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Process characterisation, optimisation and validation of production of diacetylmorphine/caffeine sachets: a design of experiments approach

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Abstract

Powder filled sachets containing a 3:1 (w/w) powder mixture of diacetylmorphine base and caffeine anhydrate were developed as a dosage form for smokable heroin used for the treatment of chronic, treatment-resistant heroin addicts. The powder mixture was filled into sachets using a micro dose auger filler machine. The goal of this study was to identify the most important process variables that influence precision of dosing. Five variables were tested: auger speed, agitator speed, hopper fill level, dose interval, and dose. An experimental design was used to study the effects of each of these variables, including possible non-linear and interaction effects. A 9-term regression model was constructed, explaining 94% of the observed variation in dose weight variation coefficient. Dose, agitator speed and hopper fill level were the most important variables. The regression model was used to identify optimal settings of the variables for four sachet doses intended for routine manufacture. The results of four test batches manufactured with these optimised settings showed that accurate (accuracy: 99.0–101.0%) and precise (CV: 3.2–5.3%) filling of diacetylmorphine/caffeine sachets is possible using the micro dose auger filler machine.

Keywords: Heroin; Inhalation; Design of experiments; Optimisation; Powder; Sachet

Abbreviations: AoR, angle of repose; AgS, agitator speed; AuS, auger speed; CCI, Carr's compressibility index; *D*, dose; DI, dose interval; DoE, design of experiment; d_p, poured density; d_t, tapped density; *F*, hopper fill level; rpm, revolutions per minute; SS, sachet speed, number of sachets made per minute

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1. Introduction

In 1998, two clinical trials were initiated in the Netherlands to evaluate the effect of co-prescription of heroin (3,6-diacetylmorphine) and methadone on mental and physical health and social functioning of chronic treatment-resistant heroin dependent patients (Van den Brink et al., 2003). In The Netherlands, only 15–25% of the heroin addicts inject heroin, the remaining 75–85% inhale the heroin fumes that arise after heating heroin on aluminium foil until it evaporates ("chasing the dragon"; (Hendriks et al., 2001). Therefore, one of the two trials concerned co-prescription of inhalable heroin as the experimental intervention. 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 non-compliance, by ensuring that the product could be used according to the long-established habits of the patients in the trial. A powder formulation was therefore preferred and a 3:1 (w/w) mixture of diacetylmorphine base and caffeine anhydrate was found to be a suitable basis for pharmaceutical smokable heroin. Diacetylmorphine base is more appropriate than diacetylmorphine hydrochloride, because it showed less degradation and larger recoveries after volatilisation (Huizer, 1987). Caffeine was added because it is commonly found in street heroin samples (Huizer et al., 1977; Kaa and Bent, 1986; de la Fuente et al., 1996; Risser et al., 2000) and because it has been shown to improve the volatilisation of diacetylmorphine (Huizer, 1987). Addition of excipients to alter the properties of the 3:1 (w/w) diacetylmorphine/caffeine powder mixture was considered undesirable, because of the possibility of adverse effects arising from volatilising and inhaling these substances. Therefore, four types of powder filled sachets were developed for the clinical trial, containing 75/25 mg, 100/33 mg, 150/50 mg, or 200/67 mg diacetylmorphine/caffeine (Klous et al., 2004). In the manufacturing process, a micro dose auger filler is used to fill the powder mixture into sachets. A long and narrow auger was designed specifically to accurately fill small amounts of powder by mechanically forced transport (ejection of several milligrams with each revolution of the auger). 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 were packaged into sachets formed on-line from packaging foil, consisting of aluminium, paper, and polyethylene layers.

Powder filled sachets are not a common dosage form in the pharmaceutical industry, especially not for small doses (<1 g of powder). No literature was available on formulation issues in auger filling of powders. Furthermore, no scientific information could be found on the influence of process variables on accuracy and precision of dosing using a micro dose auger filler. It has become common practice, however, to identify important variables and subsequently optimise manufacturing processes using experimental design, especially when complex pharmaceutical processes are concerned. Granulation processes for example, have been studied extensively using design of experiments (DoE) (Voinovich et al., 1999; Badawy et al., 2000; Rambali et al., 2001; Paterakis et al., 2002). Response surface methodology (an effective tool in DoE to demonstrate interaction effects between factors) has been used to study many other complex formulation issues: tablet coating (Rege et al., 2002), preparation of nanoparticles (McCarron et al., 1999) or self-nanoemulsifying tablets (Nazzal et al., 2002), and drug release from controlled release formulations (Sanchez-Lafuente et al., 2002; Kramar et al., 2003).

