L}$ ) and morphine-3- and -6-glucuronide (9.1 and 3.2 h  $\mu\text{mol/L}$ , respectively) after five woodruff cigarettes (500 mg) were only 27–55% of those found after ‘chasing the dragon’ by Rook et al. (dose 200–300 mg (Rook, 2003)), suggesting that smoking diacetylmorphine cigarettes is very inefficient.

#### 4.2.2. Inhalation after volatilisation

Inhalation of diacetylmorphine after volatilisation is probably safer than smoking of diacetylmorphine, since no burning is involved, thereby avoiding inhalation of carbon monoxide and tar or soot. On the other hand, high temperatures are needed for efficient volatilisation, which could lead to formation of (possibly toxic) degradation products that could be inhaled alongside with diacetylmorphine. However, formation of toxins is more likely when heating a mixture of substances, such as street heroin, because the constituents could interact chemically. This has also been considered as an explanation for the rare occurrences of spongiform leukoencephalopathy in addicts inhaling heroin vapours (see Section 3.3). Considering the above, diacetylmorphine for inhalation after volatilisation is regarded as an option for the development of non-injectable pharmaceutical heroin for prescription to heroin-dependent patients.

Higher efficiency is expected for inhalation of volatilised diacetylmorphine compared to smoking, as the temperatures involved in volatilisation will be lower, with less decomposition of diacetylmorphine. Furthermore, volatilisation of di-

acetylmorphine base is more efficient than diacetylmorphine hydrochloride. Thermal analysis and in vitro studies simulating ‘chasing the dragon’ have shown that diacetylmorphine base is less susceptible to degradation upon heating and its volatilisation results in more unchanged diacetylmorphine in vapours (Huizer, 1987; Klous, 2004) (Table 2). Moreover, additives could influence inhalation efficiency positively: recovery of unchanged diacetylmorphine in the vapours after volatilisation increased in samples containing caffeine, methaqualone (Huizer, 1987) and barbital (Huizer, 1987; Mo and Way, 1966) (Table 2). Even though the sedative properties of the latter are probably also appreciated by users of street heroin, in a pharmaceutical product additives without synergistic pharmacological activity would be preferred.

The efficacy of inhalation of diacetylmorphine vapours is also likely to depend on the method used to heat the product. Specific techniques exist for ‘chasing the dragon’, suggesting that heating diacetylmorphine for inhalation of the vapours requires certain skills. Many heroin addicts have developed tricks and habits in their ‘chasing technique’ that serve to minimise the loss of heroin vapour through charring, combustion and fumes escaping inhalation via the straw. Mimicking these street habits (that have evolved over decades) could be a suitable starting point for development of a method for volatilisation of pharmaceutical heroin that is acceptable to the users. However, it would be difficult to develop a heating device that would incorporate all these ‘tricks of the trade’, especially the movement of the molten substance. Addicts testing a heating device for inhalation of diacetylmorphine after volatilisation expressed concerns of loss of vapour, due to the lack of movement (Hendriks et al., 2001). Apparently, moving the molten substance is a way of ensuring a controlled release of vapour in the form of a neat ‘dragon’s tail’ that is easy to inhale completely. Volatilisation without movement caused the vapours to appear as a broad smoke column or cloud that was difficult to inhale efficiently (Hendriks et al., 2001). Furthermore, movement of the molten heroin might prevent overheating and subsequent decomposition of the drug.

Only two pharmacokinetic studies have been performed with addicts using heroin via ‘chasing the dragon’ (Table 1). An early study compared three modes of administration: in-

jecting, 'chasing the dragon' and 'ack ack' (smoking heroin via a tobacco cigarette) by addicts using the corresponding types of street heroin (Mo and Way, 1966). Administering heroin via 'chasing the dragon' was found to be about 1/3 as effective as intravenous heroin and about twice as effective as smoking heroin from a cigarette, based on total morphine concentrations in urine. More recent pharmacokinetic studies, comparing intravenous administration to inhalation via 'chasing the dragon' found 52% bioavailability for the latter (Rook, 2003). Addicts in this study inhaled pharmaceutical heroin for inhalation after volatilisation (a 75%, w/w diacetylmorphine base/25% caffeine anhydrate powder mixture (Klous et al., 2004a,b)) instead of street heroin containing diacetylmorphine hydrochloride in the early study. No statistically significant differences in the half-lives of diacetylmorphine, 6-acetylmorphine, morphine and morphine-3- and -6-glucuronide in plasma were found between injected or inhaled diacetylmorphine (Rook, 2003). Surprisingly, no difference was found in the subjective appreciation of the diacetylmorphine between the groups, even though equal doses were used and plasma concentrations of diacetylmorphine and metabolites were much lower in the inhalation compared to the injecting group. The authors suggest that this was due to the lack of cross-over comparison of administration methods; each patient used diacetylmorphine via his usual route of administration and therefore also rated its effect compared to what he was used to. Both methods showed dose-related craving and appreciation upon double-blinded variation of dose (dose range 66–150% of regular dose). Population pharmacokinetic models for plasma concentrations of diacetylmorphine and its metabolites after intravenous use and after inhalation were published by the same group (Rook, 2003).

