DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 7, pp. 775–784, 2004

Development and Manufacture of Diacetylmorphine/Caffeine Sachets for Inhalation Via 'Chasing the Dragon' by Heroin Addicts

M. G. Klous,[1,*] B. Nuijen,[1] W. van den Brink,[2,3] J. M. van Ree,[2,4] and J. H. Beijnen[1,5]

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

ABSTRACT

In 1998, two clinical trials were started in the Netherlands to evaluate the effect of coprescription of heroin and methadone on the mental and physical health and social functioning of chronic, treatment-resistant, heroin-dependent patients. Since 75–85% of the heroin addicts in the Netherlands use their heroin by ''chasing the dragon,'' one of the two study arms concerned the coprescription of inhalable heroin. A pharmaceutical dosage form for inhalable heroin was developed for this trial, consisting of a 3:1 powder mixture of diacetylmorphine base and caffeine anhydrate. We describe the manufacturing process that was developed for filling sachets with this mixture in four dosages using a micro dose auger filler. In order to control product quality, in-process controls were developed to monitor the filling process and quality control tests were performed on the finished product. In-process control results have shown the filling process to be accurate and precise. The diacetylmorphine/caffeine sachets were shown to comply with the specifications for content and uniformity of

*Correspondence: Mrs. M. G. Klous, Department of Pharmacy and Pharmacology, Slotervaart Hospital, P.O. Box 90440, 1006 BK Amsterdam, The Netherlands; Fax: +31–20-512-4753; E-mail: apmlk@slz.nl.

DOI: 10.1081/DDC-120040223
0363-9045 (Print); 1520-5762 (Online)

mass. The finished product was found to be stable for 2 years when stored at 25°C, 60% relative humidity and for 6 months when stored at 40°C, 75% relative humidity.

Key Words: Heroin; Pharmaceutical technology; Powder; Sachet; Smoking; Inhalation; Chasing the dragon.

INTRODUCTION

Heroin (3,6-diacetylmorphine) is a well-known drug of abuse that is usually administered intravenously. However, smoking heroin has gained popularity in many parts of the world since it was first described in Shanghai in the 1920s.[1] In a procedure called ''chasing the dragon,'' addicts typically inhale heroin fumes resulting from heating heroin powder on aluminum foil with a cigarette lighter until it melts and evaporates.

In 1998, two clinical trials were started in the Netherlands to evaluate the effect of coprescription of heroin and methadone on the mental and physical health and social functioning of chronic, treatment-resistant, heroin-dependent patients.[2] Since 75–85% of the heroin addicts in the Netherlands use their heroin by 'chasing the dragon',[3] one of the two study arms concerned the coprescription of inhalable heroin. As no pharmaceutical dosage form for inhalable heroin was available, it had to be developed specially for this trial. An important requirement was to avoid problems of patient noncompliance, by ensuring that the product could be used according to the long-established habits of the patients in the trial.

A 3:1 w/w mixture of diacetylmorphine base and caffeine anhydrate was found to be an appropriate basis for a pharmaceutical form of inhalable heroin. Caffeine is commonly found in street heroin samples[4–7] and has been shown to improve the volatilization of diacetylmorphine.[8] Furthermore, diacetylmorphine base was more suitable than diacetylmorphine hydrochloride, because it showed less degradation and larger recoveries after volatilization.[8] This pharmaceutical form of inhalable heroin was suitable for use by 'chasing the dragon:' patients placed the powder mixture on aluminum foil and heated it from below with a cigarette lighter until the powder melted. They subsequently moved the melted mass across the surface of the foil, still carefully heating it with the lighter, while inhaling the arising fumes through a plastic straw in the mouth.

For the clinical trial, four dosage units were desired, containing 75/25, 100/33, 150/50, or 200/67 mg diacetylmorphine/caffeine. It was decided to use mechanically forced transport, using a microdose auger filler machine, to fill sachets with the above amounts of powder. Powder-filled sachets, however, are not a common dosage form in pharmaceutical practice, especially not for small doses (<1 g of powder). We could not find any literature on formulation and manufacturing in auger filling of powders. Therefore, in this paper, the selection and development of dosage form and production process, as well as methods for in-process controls and quality control of the finished product are discussed.

MATERIALS AND METHODS

Materials

Diacetylmorphine base was obtained through the Central Committee on the Treatment of Heroin Addicts (Utrecht, The Netherlands). The manufacturer used quality specifications that were derived from the British Pharmacopoeia Monograph for Diacetylmorphine Hydrochloride.[9] In-house quality control consisted of infrared (IR) spectroscopy (identity) and high-performance liquid chromatography (HPLC) analysis with ultraviolet (UV) detection (identity and purity). Caffeine anhydrate [European Pharmacopoeia (Ph.Eur.) quality] was purchased from Bufa (Uitgeest, The Netherlands). In-house quality control consisted of thin layer chromatography analysis (identity) and UV/VIS-spectrophotometry (identity, content). All other chemicals used were of analytical grade and were used without further purification.