Design of experiments and response surface methodology have therefore also been employed in this study. Our first goal was to identify important process variables that influence precision of diacetylmorphine/caffeine dosing by the micro dose auger filler machine. Our second goal was to optimise the manufacturing process for each of the four diacetylmorphine/caffeine dosages intended for routine production.

2. Materials and methods

2.1. Materials

Diacetylmorphine base was obtained through the Central Committee on the Treatment of Heroin Addicts (Utrecht, The Netherlands) and caffeine anhydrate was purchased from Bufa (Uitgeest, The Netherlands). The formulation to be used in this validation experiment is a 3:1 (w/w) powder mixture of diacetylmorphine base and caffeine anhydrate. The powder mixture was prepared by mixing three parts of diacetylmorphine with

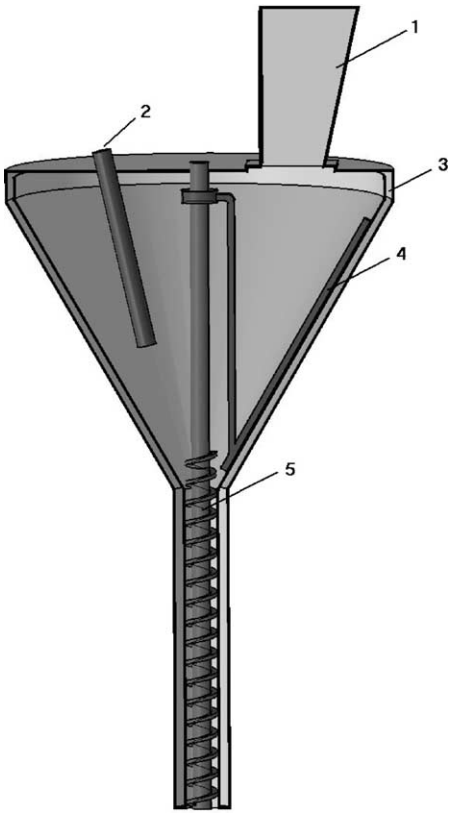


Fig. 1. Schematic representation of the micro dose auger filler (type SD1, Optima). (1) Opening with funnel for filling powder into hopper; (2) product sensor; (3) plexiglass hopper; (4) agitator; and (5) auger.

one part of caffeine using a Model UM12 Stephan mixer (Stephan Electronic 2011, Hameln, Germany).

2.2. Equipment

Dosing of the powder mixture was performed using a micro dose auger filler machine (type SD1, Optima, Schwäbisch Hall, Germany). The machine (Fig. 1) consists of a 5 L hopper (plexiglass), fitted with a dosing funnel, an agitator, a capacitive product sensor and a 340 mm auger (diameter 5 mm, pitch 5 mm), all constructed from stainless steel. It is operated by a microcomputer that enables the operator to control the process via a touch screen.

The auger filler is mounted vertically on top of a packaging unit (type EU1N1, Boato Pack, Staranzano, Italy) that forms sachets from foil simultaneous with dosing. The packaging foil consisted of 50 g/m^2 clay-coated paper on the outside, followed by a layer of 12 g/m^2 low-density polyethylene (LDPE), 7 μm aluminium foil, and a LDPE coating (23 g/m^2) on the inside.

Table 1
Study variables with selected ranges

Variable	Range	Units
Dosage (*D*)	50–300	mg
Auger speed (AuS)	300–1100	rpm
Agitator speed (AgS)	10–90	rpm
Hopper fill level (*F*)	10–90	%
Dosing interval (DI)	500–5000	ms

2.3. Powder properties

The angle of repose (AoR) of the powder mixture was determined before and after the experiment series using a granulate flow tester (type GTB, Erweka, Heusenstamm, Germany). Poured (d_p) and tapped (d_t) densities were determined before and after the experiment series and before every experiment run, using a tapped volumeter (type SVM12, Erweka, Heusenstamm, Germany) according to the procedure in §2.9.15 of the European Pharmacopoeia (Ph.Eur.IV, 2002a). Carr's compressibility index (CCI) was calculated from these densities (difference between d_p and d_t as a percentage of d_p).

