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Development of spray-dried acetaminophen microparticles using experimental designs

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Abstract

Experimental factorial designs were built to investigate the effects of five parameters on production yields and moisture contents of spray-dried products. These factors concerned both the solution feed (drug concentration, colloidal silica concentration and polymer/drug ratio) and the spray dryer (inlet temperature and feed rate). Three formulations containing cellulose derivatives and acetaminophen were tested. The aim of the study was to optimize the operating conditions to maximize production yields while minimizing moisture contents. First screening experiments consisting of fractional factorial designs revealed the most significant factors to be inlet temperature, feed rate and their interaction for both formulations containing sodium carboxymethylcellulose and feed rate and colloidal silica concentration for the formulation containing microcrystalline cellulose. Then, the optimal operating conditions were estimated by response surface methodology. Central rotational composite designs showed quadratic models were adequate. New assays were carried out using these last conditions to evaluate both the repeatability and reproducibility of the spray-drying technique. Yields above 80% and moisture content of $\sim 1\%$ were reached. The characterization of microparticles revealed the poor flowability of the spray-dried products due to significant cohesiveness and very small size (less than 55 μm). © 2000 Published by Elsevier Science B.V. All rights reserved.

Keywords: Spray-drying; Acetaminophen; Central composite designs; Optimization; Microparticle characterization

1. Introduction

Spray-drying is extensively used in the pharmaceutical industry to produce raw drug or excipients or as microencapsulation process (Brodhead and Rhodes, 1992). This technique transforms liquid feed into dry powder in a one step, continuous particle processing operation and can be applied to a wide variety of materials (Brodhead et al., 1994).

Despite the main advantages of spray-drying, processing variables must be well controlled to

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avoid difficulties such as low yields, sticking, or high moisture content, which are often encountered with laboratory scale spray-dryers (Masters, 1991). The optimization of spray-drying process involves the evaluation of parameters concerning both spray-dryer and feed formulation (Conte et al., 1994; Wendel and Celik, 1997).

A previous study (Billon et al., 1999a) demonstrated the feasibility of sustained release acetaminophen microparticulate systems containing cellulose derivatives by spray-drying with yields below 50%. Two derivatives were specially convenient for this preparation method: sodium carboxymethylcellulose (hydrosoluble) and microcrystalline cellulose (non-hydrosoluble).

The aim of this study is to evaluate the effects of process and formulation parameters on fabrication yields and moisture content of spray-dried products in order to optimize the fabrication process (production yields $>80\%$ and moisture contents $<1\%$). Statistically designed experiments were used as they allow the evaluation of both the different factors and their interaction (Brodhead et al., 1994).

A fractional factorial design experiment 2^{5-1} was initially built to estimate the influence of five factors (inlet temperature, feed rate, drug concentration, polymer/drug ratio, additive concentration) and to determine the optimal values to be applied. Then, a central composite rotational design was used to locate the experimental range containing the optimum for both production yield and moisture content.

An internal validation was carried out using the optimal conditions to assess the repeatability and reproducibility of spray-drying technique. Finally the spray-dried products were characterized.

2. Materials and methods

2.1. Materials

Acetaminophen (Rhodapap pulvérisé fin®, Rhodia Chimie organique fine, Eur. Ph. 3rd ed.) was used as model drug. The polymers were microcrystalline cellulose (MCC; Vivapur® PH101, Rettenmaier and Söhne, Eur. Ph. 3rd ed.) and sodium carboxymethylcellulose (NaCMC; Blanose® cellulose gum 7LF, Aqualon, Eur. Ph. 3rd ed.). Additives used in this study were polyvinylpyrrolidone (PVP; Kollidon® 30, BASF, Eur. Ph. 3rd ed.) with MCC and carboxylic acids including oxalic acid (OA; PROLABO) and tartaric acid (TA; Aldrich-Chemie, Eur. Ph. 3rd ed.) with NaCMC. Colloidal silicon dioxide (SiO_2; Aerosil® 200, Degussa) was added to all formulations.