Powder Properties

Poured (d_p) and tapped (d_t) densities were determined using a tapped volumeter (Type SVM12, Erweka, Heusenstamm, Germany), according to the procedure in Ph.Eur.Ed.IV/2.9.15.[10] Carr's compressibility index (CCI) was calculated from these densities (difference between d_p and d_t as a percentage of d_p). The angle of repose (AoR) and the flow rate (FR) [tested according to Ph.Eur.Ed.IV/2.9.16][11] were determined using a granulate flow tester (Type GTB, Erweka, Heusenstamm, Germany) fitted with a 25-mm nozzle and an agitator (operated at speed setting 4).

Manufacture

A microdose auger filler machine (Type SD1, Optima, Schwäbisch Hall, Germany) was used for filling sachets with 3:1 diacetylmorphine/caffeine powder mixture. This machine consists of a 5-L hopper (plexiglass) fitted with a product sensor, a dosing funnel, an agitator, and a 340-mm auger (diameter 5 mm, pitch 5 mm), the latter three all being constructed from stainless steel. The dosing principle of the filling machine is based on transportation of powder into the sachet by rotating the dosing auger. It is operated using a touch screen on a computer that displays settings and process data and enables the operator to adjust filling during manufacturing. The auger filler is mounted vertically on top of a packaging unit (Type EU1N1, Boato Pack, Staranzano, Italy) that forms heat-sealed sachets from a foil material. This foil consists of (from the inside out) a low-density polyethylene (LDPE) coating (23 g/m^2 LDPE), a 7-μm aluminum foil layer, a second layer of LDPE (12 g/m^2), and a layer of claycoated paper (50 g/m^2) printed with the desired label text. The packaging machine is fitted with an in-line printer for batch number and expiration date and an in-line labeling unit for tear-off labels for drug accountability purposes. During manufacturing, dosing accuracy was checked by weighing ejected powder portions (during start-up), sachet contents (powder shaken out, every 100 sachets), and filled sachets (total sachet weight, every 500 sachets) on a type PM480 balance (Mettler-Toledo, Tiel, The Netherlands).

For each manufacture run, the diacetylmorphine/caffeine mixture 3:1 w/w was prepared by mixing three parts of diacetylmorphine with one part of caffeine using a Model UM12 Stephan mixer (Stephan Electronic 2011, Hameln, Germany). Four different sachet types were produced, containing 100 mg of powder per sachet (75/25 mg diacetylmorphine/caffeine), 133 mg (100/33 mg), 200 mg (150/50 mg), and 267 mg (200/67 mg). Batch sizes ranged from 9000–17,000 sachets, depending on the dose. Sachets were packaged per 50 in labeled cardboard boxes ($60 \times 60 \times 146$ mm, OPG, Utrecht, The Netherlands).

High-Performance Liquid Chromatography (HPLC)

For the analysis of diacetylmorphine and caffeine, a validated, stability-indicating, reversed-phase HPLC–UV method was used. The HPLC system consisted of a model AS3000 SpectraSystems autosampler, connected to a model P1000 SpectraSystems HPLC pump, and a UV1000 SpectraSeries detector (Thermo Separation Products, Fremont, CA). Chromatograms were processed using Chromeleon software (Dionex Corporation, Sunnyvale, CA). Separation was achieved using a Zorbax Bonus RP analytical column (4.6-mm ID $\times$ 15 cm, particle size 5 μm, Rockland Technologies Inc., Newport, DE). The mobile phase consisted of 85% v/v, 0.05 M phosphate buffer (pH 6) mixed with 15% v/v acetonitrile. Detection wavelength was 214 nm, flow was 1.0 mL/min and injection volume was 20 μL. Samples and standard solutions were prepared using an 85/15% v/v mixture of 0.05 M phosphate buffer (pH 4) and acetonitrile as a solvent. Calibration lines for diacetylmorphine and caffeine were linear (r^2>0.999) in the concentration ranges of 20–60 μg/mL diacetylmorphine and 8–24 μg/mL caffeine. The relative diacetylmorphine (% w/w) content of the sachets was calculated from the diacetylmorphine and caffeine content (determined in triplicate). Identity of diacetylmorphine and caffeine was confirmed by comparison of retention times with those of reference standards. The chromatographic purity of diacetylmorphine was determined by dividing the peak area of the diacetylmorphine peak by the sum of the peak areas of all peaks, except the caffeine peak and the solvent peak.

Uniformity of Mass

For the test on Uniformity of Mass [Ph.Eur.Ed.IV/2.9.5],[12] the weight of the contents of 20 sachets was calculated by subtracting the weight of the emptied sachet from the total sachet weight. The amount of powder remaining in the sachet after shaking out the contents (residue) was calculated from the weight of the emptied sachet before and after removal of the residue.