2.4. Experiment design

Five variables were included in the experimental design: dose (*D*), auger speed (AuS), agitator speed (AgS), hopper fill level (*F*), and dose interval (DI). Ranges for the variables are given in Table 1. An experimental design was selected to study the effect of each of the five variables, including possible non-linear effects and interaction effects (in which the effect of a variable depends on the level of a second variable). The final design (Table 2) was generated using D.o.E. Fusion Pro^{TM} software (version 7.0.1, by S-Matrix Corp., Eureka, CA, USA). It consisted of 24 runs and contained two *centre points* (runs 11 and 16), two *factorial points to be replicated* (runs 3/17 and 4/5) and five *degrees of freedom points*. The centre points and replicate runs were used to calculate the experimental error. The coefficient of variation (CV) within the sets of sample weights was selected as a response parameter.

Table 2
Experiment design matrix (replicate runs: 3/17, 4/5, 11/16)

Run no.	*D*	AuS	AgS	*F*	DI
1	1	−1	−1	−1	−1
2	0.5	−0.5	−0.5	−0.5	0.5
3	−1	1	−1	1	−1
4	1	1	−1	1	−1
5	1	1	−1	1	−1
6	−1	1	1	−1	−1
7	0.5	−0.5	0.5	−0.5	0.5
8	−1	−1	−1	1	1
9	0	−1	1	−1	1
10	−0.5	0.5	0.5	−0.5	0.5
11	0	0	0	0	0
12	−0.5	−0.5	0.5	−0.5	0.5
13	1	1	1	1	1
14	1	1	1	−1	−1
15	1	−1	−1	1	1
16	0	0	0	0	0
17	−1	1	−1	1	−1
18	1	1	−1	−1	1
19	0.5	0.5	0.5	−0.5	0.5
20	−1	1	1	1	1
21	−1	−1	1	1	−1
22	−1	−1	−1	−1	−1
23	1	−1	1	1	−1
24	−1	1	−1	−1	1

D, dose; AuS, auger speed; AgS, agitator speed; *F*, hopper fill level; and DI: dose interval. Numbers represent the coded parameter settings: 1 for the maximum of the selected range, −1 for the minimum of the selected range, etc.

2.5. Sampling

Every run started with machine set-up: the hopper was filled with the desired amount of the diacetylmorphine/caffeine powder mixture and the powder was transported into the auger using standardised settings (AuS 700 rpm, AgS 50 rpm, *D* 300 mg for 30 doses). After the appropriate test values for *D*, AuS and AgS were entered into the auger filler computer, the accuracy of filling was checked. Three doses were weighed and filling was corrected by entering the mean fill weight into the auger filler computer as feedback on its performance. When the mean filled dose was within ±5 mg of the design value for *D*, DI was set by using the resulting dosing time (Dt) to calculate the suitable sachet speed setting (SS, number of sachets made per minute). Since it was known that it could take some time for the filling performance to stabilise (especially with large doses), it was decided to include a 200 doses stabilisation period in the preparation for every experiment. After this period, accuracy of filling was checked again and if a correction of *D* was necessary, DI/SS were also corrected before the experiment was started. During each experiment run, samples were collected in 8 mL glass vials (that were immediately closed with grey butyl rubber stoppers) every 40 doses during a total of 1000 doses (25 dose weights per run). The glass vials were weighed before and after sampling on a type PM480 balance (Mettler-Toledo, Tiel, The Netherlands; accuracy 0.1 mg) and dose weights were calculated and analysed statistically using spreadsheet software (Microsoft Excel) and D.o.E. Fusion Pro™ software.

The sampling procedure in the test batches was different, as the powder was filled into sachets, making it impossible to collect the powder portions in preweighed sample holders. During the test batches, one in every 100 sachets was emptied to determine the delivered weight (weight of powder contents shaken out of a sachet). This procedure did not take into account the powder residue remaining on the inside of the sachets. This residue was known to be small and reproducible (8.93 ± 1.67 mg, n = 19 batches, 20 sachets each) and independent of the sachet content. It was therefore considered a necessary surplus to deliver to the user the amount of powder claimed on the sachet label; it was decided to routinely calibrate the auger filler using feedback from the determinations of the delivered weight, disregarding the residue (Klous et al., 2004).