2.2. Preparation of spray-dried microparticles

Acetaminophen and polymers in mass ratio 1/1 were dissolved (NaCMC) or suspended (MCC) in distilled water. The quantity of additive added is function of the mass of polymer used. With NaCMC, the quantity of tartaric acid (TA-CMC formulation) or oxalic acid (OA-CMC formulation) represents 30% of the mass of polymer, whereas the ratio PVP/MCC used is 3% w/w (PVP-MCC formulation).

These feeds were spray-dried using a NIRO Minor Mobil (Niro Atomizer, Denmark) through a rotating wheel. The operating parameters were set as follows: dry air rate 85 m^3/h; atomizing air pressure 8 bar. Inlet temperature and feed pump setting were dependent on the experiment. The resulting dried products were collected and kept away from rehydration until further tests.

2.3. Experimental design

Factorial experimental designs were used to evaluate the effects of different parameters on production yields and moisture contents. In order to limit the number of experiments, fractional factorial screening designs 2^{5-1} were initially built. They allow evaluation, by 16 experiments, of five factors at two levels: feed rate, inlet temperature, drug concentration in the feed, polymer/drug ratio, and additive (colloidal silicon dioxide, SiO_2) concentration. The chosen designs, i.e. resolution V designs, consider only two-factor interactions. They do not confound main effects with the second order interactions.

Preliminary experiments were carried out to establish appropriate ranges for the processing

variables. The matrix of experiments and the values of the two levels tested are indicated in Table 1. The high level for feed rate was the maximum rate that could be used without condensation appearing in the drying chamber. As for drug concentration, the low level corresponds to the minimum acceptable to obtain a sufficient hourly yield. The range used for inlet temperature, polymer/drug ratio and additive concentration were chosen from previous studies (Moura 1994; Billon et al., 1999b).

Two responses were considered: production yield and residual moisture content of spray-dried product. Residual moisture was measured with a moisture analyzer (Sartorius MA30, Sartorius, Göttingen, Germany) on a 0.1-g sample at 105°C. For the TA-CMC formulation, two replicates were carried out to estimate the inherent variability of the experiments.

Three centre points were produced to evaluate the validity of the first order model for the three formulations.

In a second step, to optimize the goodness of fit, a central rotational composite design was performed to obtain the response surface and to determine which combination of factor values would produce maximal yield and minimal moisture content.

Statistical analyses were performed using Statgraphics 4.0 (Sigma Plus) software.

2.4. Process internal validation

Three replicates were produced on three different days to evaluate the fidelity of the technique. For these experiments the processing parameters used were the optimal conditions determined from the response surface designs. Yields and residual moisture obtained in the nine experiments were analyzed and an analysis of variance was performed. Repeatability and reproducibility were estimated.

2.5. Microparticle characterization

2.5.1. Drug content

The total amount of acetaminophen contained in the microparticles was determined spectrophotometrically (UV-1601, Shimadzu) at 244 nm after complete dissolution of the samples in distilled water. Drug loading is expressed as the ratio of actual to theoretical drug content percentage.