Stability Studies

Long-term and accelerated stability studies were performed according to International Commission on Harmonization (ICH) guidelines.[13] To assess long-term stability, samples from three batches per dosage were stored at 25±2°C, 60±5% relative humidity (RH) in their secondary packaging in a HEKK0057 climate chamber (Weiss Technik Ltd., Buckinghamshire, UK). Mean content and purity were determined at 6, 12, 18, and 24 months using the aforementioned HPLC–UV method. For accelerated stability studies, three batches of 100/33, 150/50, and 200/67 mg sachets and one batch of 75/25 mg sachets were stored at 40±2°C,

75±5% RH in their secondary packaging in a HEKK0057 climate chamber. Mean content and purity were determined after 1, 2, 3, and 6 months.

RESULTS AND DISCUSSION

Selection of Dosage Form

It was considered important for patient compliance to develop a dosage form for pharmaceutical, smokable heroin that could be used according to the long-established habits of the chronic heroin addicts in the clinical trial. Considering this requirement, powder formulations were preferred for their similarity to street heroin. Powder flow tests were performed on the drug substances used in smokable heroin, diacetylmorphine base and caffeine anhydrate, as well as on the 3:1 w/w diacetylmorphine/caffeine mixture (Table 1). Their poor flowability is demonstrated by their large angle of repose and their Carr's compressiblity index exceeding 30%.[14] Powder flow rate was also slow, and, in most cases, the entire sample even failed to flow through.

During the pilot phase of the clinical trial, capsules containing the 3:1 w/w diacetylmorphine/caffeine mixture were manufactured manually on a small scale, hence the poor flow properties of the 3:1 w/w powder mixture did not pose a major problem. The nursing staff opened these capsules before administering the contents to the patients to be smoked under supervision. This procedure resulted in symptoms of contact dermatitis in several members of staff.[15] In order to avoid such problems in the next phase of the trial, a pharmaceutical dosage form was required that was not contaminated with the diacetylmorphine/caffeine mixture on the outside. Furthermore, it was considered undesirable to add excipients other than caffeine anhydrate, since the sachet's contents were to be heated and the resulting vapors inhaled (chasing the dragon) by the patients; possible adverse effects of excipients would be unpredictable under these circumstances. Therefore, capsule or tablet formulations requiring additives such as glidants, fillers, and binders were not pursued.

It was decided to develop sachets filled with a powder formulation, containing diacetylmorphine combined with only caffeine anhydrate as an excipient. Poor powder flow properties were not expected to interfere with the selected dosing principle of mechanically forced transport by a microdose auger filler. The sachets would be easy to open and empty by the nursing staff before administration, and contact dermatitis would be less likely since the outside of the packaging material would not come into contact with the powder mixture during manufacturing.

Manufacturing Process

The manufacturing process described in this paper involves a microdose auger filler. A long and narrow vertical auger was specifically designed to accurately fill small amounts of powder by mechanically forced transport (each revolution of the auger results in ejection of several milligrams). This principle of dosing is flexible with respect to dose, without the need to add excipients or alter excipient concentration in the powder mixture in order to obtain specific flow properties. The powder portions are subsequently packaged into sachets formed in-line from packaging

Table 1. Powder flow properties.

Property	Diacetylmorphine base	Caffeine	3:1 Mixture
Poured density (mg/mL)	393.7 (23.4)	420.3 (16.0)	426.2 (20.9)
Tapped density (mg/mL)	527.5 (31.5)	557.6 (10.9)	572.7 (25.0)
CCI (%)	34.0 (2.2)	32.8 (4.4)	34.5 (4.9)
N	4	2	4
Angle of repose (°)	49.2 (2.3)	46.0 (4.1)	49.4 (3.6)
N	3	2	3
Flow rate EP (s/100 g)	$11.3-\infty$[a]	$3.3-\infty$[a]	$9.9-\infty$[a]
N	3	2	3

Note: CCI=Carr's compressibility index, N=number of batches or mixtures tested, Flow rate EP=flow rate according to Ph.Eur.Ed.IV/2.9.16; densities tested in triplicate, flow rate and angle of repose measurements repeated 4–10 times; mean values are given, with standard deviations within parentheses, both for the pooled data of all batches; ranges (for pooled data) are given for flow rate.

[a]Entire sample failed to flow through.

