Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 325 (2006) 63–74
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Spray-dried microparticles containing polymeric nanocapsules: Formulation aspects, liquid phase interactions and particles characteristics

Patrice Tewa-Tagne[a,b], Stéphanie Briançon[a,b,*], Hatem Fessi[a,b]

[a] *Laboratoire de Génie Pharmacotechnique et Biogalénique, ISPB Faculté de Pharmacie (UCB Lyon I), 8, avenue Rockefeller, 69373 Lyon Cedex 08, France*

[b] *Laboratoire d'Automatique et de Génie des Procédés (UMR CNRS-UCB Lyon I - 5007), 43, boulevard du 11 novembre 1918, 69622 Villeurbanne Cedex, France*

Received 18 January 2006; received in revised form 9 June 2006; accepted 17 June 2006
Available online 23 June 2006

Abstract

Up to now, the full potential of polymer-based nanoparticles is not yet exploited because of a lack of stability when conserved in aqueous medium. The present paper reports the water elimination from nanocapsules (NC) dispersions by means of the spray-drying technique with the aim to achieve dried solid forms of interest using colloidal silicon dioxide as drying auxiliary. The influence of formulation parameters on the suspension behaviour and on the powders characteristics was also evaluated. Our findings demonstrated that the mixing protocol, the concentrations of both NC and silica are crucial parameters that affect the feed behaviour and the spray-dried particles characteristics. Interactions occurring in the feed are directed by hydrogen bounds and were more sensitive to the silica concentration than that of NC as evidenced by rheological measurements. The NC are entrapped within solid dried matrixes following their interaction with silica particles in the feed. SEM analyses of the obtained powders showed spherical separated microparticles formed by the association of NC and silica when they are mixed at adequate concentrations in the feed before spray-drying. On the other hand, fused agglomerated particles presenting NC at their surface, characterised by irregular shapes and a strong adhesiveness were prepared when the silica concentration was not sufficient. The surface composition of the spray-dried powders was investigated using the ESCA technique and revealed the NC exclusion from the surface to obtain powders suitable for further handling.

Keywords: Nanocapsules; Formulation; Feed rheology; Spray-drying; Microparticles

1. Introduction

Modern drug carrier systems favour the controlled delivery of one active pharmaceutical ingredient to its target at a therapeutically optimal rate and dose. Among various systems developed, the polymer-based nanoparticles (NP), which are colloidal systems with sub-micronic size, have been widely studied and consist in nanocapsules and nanospheres. According to the literature, the nanocapsules (NC) correspond to a polymeric wall enveloping an oil core whereas the nanospheres (NS) consist in a polymeric matrix entrapping the drug (Couvreur et al., 1995). Colloidal particles have been developed firstly for the intra venous administration of drugs with the goal to improve their therapeutic efficacy and minimise side effects. Thereafter, they have been also administered orally either for systemic uptake or local residence within the gastrointestinal tract (Maincent et al., 1986; Damgé et al., 1987; Kreuter, 1994; Kim et al., 1997).

However, in spite of their initial promising results, the potential of these new systems become limited following the observation that NP present a lack of stability when conserved in aqueous medium. Indeed, during storage aqueous suspensions of these colloidal particles present some disadvantages such as polymer hydrolysis leading to drug leakage and physicochemical instability due to the particle agglomeration and sedimentation (Magenheim and Benita, 1991). Therefore the application of an effective technique or principle capable to enhance the shelf life of these particles will be a considerable benefit.

In order to overcome the difficulties described above, efforts to develop more stable NP preparations have been continuous for many years. Initially it was envisaged to vary the formulation of the preparation, essentially the type and the concentration of surfactants, but this often gave good results

---

[*] Corresponding author. Tel.: +33 4 72 43 18 64; fax: +33 4 72 43 16 99.
E-mail address: briancon@lagep.univ-lyon1.fr (S. Briançon).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.06.025

only in the short-term stability (Mosqueira et al., 2000). The incorporation of the colloidal particles into solid dosage forms was also investigated and resulted in phase separation for many NP/binders systems after the addition of polymeric binders to the aqueous dispersions of NP (Schmidt and Bodmeier, 1999).

