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Research Paper

Spray-drying Nanocapsules in Presence of Colloidal Silica as Drying Auxiliary Agent: Formulation and Process Variables Optimization Using Experimental Designs

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Purpose. Spray-drying process was used for the development of dried polymeric nanocapsules. The purpose of this research was to investigate the effects of formulation and process variables on the resulting powder characteristics in order to optimize them.
Materials and Methods. Experimental designs were used in order to estimate the influence of formulation parameters (nanocapsules and silica concentrations) and process variables (inlet temperature, spray-flow air, feed flow rate and drying air flow rate) on spray-dried nanocapsules when using silica as drying auxiliary agent. The interactions among the formulation parameters and process variables were also studied. Responses analyzed for computing these effects and interactions were outlet temperature, moisture content, operation yield, particles size, and particulate density. Additional qualitative responses (particles morphology, powder behavior) were also considered.
Results. Nanocapsules and silica concentrations were the main factors influencing the yield, particulate density and particle size. In addition, they were concerned for the only significant interactions occurring among two different variables. None of the studied variables had major effect on the moisture content while the interaction between nanocapsules and silica in the feed was of first interest and determinant for both the qualitative and quantitative responses. The particles morphology depended on the feed formulation but was unaffected by the process conditions.
Conclusion. This study demonstrated that drying nanocapsules using silica as auxiliary agent by spray drying process enables the obtaining of dried micronic particle size. The optimization of the process and the formulation variables resulted in a considerable improvement of product yield while minimizing the moisture content.

KEY WORDS: characterizations; experimental designs; nanocapsules; spray-drying.

INTRODUCTION

Nanocapsules (NC) are colloidal systems of submicronic size that contain a polymeric shell enveloping an oily or aqueous core (1). These particles have been developed with the aim to favor the active pharmaceutical ingredients transport towards their targets in order to improve the therapeutic activity and/or decrease the side effects. However, the full potential of NC is not yet exploited because of the lack of stability when conserved in aqueous medium for a long period (2). Polymer hydrolysis leading to drug leakage and physicochemical instabilities due to the particle agglomeration and sedimentation could be observed (3).

To overcome these stability limitations, the water elimination from the aqueous suspensions to reach a dried form was proposed as a mean of interest to improve the shelf life of NC preparations (4). Freeze drying technique was described to dry poly(ε-caprolactone) nanocapsules intended for intravenous injection using mygliol as oil phase (5–7). Successful freeze drying of these nanocapsules with the conservation of original properties after rehydration were obtained. However this technique is highly expensive and reserved for product with high added value. Then, spray-drying process appeared recently as an interesting alternative to freeze-drying in order to develop dried NC in form of powder (8).

Spray-drying is a common technique for producing a dry powder from a liquid phase. This process consists of three steps: (a) atomization, (b) dehydration, and (c) powder collection. Practically, the liquid feed is atomized by an atomizer creating a spray of fine droplets into a chamber of heated air, from which the solvent quickly evaporates resulting in dried particles (9). This technique is extensively used in the pharmaceutical field since it allows the preparation of dry powders with specific characteristics such as particle size and shape (10). In addition, formulation

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processes including encapsulation (11), complexes formation (12) and even polymerization (13) can be accomplished in a single step. It exhibits advantages like the rapidity of the process, the possibility to modulate the physicochemical characteristics of the resulting powders, added to the scale-up potential. Compared to freeze-drying, spray-drying takes less time and is cheaper process (10,14).

Nevertheless, spray-drying requires particular attention in the process control because of limitations and the high number of parameters. These limitations include problems with efficient particle collection and the potential instability of materials sensitive to high temperatures. Each process variable is critical and this explains some of the difficulties encountered in spray-drying optimization attempts by some authors. Indeed, the spray-drying process optimization involves the evaluation of parameters concerning both spray-dryer and feed formulation (15,16).

Because of the colloidal size of NC and their thermal sensitivity, a drying adjuvant is often needed for protecting them against the drying stress and to confer sufficient size of prepared particles permitting separation from the exhaust gas. To date, the total capacity of the technique for this application remains not enlightened.

We have reported previously about microparticles achieved by spray-drying of NC in presence of colloidal silica. The obtained powders presented different morphologies depending on the initial concentrations of NC and silica. By adequate adjustments of these concentrations, separated spherical microparticles suitable for handling, composed of one or several NC entrapped in a matrix were achieved. On the other hand, agglomerated particles presenting NC at their surface and characterized by irregular shapes as well as a strong adhesiveness were prepared when the silica concentration was not sufficient (17). To date, the impact of the process variables on the spray-drier outcomes and on the prepared products characteristics is still an open question that should be addressed. In this paper, we presented a more extensive investigation of this application using experimental designs. The major goal was the study of the relationship between the formulation and process variables and their influence on the resulting powders characteristics. Variables studied included formulation parameters (NC concentration, silica concentration), and process variables (inlet temperature, spray flow rate, liquid feed rate and drying air flow rate). To understand how these parameters and the interactions among them affect particle characteristics is fundamental for future development of spray-dried NC. Since spray-drying involves various parameters, the number of experiments is expected to be minimized while accomplishing a detailed evaluation of the dominant variables effects and interactions.

MATERIALS AND METHODS

Materials

Poly(ε-caprolactone) (PCL) (M_n 42,500) was purchased from Aldrich (Strasbourg, France). Caprilic/capric triglyceride (Miglyol 810®) was supplied by Condea Chemie (Witten, Germany). Sorbitan monostearate (Montane 60®) and polysobate 80 (Montanox 80®) were obtained from Seppic (Paris, France). Hydrophilic fumed colloidal silicon dioxide with a specific surface area of 200 m^2/g and a primary particle size of 12 nm (Aerosil 200®) was supplied by Degussa (Frankfurt, Germany).