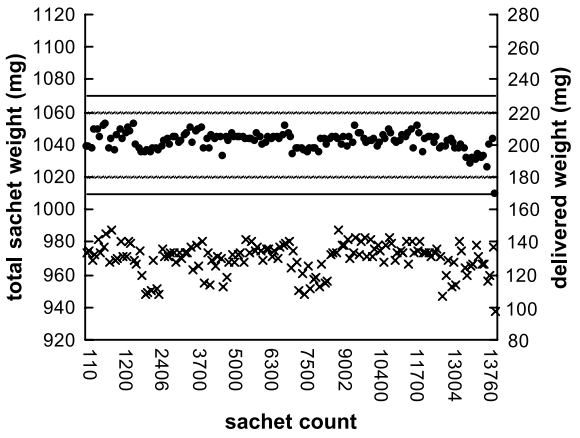

Figure 1. Results of in-process control ''delivered weight'' of a representative 150/50-mg sachet batch. Closed bullets represent delivered weights of these sachets (right *y*-axis) during manufacture, x-markings represent the total weight of the filled sachets before emptying (left *y*-axis). Dashed lines represent alert levels (±10% of label claim), solid lines represent action levels (±15% of label claim).

foil. The process of auger filling diacetylmorphine/caffeine sachets was characterized and optimized using an experimental design approach. This study showed that regular checks of the fill weight were required to ensure accuracy of dosing. Therefore, two in-process control tests were selected: determination of the delivered weight and the total weight of a sachet.

In-Process Controls

Delivered Weight

The delivered weight was defined as the weight of the powder shaken out of a sachet. It was determined every 100 sachets, to enable the operator to correct for deviations in time, thereby limiting the loss of sachets that are out of specification (OOS) and improving overall dosing accuracy. Furthermore, an accurate estimate of the mean delivered weight was necessary for reconciliation purposes (see below). Results for a typical 150/50-mg batch are shown in Fig. 1. Alert and action levels defined for the delivered weight (Table 2) were based on the maximal deviation percentages mentioned in the Ph.Eur. test for uniformity of mass of capsules weighing less than 300 mg:[12] 10% deviation from label claim (alert level) and 15% deviation from label claim (action level). The results of 19 batches (Table 3) show that all four dosages could be filled accurately. No significant difference in mean delivered weight (as a percentage of the label claim) (Table 3) was observed between the four different doses. The mean number of sachets deviating more than 10% from the label claim (alert level) was higher in sachet batches with a lower fill weight. This is easily explained by the fact that small absolute deviations will exceed the 10% alert level sooner when total fill weight is small. None of the batches showed delivered weights deviating more than 15% from the label claim; all batches were within specifications.

During manufacture, feedback from the operator on dosing accuracy to the auger filler computer was based on the delivered weight, which underestimates the fill weight, since a residue was left on the interior walls of the sachet. This surplus was considered necessary to ensure that the desired amount of drug was delivered to the patient. The amount of residue remaining in the sachet after shaking out the powder mixture was quantified routinely (Table 3) and was found to be 8.93±1.67 mg (mean±sd), independent of the sachet content.

Total Sachet Weight

It was known from experience that certain combinations of machine settings [auger speed, dose,

Table 2. Specifications for in-process controls and actions upon deviation.

Test	Specification	Action on deviation
Delivered weight	Within ±10% of label claim (derived from Ph.Eur.IV/2.9.5)	Repeated test required, if deviation is repeated, a fill correction is required (Alert level)
Delivered weight	Outside ±10% but within ±15% of label claim (derived from Ph.Eur.IV/2.9.5)	Sachets concerned are rejected, a fill correction is required (Action level)
Total sachet weight	Weight difference within 10 sachets <30% of label claim (based on ±15% in delivered weight)	Determine delivered weight of sachets with largest and smallest total sachet weight, act on deviations outside 10/15% of label claim as described above

Note: Delivered weights are judged individually, total sachet weights as part of a set of 10 sachets.

Table 3. Results of in-process weight checks and determinations of the size of the residue in the sachet.

Dose	Delivered weight (%)	N>10%	Batch size	Residue (mg)	n
75/25 mg	101.6 (0.9)	7.5 (6.5)	13205 (6368)	7.15 (1.18)	2
100/33 mg	101.1 (1.4)	2.3 (1.5)	10789 (4056)	9.97 (2.50)	4
150/50 mg	100.9 (0.6)	3.6 (4.6)	11512 (3672)	9.22 (1.33)	5
200/67 mg	100.8 (0.9)	2.8 (3.2)	11749 (3091)	8.68 (1.25)	8

Note: Mean values are given for all parameters, with sd in parentheses. Delivered weight given as a percentage of label claim; N>10%—number of delivered weights deviating more than 10% from label claim; Batch size—number of sachets manufactured per batch; Residue—amount of powder remaining inside the sachet after shaking out the contents; n—number of batches.

and packaging speed (sachets/min)] could cause the pause between the powder portions to decrease below a critical level, resulting in full and partly filled sachets to be ejected alternately. Furthermore, it was known that every time something caused the machine to stop, the 4th or 5th sachet after restart might be empty. Therefore, a test of the total weight of 10 successive sachets was introduced to screen for outliers and empty sachets. The test of total sachet weight was performed every 500 sachets and after every machine stop; a difference between the smallest and largest total sachet weight >30% of the label claim was defined as indicative of the presence of an outlier or an empty sachet (Table 2).