Table 1
Matrix of experiments of the fractional experimental design

Experiment	Inlet temperature (°C)	Feed rate (ml/min)	Drug concentration (g/l)	Additive concentration (%)	Polymer/drug ratio
1	(−) 140	(−) 30	(−) 5	(−) 0	(+) 1/1
2	(+) 160	(−) 30	(−) 5	(−) 0	(−) 0.75/1
3	(−) 140	(+) 50	(−) 5	(−) 0	(−) 0.75/1
4	(+) 160	(+) 50	(−) 5	(−) 0	(+) 1/1
5	(−) 140	(−) 30	(+) 10	(−) 0	(−) 0.75/1
6	(+) 160	(−) 30	(+) 10	(−) 0	(+) 1/1
7	(−) 140	(+) 50	(+) 10	(−) 0	(+) 1/1
8	(+) 160	(+) 50	(+) 10	(−) 0	(−) 0.75/1
9	(−) 140	(−) 30	(−) 5	(+) 10	(−) 0.75/1
10	(+) 160	(−) 30	(−) 5	(+) 10	(+) 1/1
11	(−) 140	(+) 50	(−) 5	(+) 10	(+) 1/1
12	(+) 160	(+) 50	(−) 5	(+) 10	(−) 0.75/1
13	(−) 140	(−) 30	(+) 10	(+) 10	(+) 1/1
14	(+) 160	(−) 30	(+) 10	(+) 10	(−) 0.75/1
15	(−) 140	(+) 50	(+) 10	(+) 10	(−) 0.75/1
16	(+) 160	(+) 50	(+) 10	(+) 10	(+) 1/1

Table 2
Observed and 95% predicted averages of centre points for the screening 2^{5-1} factorial design

	Yields		Moisture content	
	% Observed	95% Prediction intervals	% Observed	95% Prediction intervals
TA-CMC	69.6	[50.9–59.3]	6.1	[7.6–9.8]
OA-CMC	69.1	[46.3–66.9]	7.3	[5.6–7.0]
PVP-CMC	53.1	[20.4–49.6]	5.5	[5.7–7.6]

2.5.2. Scanning electron microscopy

The spray-dried products were coated under argon atmosphere with gold/palladium and examined under an electron microscope (Hitachi S 4000, Japan).

2.5.3. Particle size distribution

The particle size distribution of the different samples was estimated with a laser granulometer Mastersizer 2000 (Malvern Instruments) by dry dispersion using 3-bar pressure.

2.5.4. Density

Bulk and tapped densities of the microparticles were determined (Eur. Ph., 3rd ed., 1997) using an automatic tapper (Stampsvolumenometer STAV 2003). The tapped density was measured after 2500 taps on three samples. Hausner ratio corresponds to the ratio of the tapped and bulk density; the Carr index is the difference between the tapped and bulk density divided by the tapped density, expressed in percent (Wan and Lim, 1988). Particulate density was determined on 12-g samples with an air-comparison pycnometer Beckman 930. Measures were made on three batches for each formulation and means and S.D. were calculated.

3. Results and discussion

3.1. Experimental design: effects of spray-drying factors on production yields and moisture content

The 16 runs realized for TA-CMC formulation were duplicated to calculate an estimate of the standard error (SE = 2.07% for production yield and SE = 0.55% for moisture content). A total of 16 experiments were performed for the two other formulations. The spray-dried products were recovered in the collecting flask and the yields and moisture contents were measured. The yields varied from 6 to 86% with means of 67.6, 69 and 51.9% for TA-CMC, OA-CMC and PVP-MCC formulations, respectively. In parallel, moisture contents varied from 1 to 20% with means of 5.9, 7.25 and 5.5% for TA-CMC, OA-CMC and PVP-MCC formulations, respectively. In some experiments, the operating conditions fixed by the experimental design induce very low yields by promoting large sticking in the drying chamber. The resulting products cannot be removed. For these products, high moisture contents are also recorded. Particle drying is not achieved.

The first order fitted regression equations relating the response parameters to the processing factors were calculated. Three centre points were added to the 16 experiments to check the validity of the linear models. However, as the observed means of the responses obtained for yields and moisture contents were out of the prediction intervals at a 95% confidence level (Table 2), the first order models could not be validated.