Preparation and Characterization of Nanocapsules Suspensions

NC containing an oil core were prepared by interfacial deposition of PCL following solvent displacement, method described by Fessi *et al.* (18). A pilot design which allows an extrapolation of 30 folds the laboratory scale was used for this end. The organic phase contained PCL, montane 60®, miglyol 810® and acetone. The aqueous phase was constituted of Montanox 80® dissolved in demineralized water. The two phases maintained at 30°C in separate reactors and they were continuously supplied by independent peristaltic pumps to a third reactor using "T" mixing system. The diffusion of acetone in aqueous solution provokes the precipitation of polymer around the oil core shell. PCL nanocapsules were immediately formed. The resulting suspension was maintained under a gentle agitation at 30°C for complete diffusion of acetone to the external phase. Acetone and some water were then removed by evaporation under reduced pressure.

The suspension mass content was determined by freeze-drying of 1 ml of the concentrated NC preparation poured into glass vials (pilot freeze-dryer SMH45 Usifroid, France). After complete desiccation, the dry content of the vessel was measured. The results considered were a mean of at least three measurements for each preparation.

The particle size distribution and the zeta potential of the NC were determined in triplicate using a Malvern Zetasizer 3000HSA particle analyzer (Malvern Instruments, UK). The zeta potential measurements were carried out in a 10^{-3} M KCl solution to keep the ionic strength constant.

Spray-drying Nanocapsules

NC suspensions were mixed with colloidal silica before drying. Prior to the mixture, the silica particles were dispersed in demineralized water under magnetic stirring for 10 min. The preparations were thus dried with a Büchi B191 laboratory spray drier (Flawil, Switzerland), having a 0.7-mm nozzle. The atomization air pressure was 5.5 bar. The dried particles were delicately recovered, weighted and stored in a well closed glass vessel at home temperature. Following subtraction of the moisture content in the spray-dried powders, the w/w process yield was calculated by dividing the weight of the spray-dried powder by the amount of dry solids and NC fed to the spray dryer.

Spray-dried Powders Characterization

Moisture Content

The residual moisture content of the spray-dried powders was measured by Karl Fischer titration in dry methanol using a DL38 titrator (Mettler-Toledo, Greifensee, Switzerland). Sample masses were approximately 30 mg

and Hydranal® composite 5 (Riedel-de Haën) was used as the titration reagent. Measurements were performed in triplicate.

Morphological Analysis

Scanning electron microscopy (SEM) images were obtained for all of the spray-dried powders to examine their morphology (Hitachi S800, Japan). The powder sample was spread on a double-adhesive tape previously adhered to SEM aluminium stubs, and then sputter coated with a thin gold/palladium layer using a cathodic pulverizer, Hummer II Technics (6 V–10 mA). The samples were scanned at 10 kV voltage.

Particles Size Distribution

The volume particle size distribution of the spray-dried powders was determined using a laser diffraction granulometer, Mastersizer 2000 (Malvern Instruments, United Kingdom). The apparatus was equipped with a dry analyzer system to suspend particles in the air during measurements. Samples were placed into a vibrant hopper and a 2-bar air pressure was used to disperse particles in a venturi tube before their passage through the laser light to be analyzed. Analyzes were performed in triplicate and the particle size was given as the $D_{(v,0.5)}$ i.e., the particle diameter at 50% of the volume distribution.

Density Determination

The particulate density of the spray-dried powders was analyzed in duplicate by helium pycnometry, AccuPyc 1330 pycnometer (Micromeritic Ltd., UK). For one determination each sample was measured ten times after 30 purges. An equilibration rate of 0.0345 kPag/min was chosen, and the maximum measurement pressure was 134.45 kPa.

Experimental Designs

In order to prepare powders of interest containing NC, the effects of both formulation and operational parameters on the process outcomes and the powders characteristics were investigated by experimental designs (19). The independent variables examined and the two levels attributed were NC concentration (1 or 4% w/v), silica concentration (1.5 or 3% w/v), spray flow rate (600 or 700 l/h), feed flow rate (2.41 or 3.63 ml/min), drying air temperature (140 or 160°C), drying air flow rate expressed as aspiration capacity setting (70 or 100%). Concentrations values were chosen in accordance with the preceding work (17), and process high- and low-incremented values depending on the different critical points permitting a suitable atomization of the fluid and the particles separation after drying. Furthermore, the conditions leading to excessive condensation in the drying chamber, large sticking on the drying cylinder wall or droplets lost at the bottom of this chamber were excluded. The responses considered were outlet temperature, residual moisture content, process yield, particle size, particulate density, particles morphology and powder behavior.

A screening design was initially implemented to determine the most important parameters among the six factors affecting the responses considered and thus optimizing the number of experiments (19). To this end, a total of only eight experiments were conducted for factors with two levels, and structured according to Plackett and Burman. The experimental design is shown in Table I. In a second step, a 2^4 full factorial design scheme where 4 corresponds to 4 more important independent variables retained among the six, and 2 to the number of levels for each factor, was performed and constituted 16 of the experiments presented in Table II. Two center-points (runs 17–18) were added for testing the model's predictive abilities. To allow construction of more efficient models for prediction, a composite design was conducted with eight other experiments (runs 19–26) were added (Table II) to the factorial experimental design (19).

Statistical analyses were performed using the Nemrodw software (LPRAI, Marseille—France). Experimental designs resulted in a mathematical expression like: $y = k + ax1 + bx2 + cx3 + \ldots + lx1x2 + mx1x3 + nx2x3 + \ldots$, in which y is the dependent variable evaluated; k is a constant representing the mean of the dependent variable obtained in each experiment; $x1$, $x2$, $x3$,... are the independent coded level of variables; $x1x2$, $x1x3$, $x2x3$, are the interaction terms and a, b, c,...l, m, n,... are the coefficients. This equation allows the description of any response as the sum of an intercept and the product of the coded inputs and their fitted parameter estimates. Therefore, a positive parameter indicates that the output increases with increasing input variables. Conversely, the output decreases with increasing input when the parameter estimate is negative. Graphs showing the magnitude of effects for each variable and interactions were also generated for analysis.