The mean weight of an empty sachet including its tear-off label was determined using 10–20 empty sachets per batch from 19 batches: it was found to be 738.4–765.4 mg, with a standard deviation varying from 2.7–7.6 mg between batches. Since the powder contents of a sachet would form only 12–26% of the total weight of a filled sachet, it was likely that small deviations in the weight of the contents would be attributed to normal variation in sachet and/or label weight. However, ejection of an empty sachet would certainly be noticed, as well as deviations outside ±15% of the label claim in 150/50 and 200/67 mg sachets.

In routine samples from 19 batches, the mean difference between the smallest and the largest total sachet weight was found to be 14–30 mg, independent of the dose filled. This difference was attributed to the variation in weight of the packaging material combined with the normal variation in fill weight. Deviations from the mean difference always occurred in samples tested directly after a machine stop, and amounted to mean differences of 118, 161, 226, and 298 mg (for 75/25, 100/33, 150/50, and 200/67 mg sachets, respectively). This indicated that a completely empty sachet was ejected, because the auger filler skipped a dose at the moment of the stop, and dosing and packaging were resynchronized after restart. Intermediate size differences did not occur, proving the filling process to be very constant unless an emergency stop was triggered.

Reconciliation

Meeting the requirements of the Dutch Narcotics Law was an important aspect of the manufacturing process. Weighing and counting checks were developed for accurate reconciliation of the amount of bulk drug with the amount of finished product, accounting for the lost powder mixture and/or sachets. Two strategies were employed, aimed at the reconciliation of 1) the number of sachets and 2) the amount of diacetylmorphine/caffeine powder.

Reconciliation of the number of sachets means that the electronic sachet count by the packaging unit during manufacturing must be in close agreement with the manual sachet count that takes place after packaging. Empty or OOS sachets were recorded on the production protocol, so they could be accounted for. In most batches, the manual count slightly exceeded electronic count: in 19 batches (9000–18,000 sachets per batch), the mean deviation was 8±12 sachets (range 8–35). These deviations could be caused by human errors in the manual count or by errors in the electronic count. Human errors were minimized by having a second person double-check the contents of every box of sachets. Errors in the electronic count, however unlikely, might arise from the emergency machine stops that may occur during manufacturing (see also In-Process Controls: Total Sachet Weight).

Reconciliation of the amount of diacetylmorphine/caffeine powder involved subtracting several 'types' of processed powder from the amount taken into production. Some types of processed powder could simply be weighed, like the powder remaining in the machine hopper after manufacturing and the powder shaken out of the sachets during the in-process controls (delivered

Table 4. Results for quality control of 19 batches of finished product.

Quality control item	Specification	75/25 mg (n=2)	100/33 mg (n=4)	150/50 mg (n=5)	200/67 mg (n=8)
Appearance	Intact sachets, filled with a white to light yellow/pink powder mixture	Conform	Conform	Conform	Conform
Identity (HPLC–UV)	Rt DAM sample=Rt DAM reference standard	Conform	Conform	Conform	Conform
	Rt CAF sample=Rt CAF reference standard	Conform	Conform	Conform	Conform
Content (HPLC–UV)	97.5–102.5% of label claim=73.1–76.9% w/w DAM	74.62 (0.81)	74.70 (0.63)	74.74 (0.57)	75.03 (0.43)
Purity (HPLC–UV)	>95%	99.47 (0.08)	99.10 (0.31)	98.99 (0.48)	98.95 (0.28)
Uniformity of mass	Ph.Eur.Ed.IV/2.9.5	Conform	Conform	Conform	Conform
RSD (IPC)	$\leq$7.8% (derived from USP <905>)	4.81 (0.66)	3.91 (0.27)	3.78 (1.64)	3.91 (1.20)
N>15% (IPC)	No more than 1 deviate >15% from label claim	None	None	None	None

Note: Mean values are given, with sd in parentheses. DAM=diacetylmorphine base, CAF=caffeine anhydrate, IPC=in-process controls, Ph.Eur.=European Pharmacopoeia, RSD=relative standard deviation, N=number of delivered weights, n=number of batches.

weight). For the powder that was processed into sachets, another strategy was used to determine the amount involved. The weight of the contents of the sachets was calculated by multiplying the mean content of a sachet (mean delivered weight+mean residue size) by the number of sachets. Furthermore, some of the sachets were discarded during manufacturing, for being OOS (for fill weight, quality of the seals or appearance, for example). Since the mean content of these sachets was unknown, the weight of their contents was calculated by determining the combined weight of the sachets and subtracting the mean weight of an empty sachet multiplied by the number of discarded sachets. The mean amount of powder that was not accounted for using the above-mentioned calculations was 27.9± 22.3 g per batch (n=19, 1.4±1.1% of the amount taken into production). This is caused by powder loss during manufacturing, due to adhesion of the powder mixture onto the manufacturing equipment (mixer, auger/hopper of the filling machine). However, the result of these reconciliation calculations also depends on the accuracy of the determined values for mean delivered weight (n=150–200), mean residue size (n=20), and mean weight of an empty sachet (n=20). Small deviations in these factors are multiplied and contribute to the observed (variation in) loss of powder.