So, in a second step, central composite designs were built. A total of ten other experiments including star points were added to the fractional experimental design (Table 3). Rotational designs were chosen to obtain constant variances of the predicted responses at all points that are equal from the centre of the design. Analysis of variance was performed to determine the significance of each factor. Quadratic polynomial equations were generated to establish the relationship between the factors and the responses. The coefficients of the

Table 3
Values attributed to the factors for the additional experiments of the central composite design

Experiment	Inlet temperature (°C)	Feed rate (ml/min)	Drug concentration (g/l)	Additive concentration (%)	Polymer/drug ratio
1	150	40	7.5	5	1.2
2	173	40	7.5	5	0.875
3	150	40	7.5	17	0.875
4	150	40	13.3	5	0.875
5	150	40	7.5	0	0.875
6	126	40	7.5	5	0.875
7	150	40	1.6	5	0.875
8	150	63	7.5	5	0.875
9	150	17	7.5	5	0.875
10	150	40	7.5	5	0.6

regression equation linking the responses to the experimental variables and interactions are indicated in Table 4.

For the first and second formulations, containing NaCMC as polymer, yields obtained principally depend on spray-drying variables. They are essentially influenced by the liquid feed rate ($P < 0.01$), the dryer inlet temperature ($P < 0.05$), and the interaction between the two as illustrated in Fig. 1. Yields can be considerably increased by reducing feed rate. At low feed rates, yields are high irrespective of drying temperature. An increase in inlet temperature improves yields only when feed rate is high. High feed rates require more thermal energy to ensure the complete evaporation of the solvent, the energy for which is supplied by inlet temperature.

With PVP-MCC formulation, feed rate ($P < 0.01$) and quantity of SiO_2 present in the liquid feed are the most significant effects. Colloidal silicon dioxide is used as a technical agent. This compound facilitates drying by its capacity to adsorb large amounts of water (Moura, 1994). Moreover it creates an increase in droplet density, thus promoting an improvement in powder recovery. The total feed concentration also greatly af-

Table 4
Coefficients of the regression equation linking the responses to the experimental factors and major interactions

	TA-CMC		OA-CMC		PVP-MCC	
	Yield	Moisture	Yield	Moisture	Yield	Moisture
Average (%)	67.65	5.96	69.04	7.25	51.93	5.46
A: temperature	8.84*	−1.05	12.98**	−1.43*	3.80	−2.41
B: feed rate	−38.48**	7.82**	−30.25**	3.55**	24.08**	8.63**
C: drug concentration	7.19	−2.97**	−2.05	−0.95	1.61	−0.74
D: additive concentration	−1.45	−0.50	0.66	0.23	10.65	1.05
E: polymer/drug ratio	−3.19	1.18	−5.00	1.15	1.62	0.09
AB	11.20	0.25	17.91**	−3.65**	6.53	−3.75
BB	−14.63**	2.63**	−12.07**	0.51	13.41**	5.96**
BC	16.40**	−1.96*	2.62	1.35	6.42	−2.25
CC	−3.70	1.77**	−2.21	0.15	−1.21	−0.69
CE	−9.39	3.10**	−7.84	0.60	8.31	−1.75

* Significant at 95%.
** Significant at 99%.

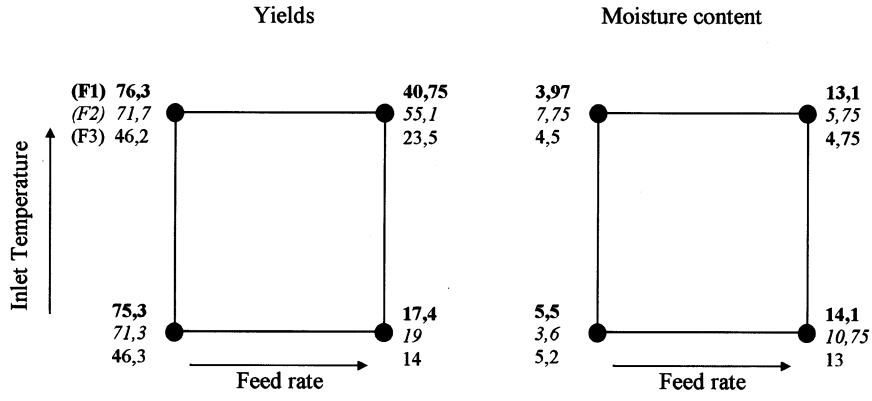

Fig. 1. Effects of feed rate and inlet temperature on yields and moisture content for TA-CMC, OA-CMC and PVP-MCC formulations (F1, F2, F3, respectively).

fects yields and moisture content. The more the feed is concentrated, the better is the drying process.