Among the strategies assayed, the water elimination from the aqueous dispersions to reach a dried form appears the most promising approach to achieve preparations with shelf life of several years. This could be achieved by lyophilization or spray-drying, after what for parenteral delivery the suspension of colloidal particles must be reconstituted prior to administration and for peroral delivery the dry powder could be incorporated into capsules or tablets (Allémann et al., 1993). The lyophilization process is more convenient when particles concerned are NS. For NC it is accompanied by technological difficulties like the selection of cryoprotectors and the particle integrity maintain during the freezing step (Chasteigner et al., 1995). Their vesicular character confers a high tendency to collapse and as result the oil core releases. Moreover, it is a high cost and long time process. Alternatively, the spray-drying technique, which consists in one continuous operation involving the transformation of feeds from a liquid state into a dried particulate form, exhibits advantages like low price, rapid process and the possibility to modulate the physicochemical characteristics of powders (Broadhead et al., 1992). Four determining stages constitute the process: (1) atomisation of the feed into a spray, (2) spray-air contact, (3) drying of the spray and (4) separation of the dried product from the drying gas (Master, 1991). This technique has been extensively applied with success in the preparation of microparticulate delivery systems by drying solutions of different compositions (Bodmeier and Chen, 1988; Conte et al., 1994; Giunchedi et al., 1994; Palmieri et al., 2001). In addition, it is convenient for the treatment of heat-sensitive molecules like proteins without significant degradation (Adler et al., 2000).

These accumulated experimental applications let foresee that spray-drying could be a potential process able to permit the storage of colloidal particles as dried powders. Although spray-drying is widely used in the pharmaceutical field, it has been used scarcely for drying polymeric NP. The first application of the technique for drying NC suspension is very recent (Müller et al., 2000). By adding colloidal silicon dioxide as drying adjuvant to the NP suspension, spray-drying NC was achieved. According to the morphological analysis of the powders by scanning electron microscopy, the authors suggested that NC accumulate at the peripheral of the particles formed due to their adsorption on the silica particle's surface (Müller et al., 2000; Pohlmann et al., 2002). However the explanation of the interactions between the two components in the feed preparation and during the drying step is still not enlightened. More, the entire characterization of the dried NP powders is still an open question that deserves much work. Since the powders prepared are intended to be intermediary pharmaceutical products, their current use requires the total control of the particles characteristics for further handling and incorporation in other pharmaceutical forms. To date, colloidal silica interactions with NP in the aqueous phase have not been investigated. Indeed several factors have to be considered, the concentrations of the two components, the NP nature and their particle size, the drying adjuvant properties and the procedure of the feed preparation.

The objective of the present work was to prepare well-designed powders in the form of microparticles containing polymeric blank NC by means of the spray-drying process, using colloidal silicon dioxide as drying auxiliary. Considering the lack of information about the interactions developed in the aqueous phase between NC and colloidal silica, the influence of formulation parameters on the NC suspension behaviour and on the powders characteristics was also evaluated.

2. Material and methods

2.1. Materials

Poly(epsilon-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). 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). All other chemicals and solvents used were of analytical grade.

2.2. Nanocapsules preparation and characterisation

2.2.1. Preparation of nanocapsules

Blank NC were prepared by interfacial deposition of PCL following solvent displacement, method described elsewhere (Fessi et al., 1988). A pilot design which allows an extrapolation of 30 folds the scale of the laboratory was used for this end. This scale-up was performed using a continuous method previously described (Briançon et al., 1999).

The organic phase was constituted by PCL, montane 60®, miglyol 810® and acetone. The aqueous phase was constituted of Montanox 80® dissolved in demineralised water. The two solutions maintained at 30 °C with a bath, were continuously supplied by independent peristaltic pumps to a "T" system for mixing and immediate formation of NC. The resulting suspension was received in a reactor and 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.

2.2.2. Characterisation of nanocapsules

The particle size distribution and the zeta potential of the NC were determined in triplicate, respectively, by photon correlation spectroscopy and electrophoretic mobility using a Malvern Zetasizer 3000HSA particle analyser (Malvern Instruments, UK). The zeta potential values were calculated from the mean electrophoretic mobility values using the Smoluchowsky's equation and the measurements were carried out in a 10^{-3} M KCl solution to keep the ionic strength constant. To check the stability of the NC, preparations samples were washed with demineralised

Table 1
Operational conditions applied with Büchi B191 for the spray-drying of nanocapsules

Spray-drying parameters	Operational conditions
Atomizing air pressure (bar)	5.5
Air flow rate (l/h)	600
Feed flow rate (ml/min)	2.41
Inlet air temperature (°C)	160
Aspiration setting (%)	70

water after ultracentrifugation 20 min at 40 000 rpm (Optima TM MAX-E, Beckman/Coulter, USA) then the particle size and the zeta potential were measured.