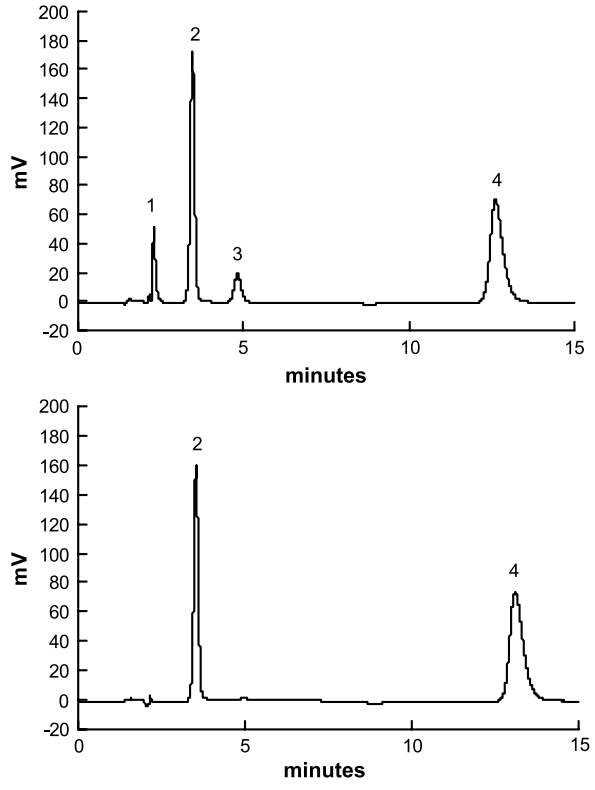

Figure 2. Representative chromatograms, for a standard solution (top) containing morphine (1), caffeine (2), 6-monoacetylmorphine (3) and diacetylmorphine (4), and a sachet sample (bottom).

Quality Control of the Finished Product

For quality control of the finished product, the following tests were selected: inspection of product appearance, determination of uniformity of mass [according to Ph.Eur.IV/2.9.5],[12] and HPLC–UV analysis. The combined results from in-process controls and the test for uniformity of mass were evaluated to ensure accuracy and precision of the filling process. Results of the quality control of 19 batches are shown in Table 4.

Table 5. Long-term stability of diacetylmorphine/caffeine sachets (n=3 batches/dosage) upon storage at 2±25°C, 5±60% RH.

		Storage time (months)					
Dose	Test item	0	6	9	12	18	24
75/25 mg	Content	73.6 (1.1)	72.8 (3.4)	73.3 (2.2)	73.5 (1.5)	75.1 (0.5)	73.7 (1.5)
	Purity	99.1 (0.2)	99.0 (0.4)	99.2 (0.7)	98.8 (0.2)	98.0 (0.4)	97.4 (0.8)
100/33 mg	Content	72.5 (1.1)	71.5 (0.6)	74.4 (2.4)	73.1 (2.0)	74.3 (0.3)	74.1 (0.6)
	Purity	99.3 (0.4)	n.d.	99.0 (0.9)	98.7 (0.2)	98.0 (0.4)	97.3 (0.5)
150/50 mg	Content	74.0 (0.3)	73.8 (0.5)	72.2 (4.8)	74.7 (0.5)	74.6 (0.5)	74.5 (0.3)
	Purity	99.2 (0.5)	98.8 (−)	99.4 (0.8)	98.8 (0.1)	97.3 (0.4)	97.1 (0.5)
200/67 mg	Content	74.6 (1.3)	74.2 (1.0)	72.5 (4.3)	74.6 (0.2)	75.3 (0.8)	75.2 (0.5)
	Purity	98.8 (0.2)	98.6 (0.3)	99.1 (0.8)	98.7 (0.2)	97.6 (0.5)	97.0 (0.6)

Note: Mean relative diacetylmorphine content (% w/w) and mean chromatographic purity (%) are given, with sd in parentheses. Diacetylmorphine content was determined in powder mixture instead of quantitatively flushed-out sachet contents up to 9 months into the study. n.d.=not determined.