The other parameters have less influence on the spray-drying process for all formulations. Polymer/drug ratio has no significant effect in either of the formulations, but the range studied (0.75/1–1/1) may be too thin to highlight the value of this parameter. Nevertheless, the low level tested was the minimum acceptable to ensure efficient drug encapsulation. In this polymer concentration range, the solution viscosity varies very slightly (from 1 to 5 mPa·s). These low values cannot have any influence on the spray-drying process.

As for moisture content, feed rate is a statistically significant parameter in the three formulations ($P < 0.01$). An increase of feed rate leads to higher moisture contents, especially at low inlet temperature (Fig. 1). With high feed rates, the evaporation of the solvent can not be achieved. The spray-dried products recovered are often agglomerated and sticky. In TA-CMC and OA-CMC formulations, inlet temperature and interaction between inlet temperature and feed rate also affect moisture content. A higher inlet temperature promotes a decrease of residual moisture by enhancing water evaporation.

During the experiments, it was observed that high moisture contents were linked with low outlet temperatures (Fig. 2). The drying temperature difference (inlet temperature – outlet temperature) represents the heat required to produce dried particles. A diminution of outlet temperature indicates that the thermal energy supplied by inlet temperature is not sufficient to allow complete drying. In these cases, sticking occurs in the drying chamber.

3.2. Process internal validation

The statistical interpretation of the results concerning both yields and moisture content using the response surface methodology, shown in Fig. 3, leads us to the choice of optimal operating conditions as indicated in Table 5. These parameters have to maximize yields while reducing moisture content. They vary depending on the formulation.

A total of nine batches for each formulation were produced using the optimal parameters to validate the fabrication process.

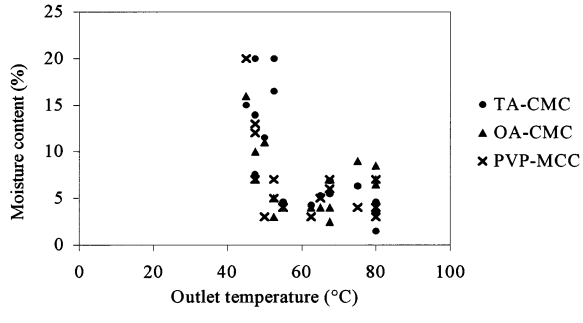

Fig. 2. Influence of outlet temperature on moisture content.