RESULTS AND DISCUSSION

NC suspensions prepared were sub-micronic size (280 ± 16 nm) and presented negative charges at their surface according to the zeta potential (-31 ± 2 mV). This negative charge is due to the carboxylic group at the end of the PCL chains. NC possess a fundamental advantage compared to other nanoparticulate drug delivery systems residing in the fact that the active pharmaceutical ingredients are incorporated in the oil core, leading to a high drug/polymer ratio (20). However, they present a structure fragility due to the potential bursting of the polymeric film which is relatively thin.

In the literature, it has been demonstrated that spray-drying of NC suspension without adjuvant was not possible due to the strong adhesion of the product on the spray-drier walls (8). Hydrophilic colloidal silicon dioxide is widely used in pharmaceuticals (21). Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders. Furthermore, it possesses a good thermal conductivity (21). From these characteristics, it is not surprising that this material was used with success in nanoparticles spray-drying attempts as drying auxiliary (8,22). It was also possible to achieve independent microparticles exhibiting interesting flow properties especially without adhesiveness, related to the NC exclusion from their external surface (17).

Table I. The Screening Experimental Design Input and Output Results

	Input Values						Output Values						
Run	1 T_{inlet} (°C)	2 Feed flow (%)[a]	3 Atom. air (l/h)	4 Asp. set. (%)	5 NC (w/v%)	6 SiO_2 (w/v%)	T_{outlet} (°C)	Yield (%)	Mois. cont. (%)	Particulate density (g/ml)	$D_{(v,0.5)}$ (μm)	Morphology[b]	Adhesiveness[c]
1	160	15	700	70	4	1.5	93	76.1	1.7	1.2293	4.479	II	+++
2	140	15	700	100	1	3	91	78.8	1.74	1.8536	3.888	I	−
3	140	15	600	100	4	1.5	91	79.3	2.28	1.2068	6.855	II	+++
4	160	10	600	100	4	3	111	83.9	2.14	1.3610	5.407	I	−
5	140	10	700	70	4	3	87	80.1	2.35	1.3618	4.211	I	−
6	160	15	600	70	1	3	98	68.3	3.5	1.8272	4.574	I	−
7	160	10	700	100	1	1.5	108	73.4	1.85	1.7518	3.189	I	−
8	140	10	600	70	1	1.5	90	68.3	2.2	1.9001	4.650	I	−

T_{inlet} Inlet temperature, *Atom.* atomising, *Asp. set.* aspirator setting, *NC* nanocapsules, T_{outlet} outlet temperature, *Mois. cont.* moisture content, $D_{(v,0.5)}$ volume median diameter

[a] Feed flow rate: 10%=2.41 ml/min, 15%=3.63 ml/min

[b] Categories for particle morphology: I=separated microparticles, II=fused-agglomerated particles.

[c] Adhesiveness to cyclone and collector walls: − non adhesive particles, +++ adhesive powders.

Table II. Matrix of Experiments and the Results of the Factorial (1 to 16) and Composite (1 to 26) Designs

	Input Values				Output Values						
Run	Atom. air (l/h)	Asp. set. (%)	NC (w/v%)	SiO_2 (w/v%)	T_{outlet} (°C)	Yield (%)	Mois. cont. (%)	Particulate density (g/ml)	$D_{(v,0.5)}$ (μm)	Morphology[a]	Adhesiveness[b]
1	600	70	1.00	1.50	84	77.7	0.99	1.9001	5.099	I	−
2	700	70	1.00	1.50	85	70.9	0.91	1.6248	3.615	I	−
3	600	100	1.00	1.50	93	75	1.02	1.5979	4.744	I	−
4	700	100	1.00	1.50	91	75.3	1.16	1.6299	4.174	I	−
5	600	70	4.00	1.50	82	78	0.79	1.1809	13.363	II	+++
6	700	70	4.00	1.50	84	81.9	0.99	1.2020	10.407	II	+++
7	600	100	4.00	1.50	91	76	1.01	1.2039	11.408	II	+++
8	700	100	4.00	1.50	91	85.1	1.04	1.1847	13.243	II	+++
9	600	70	1.00	3.00	86	81.4	1.09	1.7669	5.126	I	−
10	700	70	1.00	3.00	86	73.1	1.16	1.8473	5.540	I	−
11	600	100	1.00	3.00	96	80.6	0.96	1.7602	5.128	I	−
12	700	100	1.00	3.00	93	78.5	1.05	1.8490	4.645	I	−
13	600	70	4.00	3.00	90	74.4	0.94	1.3686	5.992	I	−
14	700	70	4.00	3.00	83	88.1	0.99	1.3618	5.339	I	−
15	600	100	4.00	3.00	92	87.2	0.99	1.3308	6.686	I	−
16	700	100	4.00	3.00	95	89.5	0.99	1.3116	4.975	I	−
17	650	85	2.5	2.25	92	88.5	0.90	1.4161	5.051	I	−
18	650	85	2.5	2.25	90	90.7	1.05	1.3916	5.126	I	−
19	600	85	2.5	2.25	92	81.0	0.53	1.3799	5.905	I	−
20	700	85	2.5	2.25	90	87.7	1.01	1.3737	3.800	I	−
21	650	70	2.5	2.25	86	84.8	0.97	1.3779	5.150	I	−
22	650	100	2.5	2.25	94	88.5	1.00	1.3762	4.225	I	−
23	650	85	1.0	2.25	89	79.4	1.00	1.6417	4.941	I	−
24	650	85	4.0	2.25	88	87.5	0.52	1.2574	4.553	I	+
25	650	85	2.5	1.50	91	83.5	0.97	1.2915	4.731	I	+
26	650	85	2.5	3.00	90	81.8	1.00	1.4514	5.840	I	−

T_{inlet} Inlet temperature, *Liq.* liquid, *Atom.* atomising, *Asp. set.* aspirator setting, *NC* nanocapsules, T_{outlet} outlet temperature, *Mois. cont.* moisture content, $D_{(v,0.5)}$ volume median diameter

[a] Categories for particle morphology: I=separated microparticles, II=fused-agglomerated particles.