3. Results and discussion

3.1. Experiment design

All machine settings that were not dependent on properties of powder or hardware were included in the experiment design. This resulted in the five variables given in Table 1; ranges for the variables were selected on the basis of technical and practical limitations. For example, for *D* the technical limits were 0.05–50 mL (equalling 0.021–21 g diacetylmorphine powder mixture), but since our purpose for the machine was to fill quantities of 50–300 mg, this range was selected. For AuS, technical limits were 0–2000 revolutions per minute (rpm); however, it was known from

experience that speeds over 1100 rpm could cause problems involving friction heat and that speeds smaller than 300 rpm caused unacceptably long dosing times, therefore a 300–1100 rpm range was used. DI can be considered a dependent variable, since it is a result of the sachet speed setting (number of sachets made per minute) of the packaging unit and the dosing time necessary to deliver the desired amount of powder. DI will preferably be as small as possible for efficient manufacturing, but because the experiment required manual sampling, its lower limit (500 ms) was based on an estimated limit of human reaction time. The selected 5000 ms upper limit was arbitrary. As F is not constant during an experiment run, the mean hopper fill level within each run was used as a variable. The powder mixture that had passed the dosing auger was not reused in the experiments, to prevent bias from changing powder properties due to (for example) grinding.

Due to technical limitations, some deviations from the design settings (Table 2) were necessary for three variables. In runs 4 and 5 (replicates), AgS was set at 13 instead of 10 rpm, and in run 23, F was 74% instead of 90. Since DI is a dependent variable that was set via SS, it was not possible to set it at exactly the levels defined by the experimental design (mean deviation: −2.9%; range: −47.7–23.4%). However, all deviations were entered into the design model matrix and the actual settings were used in the statistical analysis.

3.2. Powder properties

Powder properties were determined before, during and after performing the design of experiment runs. The high values found for CCI and AoR (Table 3) illustrate the very poor flowability of the diacetylmorphine/caffeine mixture. Poor flow ability of the powder mixture might to a certain extent be advantageous in the process of auger filling, as it is essential for dosing accuracy and precision that the ejection of powder stops as soon as the auger stops moving. But more importantly, no attempts were made to adjust powder flow ability by adding excipients to avoid toxicity during volatilisation and inhalation of the product.

Significant differences were found for the d_p and d_t just before use and after the powder mixture had passed the auger. The AoR and the CCI of the powder remaining in the hopper after the experiment were both significantly lower than just before use. After the powder passed the auger, these properties seemed to return to their initial level. The observed differences were very small and were not considered to have a significant impact on dosing accuracy or precision. Therefore, statistical bias from these differences seems unlikely, especially since none of the powder properties showed drift or time effects, nor was any confounding with study variables (D, AuS, AgS, DI, F) found.

In order to check for segregation of the powder mixture during the experiments, diacetylmorphine content in each first and last powder sample of every experiment run was determined using a HPLC–UV method described elsewhere (Klous et al., 2004). No difference (paired t-test; $P = 0.895$) was found in diacetylmorphine content (in percentage w/w): mean content before the experiment 74.2 ± 1.2% (w/w), after the experiment 74.2 ± 1.1% (w/w). This proves that no separation of the diacetylmorphine/caffeine mixture takes place during the filling process.

3.3. Accuracy and precision

The finished product was required to comply with specifications for uniformity of mass (Ph.Eur.IV, 2002c) and/or uniformity of dosage units (USP XXIV, 2000). Since we know that the diacetylmorphine

Table 3
Powder flow properties of the 3:1 diacetylmorphine/caffeine mixture

Powder	d_p (mg/mL)	d_t (mg/mL)	CCI		AoR	
			(%)	n	(°)	n
Just before use	433.8 (8.9)	582.4 (6.3)	34.3 (2.6)	24	52.8 (1.2)	6
From the hopper	443.6 (5.3)	581.2 (2.3)	31.0 (1.1)*	3	49.6 (1.9)*	6
After passing auger	408.8 (14.8)*	567.0 (4.1)*	38.8 (4.3)	3	50.9 (2.4)	6

The mean values are given (with their standard deviation within parentheses) for the powder mixture just before use in an experiment run, for the powder from the hopper and for the powder collected after passing the auger. Values differing significantly ($P < 0.05$) from the powder just before use are marked by *. d_p, Poured density; d_t, tapped density; CCI, Carr's compressibility index; AoR, angle of repose.