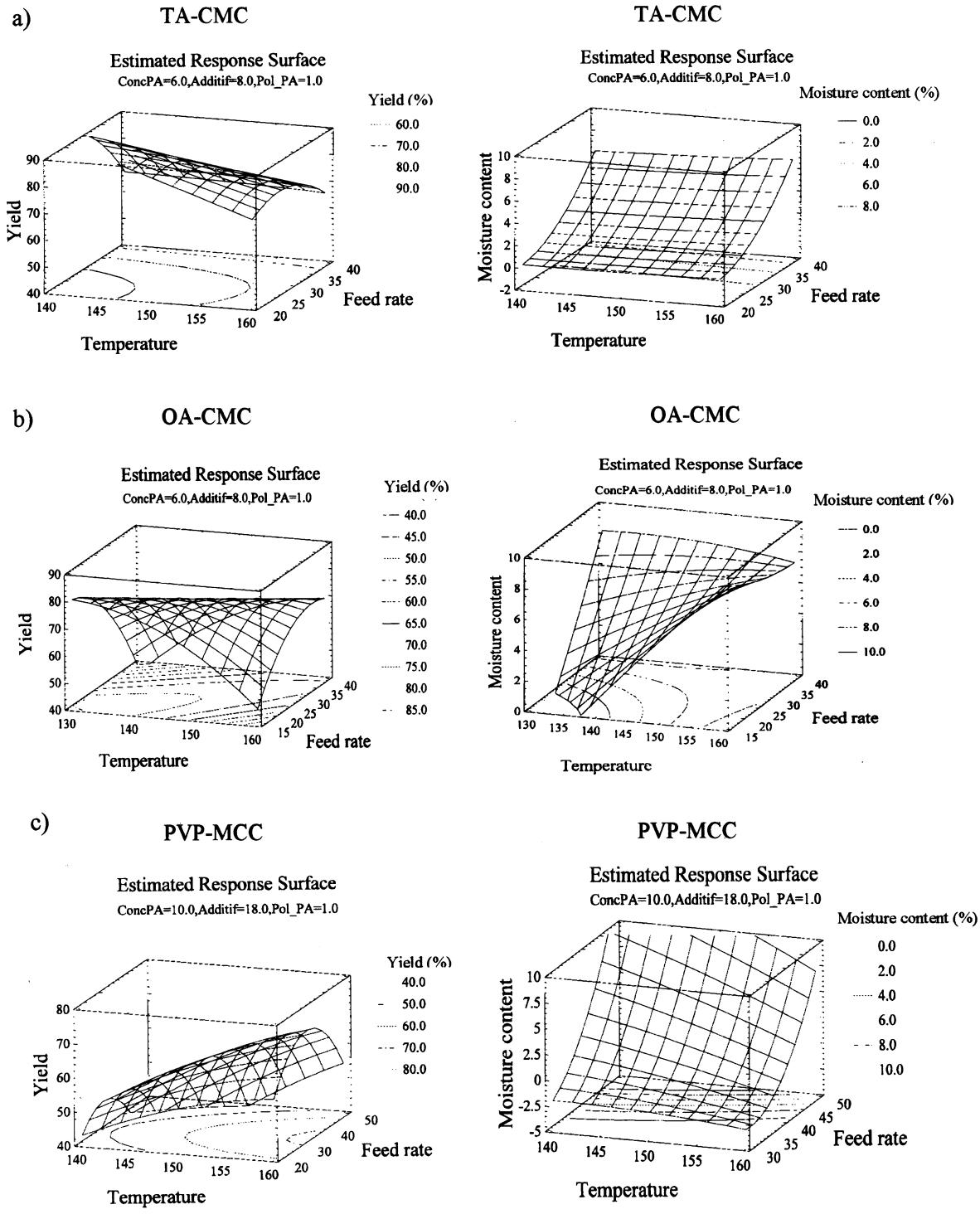

Fig. 3. Estimated response surfaces for yield and moisture content for TA-CMC (a), OA-CMC (b) and PVP-MCC (c) formulations.

Table 5
Optimal operating parameters

	TA-CMC	OA-CMC	PVP-MCC
Spray-dryer parameters			
Feed rate (ml/min)	20	20	30
Inlet temperature (°C)	140	140	160
Feed parameters			
Acetaminophen (g/l)	6	6	10
Polymer (g/l)	NaCMC: 6	NaCMC: 6	MCC: 10
Additive (g/l)	TA: 1.8	OA: 1.8	PVP: 0.3
SiO_2 (%)	8	8	18

Table 6
Responses of the internal process validation

	TA-CMC	OA-CMC	PVP-MCC
Yield (%)			
Mean	82.5 ± 1.95	80.8 ± 0.40	86.8 ± 1.91
S.D. repeatability	1.84	0.45	2.15
S.D. internal reproducibility	1.98	0.38	1.82
Residual moisture (%)			
Mean	1.03 ± 0.094	1.02 ± 0.08	1.02 ± 0.10
S.D. repeatability	0.075	0.075	0.089
S.D. internal reproducibility	0.1	0.085	0.1