[b] Adhesiveness to cyclone and collector walls: − non adhesive particles, + slight adhesion, +++ adhesive powders.

Table III. The Regression Coefficients Linking the Screening Design Responses to the Experimental Factors

Coefficient[a]	Outputs				
	Outlet Temperature	Yield	Moisture Content	Particulate Density	Particle Size
b0	96.125	76.025	2.220	1.562	4.657
b1, inlet temperature	6.375*	−0.600	0.078	−0.019	−0.244
b2, spray flow rate	−1.375*	1.075	−0.310	−0.012	−0.715*
b3, liquid feed rate	−2.875*	−0.400	0.085	−0.032	0.292
b4, aspirator setting	4.125*	2.825*	−0.218	−0.018	0.178
b5, NC concentration	−0.625	3.825*	−0.103	−0.272*	0.581*
b6, SiO_2 concentration	0.625	1.750	0.213	0.039	−0.137

*Probability <5% using residual standard deviation
[a] Calculated with all input values of Table I coded within −1 and +1

Spray-dried NC particles containing silica are suitable for oral administration. The ability of spray-dried polymeric NC in presenting similar properties than the original suspensions was evaluated by Guterres *et al.* (23). Following a repeated oral administration of diclofenac-loaded spray-dried NC dispersed in water to rats, the authors observed a protective effect on gastro-intestinal tissue. Diclofenac-loaded spray-dried nanocapsules were also valuable for reducing the gastro-intestinal irritant effect of diclofenac as the original NC suspensions.

On the other hand, spray-dried NC are known to be stable preparations. Applying the spray-drying technique using silica as adjuvant, Pohlmann *et al.* obtained a powder from indomethacin-loaded poly(ε-caprolactone) nanocapsules which presented stable drug recovery and morphological characteristics after 5 months of storage at room temperature (22).

In this study, spray-drying is employed to achieve solid dried particles containing NC with the aim to overcome the aqueous suspensions disadvantages. The variables examined, were NC concentration, silica concentration, spray flow rate, feed flow rate, drying air temperature and drying air flow rate. Determined quantities of NC suspensions were mixed with water-dispersed silica suspensions before spray-drying. In order to investigate the relationship between the different variables and the spray-drying NCoutputs, a three-step study was conducted. To describe how the different variables affected the responses, statistical models were constructed for measurable responses, and powders qualitative characteristics were also analyzed.

Screening Experimental Design

A structured experimental design matrix built in accordance to Plackett and Burman was used to screen the effects of six parameters at their lowest and highest factor levels. Table I presents the input conditions and the resulting output data for the screening experimental runs completed. The responses considered were outlet temperature, residual moisture content, process yield, particle size, particulate density, particles morphology and powder behavior. The experiments were conducted in a random sequence and none of the input behavior of the condition was modified from the original design. The model used to estimate the coefficients for each measurable answer was $y = b0 + b1X1 + b2X2 + b3X3 + b4X4 + b5X5 + b6X6$.

The regression coefficients linking the responses to the experimental factors are indicated in Table III. For each response, the model allows qualitative estimates of the influence of individual variables. Thus, these factors could be classified relative to one another. From Table III, it can be pointed that the inlet temperature and the liquid feed rate have an important effect only for one response, the outlet temperature. As expected, an increasing of the inlet temperature increases the outlet temperature while increasing of the feed flow rate decreases it. Indeed, with more droplets to dry the energy required for water removal increases and air cools off more when passing through to the drying chamber. The residual moisture content in the produced powders varied from 1.7 to 3.5% (Table I). This response is the most commonly quoted specification of a powder product and its value plays an important role for the preparation stability. Since the residual moisture was not sensitive to the inlet temperature and the liquid feed rate, the levels of these variables have been fixed for the continuation of the study at the most favorable values, 140°C and 2.4 ml/min, respectively, for inlet temperature and feed flow rate.

Two experimentations led to the formation of particles sticking on the cyclone and the collector recipient wall. These particles consist on an adhesion powders and the common inputs were 1.5% silica associated to 4% NC (Table I). According to SEM micrographs, fused agglomerated particles presenting irregular shapes were prepared with this formulation. Conversely, non-adhesive powders were obtained with the other formulations and SEM analysis showed separated spherical microparticles (Fig. 1).