Use of a heating device by addicts as an alternative for 'chasing the dragon' was described in three studies (Table 1). In the first of these studies, a computer-controlled device with a nichrome-heating coil was used to heat 2.6–10.5 mg diacetylmorphine base to be inhaled by two healthy volunteers (Jenkins et al., 1994). The whole dose was administered in one puff and maximum concentrations of diacetylmorphine and 6-acetylmorphine achieved were 0.045–0.809 and 0.043–0.428  $\mu\text{mol/L}$ , respectively, depending on the smoked dose. The diacetylmorphine AUC at the 10.5 mg dose level was also quite high (0.041 h  $\mu\text{mol/L}$ ), considering the low doses that were administered. 'Chasing' a 20–30 times higher dose yielded a diacetylmorphine AUC that was only 10 times higher than with this heating device (Rook et al., Table 1). The apparent efficiency of this method might be explained by the high in vitro recovery of diacetylmorphine from the smoking device (89%, Table 1) (Jenkins et al., 1994).

Two Swiss addicts, selected from participants of the heroin-assisted treatment program, were asked to inhale the fumes that resulted from heating 100/50 mg tablets of diacetylmorphine base and caffeine in a TAS-oven apparatus, fitted with an insulated mouthpiece. Caffeine anhydrate was the only additive present in the tablets and it was added to diacetylmorphine base for its positive influence on volatili-

sation. Tablets were manufactured manually from granulate prepared using a diacetylmorphine/caffeine powder mixture and a 2% (w/w) caffeine solution in water. In vitro recovery of diacetylmorphine from heating these tablets in the TAS-oven was 53%. One patient smoked one tablet, the other three; smoking sessions lasted 16–22 min per tablet (Speich, 1998). The bioavailability was similar to the in vitro recovery (37%) and 'rush' and 'high' effects were achieved. However, maximum concentrations of diacetylmorphine were lower than in the study by Rook (2003) (Table 1), as was the AUC of morphine, while bioavailability and dosages were similar, indicating that the TAS-oven procedure is not quite as efficient as 'chasing the dragon'. The third study using a heating device for volatilisation of diacetylmorphine reported a bioavailability of the same order (38–45%), based on measurements of total morphine in urine (Table 1) (Hendriks et al., 2001).

#### 4.2.3. Nebulisation

In the Swiss study by Speich and co-workers, inhalation after volatilisation and nebulisation were compared in in vivo and in vitro experiments (Speich, 1998). In vitro tests were performed on 100 and 200 mg/mL solutions of diacetylmorphine hydrochloride in distilled water that showed antimicrobial activity, limited stability, hyperosmolarity and pH values of 3–4 (near the lower limit of the range suitable for solutions for inhalation: 3–8.5 (European Pharmacopoeia, 2002)). However, as large doses are required for heroin-assisted treatment and nebulising volume is limited (1–3 mL), the authors decided that use of concentrated solutions could not be avoided. Three types of nebuliser were tested, one of which (Pari IS-2 jet nebuliser) generated an aerosol that was suitable for delivery to the peripheral parts of the lungs (mean particle size: 2.4–2.6  $\mu\text{m}$ , 80% of the particles 0.8–4.8  $\mu\text{m}$ ). The nebuliser released a mean of 45% of the diacetylmorphine solution. In vivo tests were limited to a single patient inhaling 536 mg (effective dose: 240 mg) of diacetylmorphine as a 200 mg/mL solution (Table 1). The inhalation session lasted for 95 min (with 43 min of actual inhaling), because many breaks were necessary due to the very bitter taste of the inhalation solution. Even though the total exposures to diacetylmorphine and morphine were not much lower than those measured after 'chasing the dragon', the time to reach the first maximum concentration of diacetylmorphine was quite long (5.6 min), while a second  $C_{\text{max}}$  was measured at 12.7 min after a 6-min break. This pharmacokinetic profile, combined with the bitter taste of the inhalation solution will probably not contribute to the acceptability of this inhalation method in a heroin-assisted treatment program, particularly since the latter was reported to lead to nausea and retching (Speich, 1998). It is likely that the bitter taste of the diacetylmorphine solution is associated with its high concentration, but solutions with lower concentrations cannot deliver large diacetylmorphine doses in a volume suitable for nebulisation. Therefore, nebulisation of diacetylmorphine is not likely to be pursued further for use in heroin-assisted treatment of heroin dependent patients.