Table 7
Particle size determined by laser granulometry

	Mean diameter (μm)	S.D.
TA-CMC	9.835	4.4
OA-CMC	9.339	4.4
PVP-CMC		
Population 1	9.816	5.6
Population 2	53.303	43

These productions resulted in a neat improvement of spray-dried product yields (above 80%) as shown in Table 6. The powder was easily recovered and spray-dried products appear as fine, well separated dry particles. The minor lost of product can be explained by slight sticking on the chamber walls and the loss of too fine particles (as SiO_2) which are not dissociated from the air by the cyclone separator. The residual moisture content obtained was very low ($\sim 1\%$) for all formulations, indicating complete drying.

The yields and moisture content obtained for the different batches are very close (low SEM were obtained: 0.4–2 for production yields and 0.08–0.1 for residual moisture). The statistical computing of the nine responses demonstrated both reproducibility and repeatability of the process. The S.D. of repeatability and S.D. of reproducibility are indicated in Table 6.

These results prove that the parameters evaluated by the response surface methodology concerning formulation and spray-dryer are convenient. As described above, with well controlled operating conditions, spray-drying is a technique which can be applied to our components to produce microparticles of high quality.

3.3. Spray-dried product characterization

Acetaminophen content in spray-dried product was measured in nine samples and the results indicate a mean drug content close to 100% for all formulations (97.4 ± 2.1, 103.5 ± 2 and $101.3 \pm 1.4\%$ for TA-CMC, OA-CMC and PVP-MCC formulations, respectively), indicating that no loss of active compound occurred during spray-drying. Moreover a previous work showed that acetaminophen was not altered by the drying process (Billon et al., 1999a).

The size distribution of the microparticles was measured by laser granulometry on three batches for each formulation (Table 7). For both formulations containing NaCMC, the mean diameter varies from 9 to 10 μm. With MCC as polymer, the final product particle size follows a bimodal distribution indicating the presence of two populations: one (60%) of ~ 9 μm and a much larger one (40%) of ~ 53 μm corresponding to MCC

Table 8
Flowability parameters of the spray-dried products (mean ± S.D.)

	TA-CMC	OA-CMC	PVP-MCC
Bulk density (g/ml)	0.40 ± 0.015	0.40 ± 0.01	0.52 ± 0.015
Tapped density (g/ml)	0.64 ± 0.04	0.55 ± 0.03	0.70 ± 0.02
Hausner ratio	1.59 ± 0.03	1.38 ± 0.07	1.35 ± 0.01
Carr index (%)	36.9 ± 0.017	27.1 ± 0.038	26.2 ± 0.004
Particulate density (g/ml)	1.44 ± 0.01	1.45 ± 0.007	1.48 ± 0.005

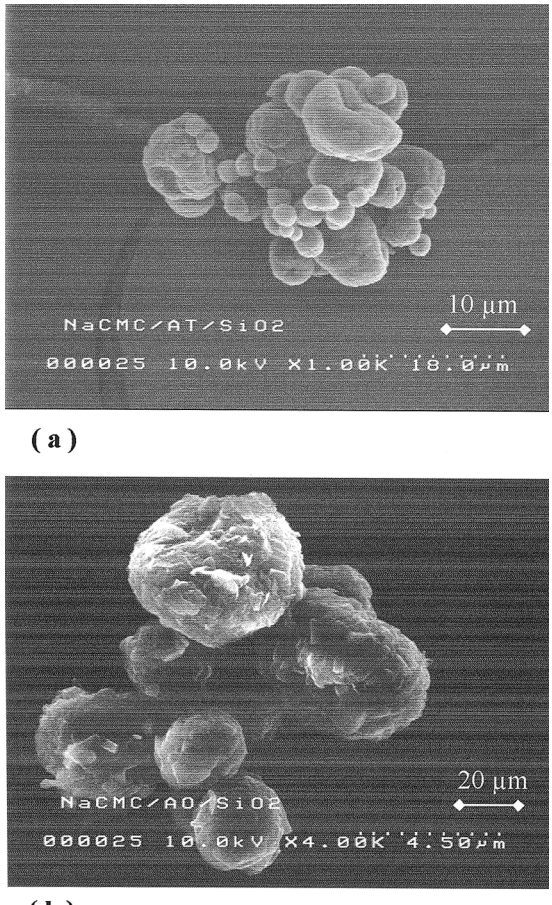

Fig. 4. SEM photographs of spray-dried particles of TA-CMC (a) and OA-CMC (b) formulations.