Some images revealed the presence of small whitish and non-porous particles among the preparations, and which seemed to be silica aggregates (Fig. 1b). Keep in mind that the silica used in this study is composed of small branched chain submicron sized aggregates, formed by fusion during the preparation by flame hydrolysis (24,25), it was envisaged to check the effective water-dispersed state of silica before adding NC preparations. Thus, the particle size distribution in water after magnetic stirring was measured using the laser diffraction technique. The results showed that silica particles remained in micrometer size primarily, although the colloidal suspension was achieved (Fig. 2). The absence of a smallest particles population could be explained by the great sensitivity of the volume distribution model to largest particles. In addition, the fractal nature of the aggregates is in favor of particle size increase. Magnetic stirring is not sufficient to

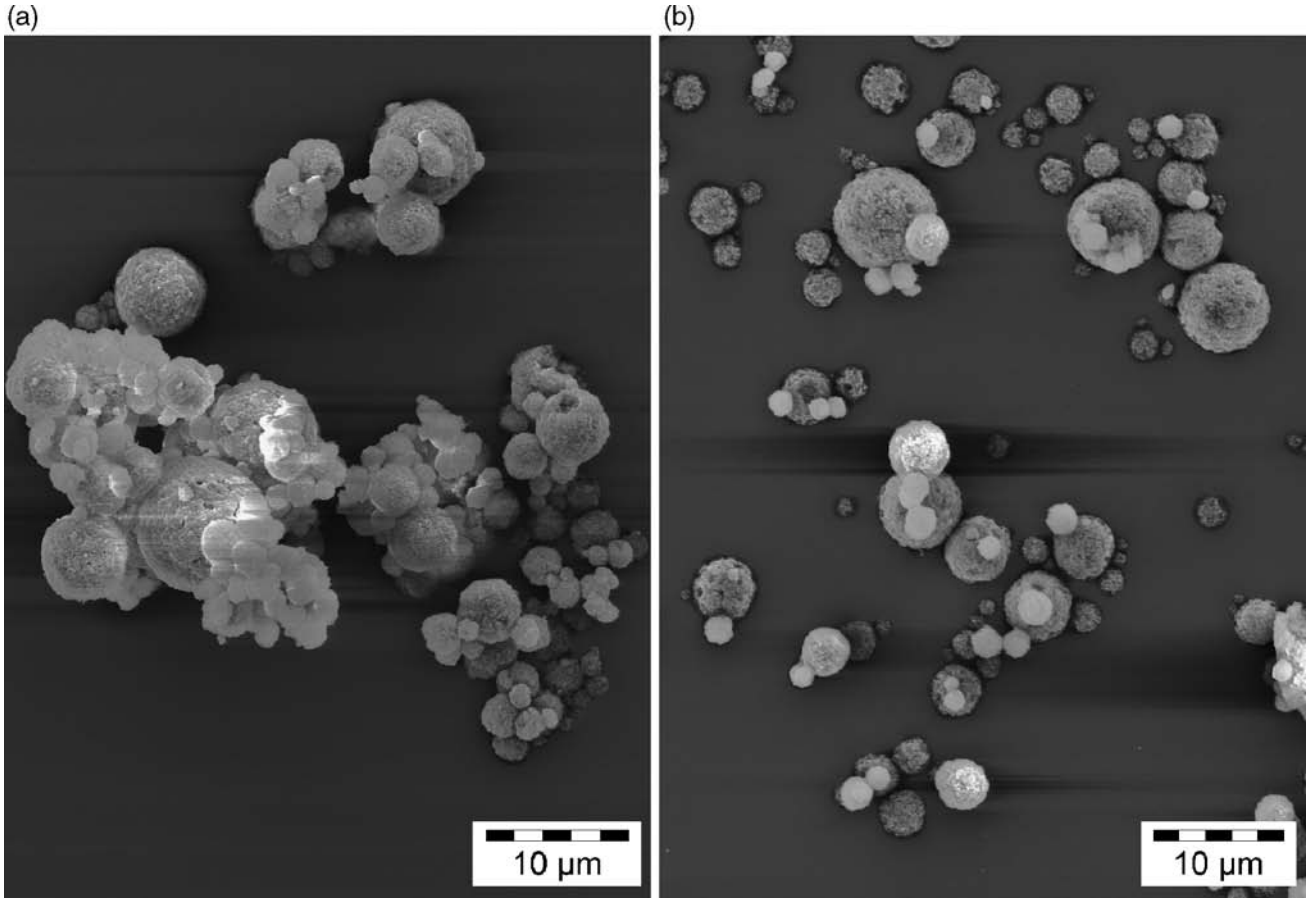

Fig. 1. Visualisation of particle morphology by scanning electron microscopy (*SEM*). **a** NC4%+Silica 1.5% spray-dried powders; **b** NC4%+Silica 3% spray-dried powders (screening design samples).

disperse efficiently colloidal silica in sub-micronic particles and the mix with NC in the feed is not optimised. Following this observation, a new method was considered for the silica dispersion in order to avoid the presence of silica micro-particles in the feed. The silica suspensions obtained under magnetic stirring were thereafter treated in an ultrasounds bath for 5 min (35 KHz), and this protocol resulted in effective sub-micronic particles (Fig. 2). A mechanical agglomeration of the silica aggregates which can be reversed by dispersion was described elsewhere (26). The authors also supported that the aggregates might not be disrupted into primary particles. Nevertheless, in the absence of these last-mentioned particles of 12 nm, a high level of dispersion was achieved following the ultrasonic treatment.

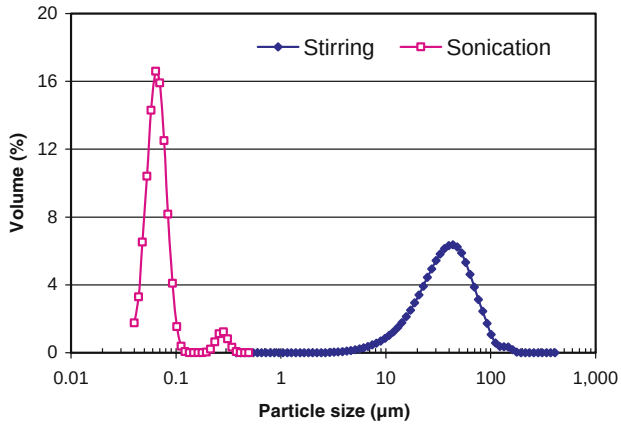

Fig. 2. Comparative volume particle size distributions of water-dispersed colloidal silica after magnetic stirring or ultrasounds treatment (Laser diffraction analysis data, Coulter® LS 230).