### 4.3. Intranasal diacetylmorphine

Intranasal use of diacetylmorphine could be acceptable to addicts in a heroin-assisted treatment program, since it is a well-known route of administration on the streets as well. However, snorting heroin does not give the user the same intense ‘rush’ feeling that injecting does, the ‘high’ begins more gradually (Casriel et al., 1988), which might hinder its acceptance by chronic addicts. There is no reason to question the safety of intranasal use of diacetylmorphine, as it has been used clinically, even in children (see Section 3.1). Clinically, diacetylmorphine hydrochloride solutions are administered as nasal spray or nasal drops, but such liquid formulations are not suitable for administering large doses (up to 300–400 mg) to addicts in heroin-assisted treatment, because of the maximum volume for nasal spray or nasal drops (about 0.1–0.2 mL). Therefore, intranasal use of diacetylmorphine by addicts requires a solid pharmaceutical dosage form, e.g., diacetylmorphine hydrochloride powder, which can be snorted through a straw in the nose. The only pharmacokinetic studies (in opioid dependent patients) on intranasal use of powdered diacetylmorphine concern quite small doses, mixed with lactose for blinding reasons (Comer et al., 1999; Cone et al., 1993; Skopp et al., 1997) (Table 3). Snorting diacetylmorphine powder was found to be about half as efficient as intramuscular administration, based on the behavioural and physiological effects (Cone et al., 1993) as well as based on the ratio of morphine-3-glucuronide AUCs for both routes of administration (Skopp et al., 1997). Intranasal compared to intravenous administration of diacetylmorphine resulted in 30 times lower diacetylmorphine peak concentrations and longer  $T_{max}$ , 4 and 10 min for diacetylmorphine and 6-acetylmorphine, respectively, compared to 2 min for both after intravenous administration (Comer et al., 1999). Concentrations of diacetylmorphine and 6-acetylmorphine were elevated three to four times longer than after intravenous administration. A fourfold difference in potency between the two routes of administration was observed with several pharmacodynamic parameters, i.e., visual analog scale (VAS) ratings of ‘high’, ‘good drug effect’, ‘drug liking’ and ‘sedated’ (Comer et al., 1999).

Further investigation of intranasal administration of diacetylmorphine for prescription to addicts is required to clarify the pharmacokinetics of larger doses. Furthermore, intranasal administration might become more acceptable if

its pharmacokinetic profile could be modified to be more similar to that of injectable diacetylmorphine, for example, by using controlled release techniques. Such a technique was successfully used to achieve an optimal pulsatile and sustained plasma nicotine profile by controlled release of nicotine from a nasal formulation (Cheng et al., 2002). This research group also reported improving nasal administration of morphine by formulating it as a powder or a solution with chitosan as an excipient (absorption-promoter) (Illum et al., 2002). Such absorption-promoters might be used to achieve a ‘rush’ effect after nasal administration of diacetylmorphine similar to that after injection, which would make intranasal administration much more acceptable to chronic addicts.

### 4.4. Oral diacetylmorphine

Oral administration of diacetylmorphine (as tablets or solution) is known to be a safe and effective route of administration of diacetylmorphine for analgetic purposes (see Section 3.1). However, its pharmacokinetic profile (in terms of delivery of diacetylmorphine and 6-acetylmorphine to the brain) does not seem to favour use of this route in heroin-assisted treatment. Despite this, several publications describe use of oral diacetylmorphine in the treatment of addicts: as a solution (Ghodse et al., 1990), or in the form of tablets (Metrebian et al., 2002). A Spanish protocol for heroin-assisted treatment proposes to study oral diacetylmorphine versus oral methadone (Fischer et al., 2002) and oral formulations of diacetylmorphine were tested for use in the Swiss heroin-assisted treatment program (Uchtenhagen et al., 1996).