High-performance liquid chromatography–UV analysis was used for confirmation of the identity of diacetylmorphine and caffeine and determination of purity and relative content of diacetylmorphine. Relative content was defined as the % w/w of diacetylmorphine in the powder mixture and was calculated from the absolute contents of diacetylmorphine and caffeine. Interestingly, when relative content was determined in a sample of the powder mixture removed from the sachets (n=20) used for the determination of uniformity of mass, it was consistently lower (T-test: p=0.0007) in 75/25-mg sachets (72.2±1.5% w/w) than in 200/67-mg sachets (74.0±0.9% w/w). This could be explained by a stronger adhesion of diacetylmorphine to the LDPE insides of the sachets relative to caffeine. When the contents of a sachet were flushed out quantitatively (n=3) instead of shaken out, relative diacetylmorphine content was consistently close to the label claim for all doses (74.7±0.5% w/w). Therefore, the latter method was used in the determination of diacetylmorphine content.

Initially, a specification of 90–110% of label claim (67.5–82.5% w/w diacetylmorphine) was used. Based on the results of 17 batches and evaluation of the risk of batch failure per dose [100/33 mg: 2×10^{-28}%, 150/50 mg: 8×10^{-36}%, 200/67 mg: 6×10^{-67}%, calculated according to Stafford],[16] this specification was tightened to 97.5–102.5% (73.1–76.9% w/w diacetylmorphine, risks of batch failure: 6×10^{-1}, 2×10^{-1}, and 9×10^{-4}%, respectively). The batches of 75/25-mg sachets could not be evaluated statistically, since there were only two. However, the content of both batches was within the tightened specifications.

The HPLC–UV method was shown to separate diacetylmorphine, caffeine, and the main degradation products of diacetylmorphine, 6-monoacetylmorphine, and morphine (Fig. 2). 6-Monoacetylmorphine was

Table 6. Accelerated stability of diacetylmorphine/caffeine sachets (n=3 batches/dosage, 1 batch of 75/25 mg) upon storage at 2±40°C, 5±75% RH.

		Storage time (months)				
Dose	Test item	0	1	2	3	6
75/25 mg	Content	74.48 (−)	75.52 (−)	76.12 (−)	75.29 (−)	74.68 (−)
	Purity	99.41 (−)	98.46 (−)	98.83 (−)	99.05 (−)	98.70 (−)
100/33 mg	Content	74.86 (0.68)	74.98 (0.10)	75.29 (0.08)	74.79 (0.53)	74.38 (0.21)
	Purity	99.05 (0.36)	98.40 (0.07)	98.86 (0.03)	98.94 (0.07)	98.98 (0.13)
150/50 mg	Content	74.88 (0.51)	75.32 (0.22)	75.63 (0.29)	74.60 (0.34)	74.36 (1.19)
	Purity	99.13 (0.07)	98.32 (0.05)	99.03 (0.09)	98.75 (0.12)	99.01 (0.14)
200/67 mg	Content	75.09 (0.57)	74.94 (0.22)	75.48 (0.63)	74.80 (0.73)	74.45 (0.61)
	Purity	98.84 (0.17)	98.18 (0.04)	99.13 (0.01)	98.63 (0.03)	98.83 (0.11)

Note: Mean relative diacetylmorphine content (% w/w) and mean chromatographic purity (%) are given, with sd in parentheses.

found to be the main degradation product of diacetylmorphine in the finished product with levels equivalent to the drug substance used for manufacture (peak area 0.3–1.6% of diacetylmorphine peak area). All 19 batches conformed to the specification for chromatographic purity (>95%) (Table 4).

After completion of the batch, the in-process control results for delivered weight were evaluated. Mean, standard deviation, and relative standard deviation (RSD) were calculated, and the number of weights exceeding 15% deviation from the label claim was determined. An RSD$\leq$7.8% was used as a specification, based on the maximum RSD used in the United States Pharmacopeia (USP) test for Uniformity of Dosage Units <905> performed on 30 units.[17] The results in Table 3 show that all four dosages could be filled precisely, no significant difference in mean RSD was observed between the four different doses, and none of the batches showed delivered weights in the in-process controls deviating more than 15% from the label claim (Table 4).

Stability Studies

Long-term stability results for diacetylmorphine/caffeine sachets are given in Table 5. The powder mixture shaken out of the sachets was used for determination of diacetylmorphine content instead of the sachet contents flushed out quantitatively up to 9 months into the stability study. Therefore, in this period, smaller dosages show lower diacetylmorphine contents due to adhesion of diacetylmorphine to the inside of the sachet. The final results, however, show that diacetylmorphine/caffeine sachets are stable for 2 years when stored at 25±2°C, 60±5% RH. No change in diacetylmorphine content was observed and chromatographic purity remained well above 95%, with 6-monoacetylmorphine appearing as the only degradation product.

The results of the accelerated stability studies (Table 6) indicate that all types of diacetylmorphine/caffeine sachet can withstand storage at 40±2°C, 75±5% RH for 6 months. 6-Monoacetylmorphine was found to be the main degradation product (mean peak area 1.28±0.40% of diacetylmorphine peak area), while morphine was mostly undetectable (peak area <0.25% of diacetylmorphine peak area).