The screening design used allows only analyzing the influence of individual variables and it would be difficult to make predictions as to whether the interactions actually existed between the variables and their impact on each response.

Factorial Experimental Design

For the continuation of the study, it was decided to examine all the effects and interactions between the four experimental factors retained (including NC and silica concentrations, spray flow rate and drying air flow rate), using a complete factorial design at two levels (2^4) by preserving the same variation intervals. It resulted in 16 experiments and 2 added runs at the center of the field (Table II) were used to evaluate standard deviation for each response and to validate the model. The regression coefficients (based on the first 16 runs) for each response were carried out according to the following model, $Y = b0 + b1X1 + b2X2 + b3X3 + b4X4 + b12(X1X2) + b13(X1X3) + b23(X2X3) + b14(X1X4) + b24(X2X4) + b34(X3X4) + b123(X1X2X3) + b124(X1X2X4)$

Table IV. The Regression Coefficients Linking the Screening Design Responses to the Experimental Factors and Interactions for the Factorial Design

Coefficient[a]	Outputs				
	Outlet Temperature	Yield	Moisture Content	Particulate Density	Particle Size
b0	88.875	79.530	1.005	1.508	6.843
b1, spray flow rate	−0.375	0.754	0.031	−0.006	−0.351*
b2, aspirator setting	3.875*	1.365	0.023	−0.024	0.033
b3, NC concentration	−0.375	2.976*	−0.038	−0.239*	2.084*
b4, SiO_2 concentration	1.250	2.054	0.016	0.067*	−1.414*
b12	0.125	0.461	0.001	0.016	0.234*
b13	0.125	2.870*	0.004	0.003	−0.085*
b23	−0.125	0.571	0.018	0.014	0.119*
b14	−0.500	−0.050	−0.005	0.024	0.046
b24	0	0.999	−0.046	0.012	−0.103*
b34	0.250	0.218	−0.006	0.008	−1.765*
b123	0.875	−1.223	−0.029	−0.023	0.232*
b124	0.750	−1.103	−0.005	−0.017	−0.479*
b134	−0.250	0.444	−0.018	−0.028	−0.202*
b234	−0.250	0.633	0.019	−0.024	0.034
B1234	0.750	−0.969	0.020	0.020	−0.252*

*Probability <10% using standard deviations calculated with experiments 17–18 of Table II
[a] Calculated with runs 1–16 (Table II) inputs values coded within −1 and +1

+ $b134(X1X3X4)$ + $b234(X2X3X4)$ + $b1234(X1X2X3X4)$. From Table IV, it could be pointed that there was no important interactions occurring between more than two experimental factors, they have been thus neglected. There are few first order interactions among two variables, which were not very prominent for outlet temperature and particulate density responses. Nevertheless for each of the other responses, at least one interaction could be considered.

Outlet Temperature

The range of outlet temperature seen in this study was 82 to 96°C (Table II). The most important factors influencing this temperature were the aspirator setting (drying gas flow rate) and the silica concentration which had positive parameter estimates (Table IV). Specifically, the outlet temperature increased with increasing the aspirator capacity and the silica concentration in the feed. Goula and Adamopoulos found also an increase of outlet temperature with increases of aspirator setting (27). A lower drying air flow rate causes an increase in product residence time in the drying chamber leading to a greater degree of moisture removal and thus outlet temperature diminution.

Yield

The yields obtained ranged from 70 to 90% (w/w). These values gathered as an indication of the process performance. They were essentially influenced by the NC concentration, the silica concentration and the interaction between the NC concentration and the atomising flow. So, the more the feed was concentrated and/or the more was the NC/spray flow rate interaction, the better was the drying process. The increase of the feed solid content may favor the capture of the particles in the cyclone increasing therefore the yield. Moreover, spray-drying of more concentrated samples resulted in the formation of large particles and consequently led to low losses of the lightest particles through the exhaust (27–29).

Spray-drying operation frequently results in unsatisfactory yields because of the difficulties in small size and low weight particles collection. According to some published work involving experimental designs, yields values up to 70% are not current (29–32). In addition, with respect to the mean values (intercepts), yields resulted from factorial design were higher than that from screening design. This observation could be associated to the fact that more homogeneous droplets are formed since the silica dispersion is improved due to the ultrasonic treatment, and leading to a better interaction with NC. It should be noted that fused-agglomerated particles (adhesive powders) with the major proportion of particles being collected from the cyclone also provided satisfactory results with respect to the yield.

Moisture Content

Generally for a drying operation, the lower the moisture content, the better will be considered the product. The values measured for the moisture content were very weak with a low variation (0.8 to 1.2%). These values were substantially lower than those obtained previously (Table I). It was found, within the limitations of the factorial design, that none of the factors tested was responsible for controlling the moisture content. The interaction between the drying air flow rate and the silica concentration is the principal parameter. More is this interaction, lower is the moisture content.

The moisture content is of primary interest for this application and, a residual moisture of about 1% is an indication of a complete drying. The important reduction comparatively to screening results can be attributed in first intention to the formulation modification. Colloidal silicon dioxide is a compound which facilitates drying by its capacity

Table V. Comparison Between the Model Constant and the Average Experimental Results in the Center of the Domain

Coefficient	Outputs				
	Outlet Temperature	Yield	Moisture Content	Particulate Density	Particle Size
b0	88.875	79.530	1.005	1.508	6.843
Average result	91	89.555	0.975	1.404	5.089

to adsorb large amount of water added to its good thermal conductor property (32). By dispersing efficiently the silica aggregates before the mix with NC, a better interaction between the two components is favored leading to more homogenous droplets formation after atomisation. The water removal from the inter-particles (NC and/or silica) space is thus improved and as result the moisture content was decreased significantly.