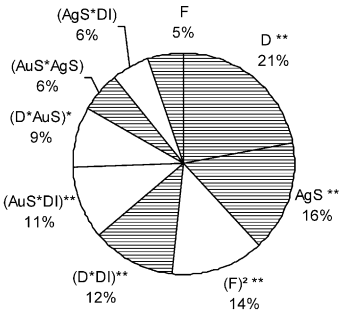
content of the filled powder was constant (see Section 3.2), we could use dose weights to evaluate content uniformity. In that case, the specifications from the United States Pharmacopeia (USP) and the European Pharmacopoeia (Ph.Eur.IV, 2002b) would be similar: both state that a maximum of 3 out of 30 units deviates outside 85–115% from the label claim and none deviate outside 75–125%. However, the USP also requires the relative standard deviation (equal to CV) to be $\leq$7.8% and relates the percentages to the label claim, whereas in Ph.Eur. percentages relate to the average content. The specifications for uniformity of mass in Ph.Eur. (Ph.Eur.IV, 2002c) are more stringent, but also relate deviation percentages to mean mass instead of the label claim. The consequences of these differences for the results of the experiment runs are demonstrated in the last columns in Table 4, where the number of weights deviating >10 and >15% from the mean weight are given (origin: Ph.Eur.IV, 2002c), as well as the number of weights deviating >15 and >25% from *D* (label claim; origin: USP XXIV, 2000). The difference in sample size as prescribed by Ph.Eur. (n = 20) and USP (n = 30) to the sample size tested (n = 25) should be taken into account when interpreting these data, but it is obvious that only run 22 does not conform to the specifications in Ph.Eur., whereas it does conform to USP specifications. The opposite is true for the runs 3, 21 and 24; they do not conform to USP, but do conform to Ph.Eur. specifications. None of the runs in Table 4 show CV values that exceed or even approach the 7.8% limit (USP XXIV, 2000).

Considering that both the uniformity of mass specifications from the Ph.Eur. and the CV limit from the USP primarily test precision of dosing, it can be concluded that the micro dose auger filler is suitable for precise filling of the diacetylmorphine/caffeine mixture. However, some problems with accuracy of dosing were observed: three out of eight runs with the minimum dose did not comply with USP specifications. This might be explained by the absence of dosing

Table 4
Design of experiment with tested values for independent variables and dose weight statistics per run (n = 25 dose weights per run)

Run	*D* (mg)	AuS (rpm)	AgS (rpm)	*F* (%)	DI (ms)	Mean (mg)	S.D. (mg)	CV (%)	Dev. 10/15	Dev. 15/25
1	300	300	10	10	617	287.2	9.1	3.2	0/0	0/0
2	237.5	500	30	30	4146	246.8	4.8	1.9	0/0	0/0
3	50	1100	10	90	498	57.6	2.1	3.7	0/0	13/0
4	300	1100	13	90	505	302.4	9.7	3.2	0/0	0/0
5	300	1100	13	90	479	310.0	11.2	3.6	0/0	0/0
6	50	1100	90	10	502	53.2	0.8	1.6	0/0	0/0
7	237.5	500	70	30	4145	240.7	3.8	1.6	0/0	0/0
8	50	300	10	90	4947	53.9	2.3	4.2	0/0	1/0
9	175	300	90	10	4085	178.9	4.3	2.4	0/0	0/0
10	112.5	900	70	30	3806	117.2	2.5	2.2	0/0	0/0
11	175	700	50	50	2713	184.1	3.0	1.6	0/0	0/0
12	112.5	500	70	30	4063	117.6	3.0	2.5	0/0	0/0
13	300	1100	90	90	5132	305.7	3.4	1.1	0/0	0/0
14	300	1100	90	10	531	304.5	6.1	2.0	0/0	0/0
15	300	300	10	90	2891	303.6	5.4	1.8	0/0	0/0
16	175	700	50	50	2719	177.3	3.9	2.2	0/0	0/0
17	50	1100	10	90	507	52.6	2.0	3.9	0/0	0/0
18	300	1100	10	10	4772	301.7	11.8	3.9	0/0	0/0
19	237.5	900	70	30	3884	248.3	3.8	1.5	0/0	0/0
20	50	1100	90	90	4899	53.4	2.4	4.4	1/0	1/0
21	50	300	90	90	508	55.0	1.9	3.4	0/0	4/0
22	50	300	10	10	510	51.1	2.7	5.4	1/1	1/0
23	300	300	90	74	261	305.3	2.9	0.9	0/0	0/0
24	50	1100	10	10	4832	54.3	2.9	5.4	1/0	4/0