initial particle size (mean diameter of Vivapur PH101® ≈ 50 µm). This polymer is not soluble in the feed medium and thus cannot be modified during the fabrication process.

The bulk and tapped density were determined on three batches for each formulation, the highest densities (0.52 and 0.7 g/ml, respectively) being obtained with formulation 3 as indicated in Table 8. This is due to the greater content of colloidal silicon in this formulation which densifies the powder and thus improves flowability.

TA-CMC and OA-CMC formulations give rise to spray-dried products of equal bulk density (0.4 mg/ml). Nevertheless, their tapped density is different. This characteristic has to be related to differences in particle size, the biggest microparticles (PVP-MCC formulation) having the highest tapped density.

The high Hausner ratio, which measures the interparticulate friction, indicates greater cohesion between particles. High Carr index reveals a tendency of powders to form bridges (Guo and Bodmeier, 1997). These results suggest that the spray-dried microparticles are likely to have poor flowability, a constraint to be considered in further tabletting experiments. This is mainly due to their small particle size and high interparticulate cohesiveness.

Moreover, this high cohesiveness indicates that the particles will tend to agglomerate leading to a comparatively reduced area. This phenomenon could influence drug release when the particles are exposed to a dissolution medium.

SEM photographs show two behaviors depending on polymer solubility. Spray-drying of TA-CMC and OA-CMC formulations containing hydrosoluble NaCMC, gives rise to the formation of spherical particles in which the drug is encapsulated. Spray-dried products are more or less agglomerated (Fig. 4).

As for MCC including formulations, two types of microparticles are present (Fig. 5), some particles in MCC have the shape of large porous plates; acetaminophen, in the form of small spherical particles, seems adsorbed or incorporated in MCC pores, creating agglomerates. Other well separated spherical particles are present, probably corresponding to colloidal silicon dioxide.

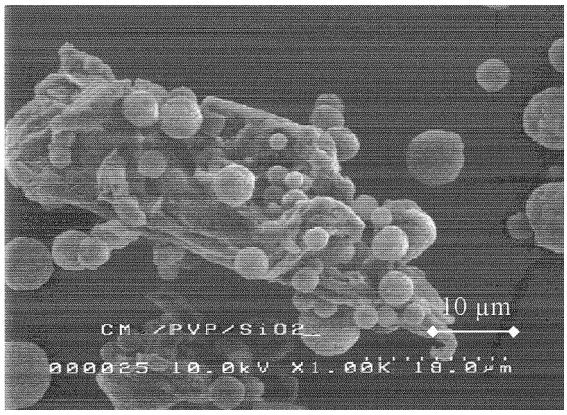

Fig. 5. SEM photograph of spray-dried particles of PVP-MCC formulation.

4. Conclusion

This work shows that spray-drying is a suitable technique for the preparation of sustained release microparticulate systems containing acetaminophen. The control of processing variables, especially inlet temperature and feed rate, allows production of microparticles of low moisture content with high yields. Experimental factorial designs are necessary before new production runs to determine the values of the parameters to be used for the optimization of the spray-drying process.

Validation proved that the spray-drying process is repeatable and reproducible ($0.075 < \text{S.D. repeatability} < 2.15$ and $0.085 < \text{S.D. reproducibility} < 1.98$). No 2significant variability in the spray-dried particles' characteristics was observed between the different batches, which are suitable for effective scale-up.

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