Particulate Density

The average particulate density of the collected powders was 1.5076 g/cm^3. This response was essentially influenced by the NC concentration which presented a negative parameter estimate. An increase in NC concentration led to a decrease of the particulate density. Within the microparticles, NC were responsible of an effective volume increase by two possible ways, the voids reduction in the dried particles matrix or the formation of non-porous shells following NC fixation at the peripheral of these particles, leading to density decrease.

Colloidal silica is well known as a technical agent in spray-drying for increasing the particles densities (32,33). It should be noted that increasing the silica fraction led to a moderate increase in the density. With a greater content of silica in the formulation, even if more silica is entrapped in the powder matrix this reorganization was not accompanied by a significant volume increase which could be responsible of the particulate density decrease. This result may be in conformity with the preservation of a certain porosity degree within the matrix.

Particle Size

The particle size of spray-dried preparations is a characteristic strongly related to the feed concentration. In general, the particle size increases as the feed concentration

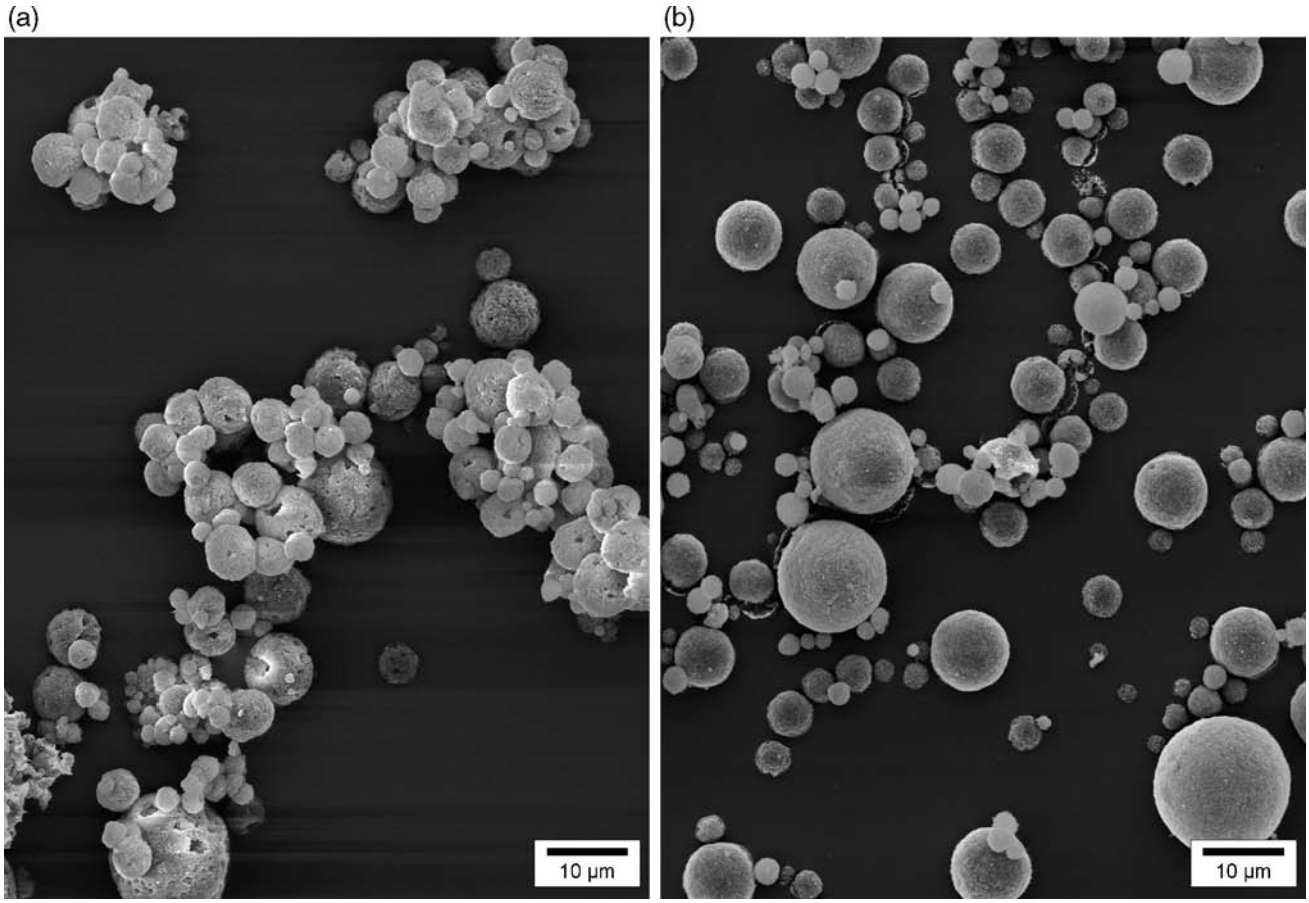

Fig. 3. SEM images of spray-dried particles exhibiting the two categories of particles: **a** fused agglomerated particles obtained with insufficient silica concentration, **b** separated spherical microparticles obtained with suitable silica concentration (factorial design samples).

increases. With low concentrated feeds, less dry substance will be kept in a droplet after atomisation, thus causing the droplet to dry to a smaller particle (34). This observation may account only if it is assumed that one droplet led to one particle. In addition, the presence of different components (NC, silica) in the same feed should be considered.

The particle size varied from 3.6 to 13.4 μm with a mean value of 6.8 μm. For this response, the main variables are the NC and the silica concentrations which had positive and negative regression coefficients, respectively, and their interaction with a negative estimate (Table IV). As it can be drawn from Table II, runs 5 to 8 produced the largest particles (up to 10 μm), and the common input conditions for these runs were low silica concentration associated to high NC concentration. This can be attributed to a combination of events associating the NC fixation at the peripheral of dried microparticles and because primary particles collide with each other, to their aggregation during the last stages of drying following NC fusion (17).