D, dose; AuS, auger speed; AgS, agitator speed; *F*, hopper fill level; DI: dose interval; mean, mean dose weight; S.D., standard deviation; CV, coefficient of variation; Dev. 10/15, number of weights deviating more than 10/15% from the mean weight, respectively; Dev. 15/25, number of weights deviating more than 15/25% from *D*.



$$CV = 0.0188 - 0.00961 \cdot D - 0.00709 \cdot AgS - 0.00229 \cdot F + 0.0121 \cdot F^2 + 0.00394(D \cdot AuS) - 0.00528(D \cdot DI) - 0.00250(AuS \cdot AgS) + 0.00487(AuS \cdot DI) + 0.00248(AgS \cdot DI)$$

Fig. 2. Experiment variable ranking for the regression model of dose weight coefficient of variation (CV). The pie chart shows the relative effect of each experiment variable across its range as a percentage of the total combined effects of all variables across their ranges ($^{*}P < 0.01$; $^{**}P < 0.001$). Shaded areas indicate a negative effect on CV. *D*, dose; AuS, auger speed; AgS, agitator speed; *F*, hopper fill level; and DI, dose interval. The regression model is given below (CV can be calculated by entering parameter values, after coding them by rescaling their tested range from −1.0 to 1.0 and calculating the corresponding coded value).

checks and dose correcting feedback into the machine during the experiments. They were not included in the sampling procedure to avoid possible bias in precision data, caused by these manipulations. Dose correcting feedback might be extra important when filling the 50 mg dose, as this is close to the lower technical limit of the auger filler (0.05 mL ≈ 22 mg diacetylmorphine/caffeine mixture).

The results for dose weight CV from the experimental design were analysed statistically, resulting in a 9-term regression model (Fig. 2) with an R^2 of 0.9403 (adjusted R^2 0.9020), indicating that the regression model explained 94% of the observed variation in CV. One quadratic term and five interactions factors were required to adequately describe the variation in CV, as can be seen in Fig. 2. *D*, AgS and *F* show the most important main effects on the precision of dosing, whereas DI is only involved via interaction effects with these parameters and AuS. The effects of the main response factors (*D*, AgS and *F*) on CV are presented in response surface plots in Fig. 3. Plots a and b show that a combination of high *D* and high AgS will result in a low CV. No interaction between *D* and AgS is evident, since the slopes of the individual effects are independent of each other in both plots. However, when plots a and b are compared, there is an obvious difference in the slopes of both factors, indicating both parameters show an interaction with AuS. Dose level in particular shows more effect on CV when AuS is low (plots a and c) than when it is high (Fig. 3 plots b and d). The influence of dose on filling precision is easily understood, as CV is a relative measure and a given deviation from the target weight will have less impact on CV when a high dose is filled. Agitator speed probably influences filling precision by achieving optimal aeration of the powder mixture in the hopper at higher agitator speeds, resulting in uniform filling of the auger and reproducible fill weights. The influence of *F* on precision of dosing is illustrated in Fig. 3c and d: intermediate levels of *F* are optimal in both plots. The increased CV that is observed at large *F* values might be caused by sub-optimal performance of the agitator with very large amounts of powder. Increased CV at small values for *F* might result from sub-optimal filling of the auger, due to the decreasing influence of gravity feeding the powder mass into the auger.

In summary, a complex regression model was constructed that accurately predicts dosing precision under the experimental conditions. The multidimensional character of the auger filling process was illustrated by the number of terms involved in the model, many of which were however readily explicable in view of process characteristics.