Capsules, controlled release tablets and rectally administered diacetylmorphine hydrochloride were tested for use by addicts in a two-patient pilot study (Gyr, 1998; Gyr et al., 2000). Interestingly, even though no diacetylmorphine or 6-acetylmorphine was detected in plasma after oral or rectal administration of diacetylmorphine, ‘rush’ and ‘high’ effects were experienced, although peak effects occurred much later and were less intense than after intravenous administration ( $\pm 15$  min;  $\pm 90\%$  of VAS scale) (Gyr et al., 2000). These pharmacodynamic results deviate so much from what is known about the pharmacokinetics of heroin in relation to the occurrence of ‘rush’ effects that they should be verified in double blind studies with more patients, before pharmaceutical development of (oral and rectal) diacetylmorphine for prescription to addicts can extend its focus to formula-

Table 3  
Comparison of studies on intranasal use of diacetylmorphine powder (snorting)

Study	Cone et al. (1993)	Cone et al. (1993)	Skopp et al. (1997)	Skopp et al. (1997)	Comer et al. (1999)
Number of patients	6	6	4	4	6
Dose (mg)	6 <sup>a</sup>	12 <sup>a</sup>	6 <sup>a</sup>	12 <sup>a</sup>	50 (12.5–100) <sup>a</sup>
$C_{max}$ ( $\mu\text{mol/L}$ )	0.025	0.043	0.042	0.097	0.144
$T_{max}$ (min)	<5	<5	<5	<5	4
AUC (h $\mu\text{mol/L}$ )	–	–	0.0066	0.0138	–
$T_{1/2}$ (min)	5.4	4.2	6	4.8	–
AUC <sub>M</sub> (h $\mu\text{mol/L}$ )	–	–	0.0287	0.0926	–

<sup>a</sup> Diacetylmorphine hydrochloride, with lactose added to a total weight of 100 mg; total dose inhaled divided between two nostrils.

tions that are unable to deliver unchanged diacetylmorphine to systemic circulation.

Two other pharmacokinetic studies were published on oral diacetylmorphine (Girardin et al., 2003; Inturrisi et al., 1984). The first study compared the pharmacokinetics of low doses (26–52 mg) of oral diacetylmorphine and oral morphine in healthy volunteers and found that diacetylmorphine resulted in 80% lower bioavailability than morphine (bioavailability 38%) (Inturrisi et al., 1984). However, in the second study the pharmacokinetics after oral administration of large doses to addicts appeared to be very different (Girardin et al., 2003). In both studies, neither diacetylmorphine nor 6-acetylmorphine was detected in plasma, so morphine bioavailability was calculated from oral diacetylmorphine in both studies. Mean bioavailability of morphine after ingestion of up to 600 mg of diacetylmorphine by opioid dependent patients was much higher ( $67 \pm 19\%$ ) than expected based on the study in healthy volunteers (Girardin et al., 2003). Furthermore, morphine absorption from oral diacetylmorphine was more rapid and more complete than absorption from concomitantly administered morphine-d3 (Girardin et al., 2003). The authors suggest that intestinal metabolic or transporter alterations could have occurred in tolerant persons, which could explain these findings.

Future studies into oral formulations of diacetylmorphine could attempt to avoid first-pass metabolism via the buccal mucosa: a bioadhesive buccal tablet (as developed for morphine (Beyssac et al., 1998)) or a chewing gum formulation (as developed for methadone (Christrup et al., 1990)) might be able to deliver sufficient amounts of diacetylmorphine or 6-acetylmorphine into the systemic circulation to achieve the desired ‘rush’ effect. However, these attempts might be hindered by the bitter taste of diacetylmorphine that was responsible for abandoning nebulised diacetylmorphine (Speich, 1998).

## 5. Conclusion

Heroin dependent patients in heroin-assisted treatment will often prefer diacetylmorphine for injection as the prescribed drug, as it is the most efficient way to achieve their goals of feeling an almost instantaneous ‘rush’ followed by more sustained euphoria. Acceptability of this form of pharmaceutical heroin will therefore be high. Safety can only be ensured by strict dosing schemes to prevent overdose, by supervision following the first 10–15 min after use and by providing a high quality product for injection and clean needles and syringes for its administration. However, alternative formulations are necessary for those who want to change routes of administration to minimise the risk of overdose or that have to, due to damaged veins. Diacetylmorphine for inhalation is an obvious candidate, because many addicts in Europe already use heroin this way and studies indicate that especially inhalation after volatilisation (‘chasing the dragon’) could be an effective route of administration: first-pass metabolism is

avoided and rapid peak concentrations of diacetylmorphine and 6-acetylmorphine are achieved. Intranasal diacetylmorphine could also be a safe and effective alternative, but further research into enhanced absorption techniques and the pharmacokinetics and pharmacodynamics of large doses is required. The same could be said for oral administration, which is however theoretically less likely to be acceptable to treatment-resistant addicts, due to its failure to deliver diacetylmorphine or 6-acetylmorphine to the systemic circulation.

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