The more is the interaction between NC and silica the lower will be the particle size. The smallest particles size obtained with other formulations are thus related to a suitable interaction between the two components leading to NC exclusion from the microparticles surface and the absence of the later agglomeration of primary particles. Surprisingly, the changes in spray air flow did not affect significantly the particle size as commonly described elsewhere (35). In the limitations of our experimental conditions, the formulation adjustment remains the principal criterion for the particle size control.

The two center-points experiments resulted in important differences between the model constants and the average results (Table V): the calculated model did not always permit to envisage good prediction of responses everywhere in the experimental domain. So, a central composite design was built, and a total of eight other experiments were added to the factorial design (runs 19 to 26 in Table II).

Morphology

From the morphological analysis the formulation variables effects were easily characterized. The obtained powders presented different morphologies depending on the initial concentrations of NC and silica. The spray-dried particles appeared fused-agglomerated presenting irregular shapes with the formulation NC4%+S1.5% whatever the process conditions (Fig. 3a). These preparations are unsuitable for handling and future utilizations as intermediary pharmaceutical powders. With the other formulations separated microparticles presenting spherical shapes were obtained and the threshold of 1.5% silica associated to 1% NC was not modified by varying the process variables (Fig. 3b).

Because the moisture contents are in the same range for all the preparations, the global powder particle shape must be explained by other reasons. Separated microparticles are composed of one or several non-agglomerated NC entrapped in a matrix which presents silica particles at its surface. This silica adsorbed at the microparticles surface allows the prevention of inter-particles from agglomeration or aggregation. It also prevents the adhesion of microparticles on the cyclone and collector walls following NC shell degradation. The irregular shape of the agglomerated particles is explained by a conjunction of the aggregation of primary microparticles following the surface NC degradation, and the subsequent inter-particle adherence supported by the oil core deployment through the particle matrix (17). As expected, we noted the absence of structures similar to colloidal silica with particular contrasts in the SEM micrographs (Fig. 3). This result definitively showed the importance of the formulation variables and their control.

Composite Experimental Design

The centred faces composite design was set up in order to better modeling the responses inside the explored experimental field. For this end, quadratic models of this form were used: $Y = b0 + b1X1 + b2X2 + b3X3 + b4X4 + b11(X1X1) + b22(X2X2)\ b33(X3X3) + b44(X4X4) + b12(X1X2) + b13(X1X3) + b23(X2X3) + b14(X1X4) + b24(X2X4) + b34(X3X4)$.

The coefficients calculation of the particular models preserving only the most statistically significant (probability

Table VI. Coefficients of the Regression Equation Linking the Responses to the Experimental Factors with a Particular Quadratic Model for the Composite Experimental Design

Coefficient[a,*]	Outputs				
	Outlet Temperature	Yield	Moisture Content	Particulate Density	Particle Size
b0	90.63	86.00	0.87	1.38	4.84
b1, spray flow rate			0.05		
b2, aspirator setting	3.89	1.42			
b3, NC concentration		3.09	−0.06	−0.23	1.83
b4, SiO_2 concentration	1.06	1.73		0.07	−1.19
b11					
b22			0.13		
b33					
b44	−1.79	−6.12		0.11	1.83
b13		2.87			
B34					−1.76

*All coefficients have a probability <5% using standard residual deviation.
[a] Calculated with all inputs values of Table II coded within −1 and +1

<5%) terms was carried out for the five responses (Table VI). From this table, one can observe that the spray flow rate is the least influencing factor. As expected, the drying air flow rate affected prominently the outlet temperature. NC concentration and silica concentration were the main factors for the operation yield, particulate density and particle size. In addition, they were concerned for the only significant interactions occurring among two different variables.

These models estimates permitted to find the operating conditions of interest for the responses yield, particulate density and particle size, which could be controlled by adjusting the different variables. In our operational conditions, it was not reasonable to model the moisture content because of its very thin variation. The amelioration observed is related to the feed preparation protocol. It appeared that the preliminary efficient silica dispersion promoted a better interaction between the two components and improved not only the product recovery but also the drying efficiency, according to the residual moisture content. Increasing yield was possible within the range of input conditions tested on the lab-scale spray-dryer.

Regarding the qualitative results, an intermediate behavior could be described. The microscopic analysis showed that only separated microparticles were achieved with these supplementary essays. Nevertheless, a slight adhesion of preparations on the cyclone wall was observed for two experiments (runs 24 and 25, Table II). We have previously shown that the NC exclusion from the surface is needed to achieve separated microparticles (17). With appropriate concentrations of the two components, the NC are covered by the silica particles in the dry state avoiding the microparticles adhesion and aggregation to occur. From this point, the particles adhesion to the cyclone without their massive aggregation also evidenced by the size measurements, is related to a limited protection of the NC at the microparticles surface. The silica concentration is just sufficient to avoid primary particles aggregation but not enough to avoid completely particles adhesion. One can conclude that with 4% NC the silica threshold is 3% and, with 1.5% silica it is not possible to increase the NC proportion to reach a concentration of 2.5% without modifying the powders behavior.

CONCLUSION

In this study, experimental designs have been used in order to investigate the effects of formulation and process variables on the resulting powders characteristics. Within the studied experimental conditions, it has been found that the absence of strong interaction contributions on the quantitative results and a better interaction between NC and silica in the feed is determinant on both of qualitative and quantitative responses. As described above, with a well controlled process variables and formulation parameters, powders of interest as intermediary pharmaceutical powder convenient for handling and future manipulations have been prepared. The optimization of the process resulted in a considerable improvement of spray-dried product yield, while minimizing the moisture content and conferring better appearance to microparticles. Producing spray-dried microparticles containing NC with controlled characteristics is a mean to promote the development of this application.

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