3.4. Optimisation

The regression model for CV was used to optimise the machine settings for the minimum and

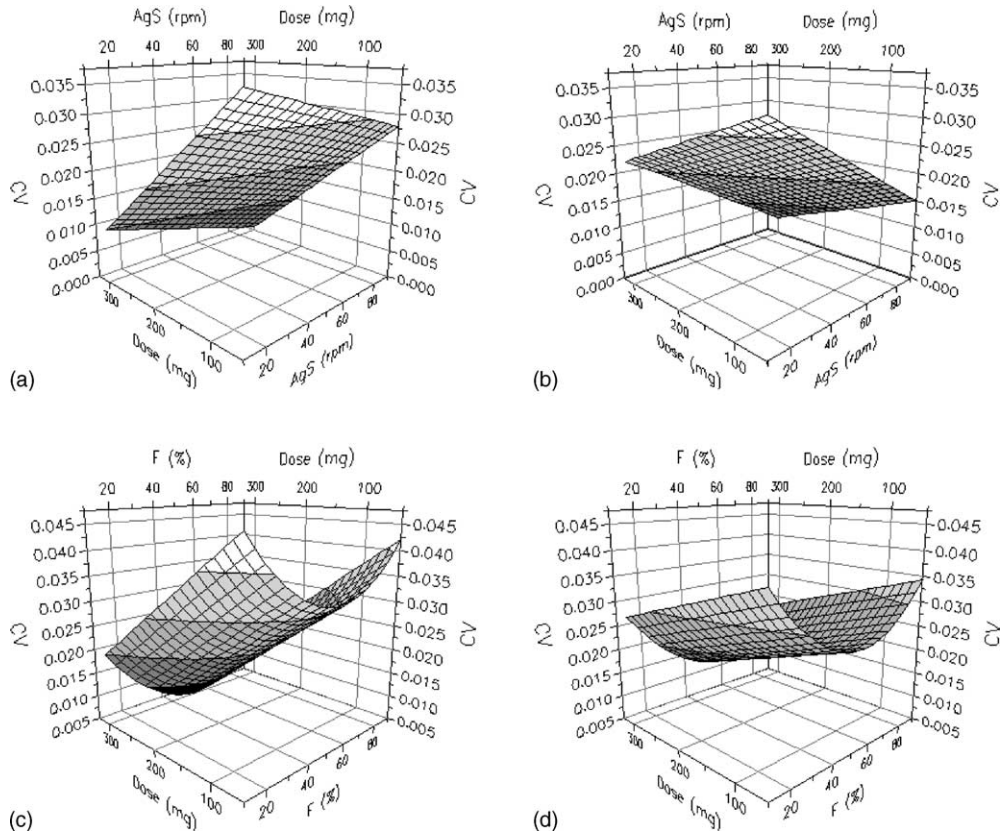


Fig. 3. Response surface plots for the effects of dose, agitator speed (AgS) and hopper fill level (*F*) on dose weight coefficient of variation (CV), at minimum auger speed (AuS, a and c) and at maximum AuS (b and d).

maximum dose in the tested dose range and the four dose unit contents that were selected for manufacture. The range chosen for DI in the optimisation procedure was 261–500 ms (261 is minimum DI tested), because DI will preferably be as low as possible in routine production for optimal manufacturing efficiency. The optimisation goal was to minimise CV; the results are given in Table 5, including the predicted values for CV with their 95% confidence intervals. The optimal settings for DI and AuS are ideally compatible with efficient manufacturing, since maximum AuS and minimum DI will result in the maximal sachetting speed for each

Table 5
Optimisation results for minimising the dose weight coefficient of variation (CV): predicted optimal settings and mean predicted values for CV are given, with their 95% confidence interval

Dose (mg)	DI (ms)	AuS (rpm)	AgS (rpm)	*F* (%)	CV (%)
50	261	1100	66	54	1.07 (1.0–1.1)
100	261	1100	66	54	0.93 (0.8–1.1)
133	261	1100	65	54	0.95 (0.8–1.1)
200	261	1100	65	54	0.94 (0.6–1.3)
267	261	1100	64	54	0.94 (0.5–1.3)
300	261	1100	64	54	0.93 (0.5–1.4)

DI, dose interval; AuS, auger speed; AgS, agitator speed; *F*, hopper fill level.