CONCLUSIONS

A dosage form was selected for pharmaceutical, smokable heroin (3:1 w/w diacetylmorphine base/caffeine anhydrate). A microdose auger filler was used in the manufacturing process, which was developed for filling four sachet doses, containing 75/25, 100/33, 150/50, and 200/67 mg diacetylmorphine/caffeine. In-process controls were developed to monitor the filling process as well as quality control tests on the finished product. In-process control results were within specifications for all doses. The resulting powder-filled sachets were shown to comply with the specifications for content and uniformity of mass. The diacetylmorphine/caffeine sachets were found to be stable for 2 years at 25°C, 60% RH and for 6 months at 40°C, 75% RH.

ACKNOWLEDGMENTS

The authors would like to thank K. Ogbemichael, E. Vermeij, D. Meijer, and other pharmaceutical and analytical technicians for their work in manufacturing and quality control of the diacetylmorphine/caffeine sachets. This study was financially supported by the Netherlands Ministry of Health, Welfare and Sports through the Central Committee on the Treatment of Heroin Addicts (www.ccbh.nl).

REFERENCES

1. Strang, J.; Griffiths, P.; Gossop, M. Heroin smoking by 'chasing the dragon:' origins and history. Addiction **1997**, *92* (6), 673–683.
2. van den Brink, W.; Hendriks, V.M.; Blanken, P.; Koeter, M.W.J.; van Zwieten, B.J.; van Ree, J.M. Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. BMJ **2003**, *327* (7410), 310–315.
3. Hendriks, V.M.; van den Brink, W.; Blanken, P.; Bosman, I.J.; van Ree, J.M. Heroin self-administration by means of 'chasing the dragon:' pharmacodynamics and bioavailability of inhaled heroin. Eur. Neuropsychopharmacol. **2001**, *11* (3), 241–252.
4. Risser, D.; Uhl, A.; Stichenwirth, M.; Honigschnabl, S.; Hirz, W.; Schneider, B.; Stellwag-Carion, C.; Klupp, N.; Vycudilik, W.; Bauer, G. Quality of heroin and heroin-related deaths from 1987 to 1995 in Vienna, Austria. Addiction **2000**, *95* (3), 375–382.
5. de la Fuente, L.; Saavedra, P.; Barrio, G.; Royuela, L.; Vicente, J.; Spanish Group for the Study of the Purity of Seized Drugs. Temporal and geographic variations in the characteristics of heroin seized in

Spain and their relation with the route of administration. Drug Alcohol Depend. **1996**, *40* (3), 185–194.
6. Kaa, E.; Bent, K. Impurities, adulterants and diluents of illicit heroin in Denmark (Jutland and Funen). Forensic Sci. Int. **1986**, *31* (3), 195–210.
7. Huizer, H.; Logtenberg, H.; Steenstra, A.J. Heroin in the Netherlands. Bull. Narc. **1977**, *29* (4), 65–74.
8. Huizer, H. Analytical studies on illicit heroin. V. Efficacy of volatilization during heroin smoking. Pharm. Weekbl., Sci. **1987**, *9* (4), 203–211.
9. Diamorphine hydrochloride. *British Pharmacopoeia*; The Stationery Office: London, 1999; 487.
10. Apparent volume, 2.9.15. *European Pharmacopoeia*, 4th Ed.; Council of Europe: Strasbourg, 2002; 207–208.
11. Flowability, 2.9.16. *European Pharmacopoeia*, 4th Ed.; Council of Europe: Strasbourg, 2002; 208–209.
12. Uniformity of mass of single-dose preparations, 2.9.5. *European Pharmacopoeia,* 4th Ed.; Council of Europe: Strasbourg, 2002; 199–200.
13. ICH Steering Committee. *ICH Q1A R Stability Testing Guidelines: Stability Testing of New Drug Substances and Products*; European Agency for the Evaluation of Medicinal Products, International Commission on Harmonisation: London (CPMP/ICH/2736/99), 2000.
14. Guerin, E.; Tchoreloff, P.; Leclerc, B.; Tanguy, D.; Deleuil, M.; Couarraze, G. Rheological characterization of pharmaceutical powders using tap testing, shear cell and mercury porosimeter. Int. J. Pharm. **1999**, *189* (1), 91–103.
15. Coenraads, P.J.; Hogen Esch, A.J.; Prevoo, R.L. Occupational contact dermatitis from diacetylmorphine (heroin). Contact Dermatitis **2001**, *45* (2), 114.
16. Stafford, J. Calculating the risk of batch failure in the manufacture of drug products. Drug Dev. Ind. Pharm. **1999**, *25* (10), 1083–1091.
17. Uniformity of dosage units, <905>. *United States Pharmacopeia*, 24th Ed.; United States Pharmacopeial Convention Inc.: Rockville, MD, 2000; 2000–2002.