Table 6
Results of routine manufacturing using optimised settings

Dose (mg)	75/25	100/33	150/50	200/67
Accuracy (%)	101.0	99.0	99.5	99.8
Number deviating >10% from label claim (%)	6.3	0.5	0.6	0.0
Number deviating >15% from label claim (%)	0	0	0	0
Standard deviation (mg)	5.3	5.0	6.1	8.5
Coefficient of variation (%)	5.3	3.8	3.1	3.2
Number of sachets in IPC	191	212	157	175
Number of dose corrections	3	4	2	6
Batch size	18019	20220	15240	15723
Dose interval (ms)	813	572	513	438
End of batch hopper fill level (%)	11	3	1	4

Statistics for delivered weights are given, the mean filling accuracy as a percentage of the label claim, as well as the number of dose corrections performed and the batch size. IPC, in-process control.

dose (Table 5). The optimal value for F was found to be 54%, but F is not a constant value during routine manufacturing, therefore, its influence on dosing precision was visualised in a two-dimensional contour plot in Fig. 4. It can be derived from this plot that, when filling a 300 mg dose (at the optimised settings for AuS, AgS and DI), a decrease in *F* from 50 to 10% would increase CV from 0.8–1.0% to 2.2–2.4%. Thus it is not likely that variation in hopper fill level during manufacture alone would compromise dosing precision.

3.5. Test batches

The optimised settings were tested in routine manufacturing: one test batch (15–20,000 sachets) was produced for each of the four doses selected for the clinical trial (75/25 mg, 100/33 mg, 150/50 mg and 200/67 mg diacetylmorphine/caffeine). AuS and AgS were set at their optimised levels (Table 5) and DI was calculated from the sachet speed used and the dosing time. *F* was maintained between 30 and 70% during most of the batch, but was allowed to decrease below 10% near the end of the batch. Every 100 sachets, one sachet was emptied to determine the delivered weight (weight of powder contents shaken out).

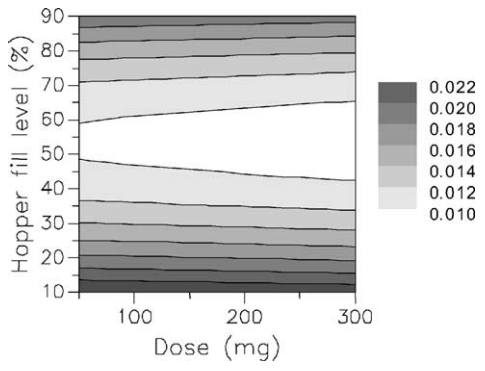


Fig. 4. Two-dimensional contour plot of CV as a function of dose and hopper fill level, at AuS = 1100 rpm, AgS = 65 rpm, and DI = 261 ms. CV ranges from 0.8–1.0% in the middle, and to 1.8–2.0% and 2.2–2.4% in the upper and lower part of the graph, respectively.

To ensure filling accuracy, the operator was allowed to give dose correcting feedback (mean of last two to three weights) to the auger filler when the delivered weight consistently deviated >5% from the label claim; feedback was required on consistent (repeated two to three times) deviations >10%. When the delivered weight deviated >15% from the label claim, the sachets concerned were discarded.

Results for accuracy and precision of dosing in routine manufacturing are given in Table 6. The CV values found in the test batches exceed the predicted levels from the optimisation experiment. Extra variation is probably introduced because the weight delivered by the sachets was determined instead of the weight of the powder portions. Furthermore, in routine manufacturing it was not possible to set the optimised settings for DI and F exactly or to maintain them. Other factors possibly influencing dose weight variation are: the larger number of samples, the different sampling interval, and the inclusion of dose correcting feedback in the in-process control procedure. However, the results show that the micro dose

auger filler can fill the four doses into sachets precisely using the optimised machine settings. Only few dose corrections were necessary to ensure excellent filling accuracy (99–101% of set dose). No sachets were discarded due to deviation >15% from the set dose.

4. Conclusion

The complex pharmaceutical manufacturing process of micro dose auger filling of diacetylmorphine/caffeine powder was successfully characterised using design of experiments. All parameters tested in the experiment design, but especially dose, agitator speed and hopper fill level were found to affect dosing precision either through linear, quadratic or interaction effects. A regression model was obtained that explained 94% of the observed variation in the dose weight CV. This model was used to optimise the manufacturing processes of four types of diacetylmorphine/caffeine sachets. It was found to be necessary to include dose-correcting feedback in the in-process controls to ensure dosing accuracy. Four pilot batches showed that routine manufacturing using the optimised process resulted in a precise (e.g., CV: 3.2–5.3%) and accurate (e.g., accuracy: 99.0–101.0%) filling of diacetylmorphine/caffeine sachets.

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