2.2.3. Determination of the suspensions mass content

One millilitre of the concentrated NC suspension was poured into glass vials and lyophilised using a pilot freeze-dryer SMH45 (Usifroid, France). After complete desiccation, the dry content of the vessel was measured. The considered results were a mean of at least three measurements for each preparation.

2.3. Spray-drying nanocapsules

Spray-drying was performed with a Mini Spray-dryer Büchi B191 (Flawil, Switzerland), which operates in a co-current mode and was equipped with a two-fluids nozzle. A 0.7 mm diameter nozzle was used. The applied operational spray-drying parameters used are listed in Table 1. A precise volume of NC suspension according to the suspension mass content, was measured and mixed to a beforehand dispersed colloidal silica in demineralised water by magnetic stirring for 10 min. The mixture volume was then adjusted to the desired final volume with additional water. The preparation was thus maintained in moderate agitation and fed into the spray-dryer with the peristaltic pump. The dried powders were delicately recovered, weighed and stored in a well closed glass vessel at home temperature. Aqueous suspensions of colloidal silica were also spray-dried in the same conditions as controls.

2.4. Rheology studies

Dynamic rheological measurements of silica suspensions and mixed NC/silica suspensions were conducted using a controlled shear-rate rheometer, Rheomat 180 (ProRheo, Germany). The measurements were made in simple shearing by imposing a given gradient of shearing while following the constraints in the course of time, using the coaxial cylinders type configuration (cup of measurement with 16.24 mm radius, measurement mobile with 15 mm radius and 45 mm height). All experiments were carried out at ambient temperature (23 ± 2 °C). For each preparation, the shear rate range was function of the measurement system limits and the measured torque, which must be above the sensitivity of the instrument. Experiments were carried out in duplicate with at least two batches for each formulation to make sure that the observed phenomena are real rheological effects and not experimental artefacts.

2.5. Spray-dried powders characterisation

2.5.1. 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.

2.5.2. Process yield determination

The weights of the spray-dried powders collected were corrected according to their moisture content. The yield was calculated by dividing these quantities by the total mass introduced in the preparation submitted to drying.

2.5.3. Morphological analysis

The morphological examination of the spray-dried powders was performed by scanning electron microscopy (SEM) (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.

2.5.4. Particles size distribution

The volume particle size distribution of the spray-dried powders was determined using a laser diffraction granulometer, Mastersizer 2000 (Malvern Instruments, UK). The apparatus was equipped with a dry analyser 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 analysed. The particles whole size distribution was considered preferentially to the different particle diameter values, and analyses were performed at least in duplicate for each batch.

2.5.5. Density determination

The powder bulk (D_0) and tapped (D_f) densities were determined (European Pharmacopoeia, 2005) in duplicate using an automatic tapper (Stampsvolumenometer STAV 2003) with a graduated 100:1 ml cylinder to measure the volume occupied by 3 g of powder. Each powder sample was poured into the cylinder through a funnel. The tape density was measured after 1250 taps, which allowed the density to plateau. Carr index as a measure of flowability was determined according to the equation reported by Staniforth: $\% \text{ compressibility} = 100(D_\mathrm{f} - D_0)/D_\mathrm{f}$ (Staniforth, 1988).

The particulate density of the spray-dried powders was analysed in duplicate by helium pycnometry, with the AccuPyc 1330 pycnometer (Micromeritic Ltd., UK). For one determination each sample was measured 10 times after 30 purges. An equilibration rate of 0.0345 kPa g/min was chosen, and the maximum measurement pressure was 134.45 kPa.

2.5.6. *Surface powders characterisation*

The surface coverage of the spray-dried NC powders was analysed by electron spectroscopy for chemical analysis (ESCA). Using this technique, it is possible to identify quantitatively the chemical elements presents at the surface of dried particles. Briefly, the powders samples are exposed to an X-ray beam, and electrons contained in the near-surface region (approximately 10 nm) that have a binding energy less than the photon energy will be ejected from the atom. The kinetic energy of the ejected electrons will be equal to the difference between photon energy and binding energy, allowing for an instrument response function. As the binding energy of electron is characteristic of the atom from which it is ejected, the elements present in the specimen can be identified quantitatively (Fäldt et al., 1993).

A photoelectron spectrometer ESCALAB 200R (VG Scientific Co., UK) with a monochromatic Al Kα X-ray source (1486.6 eV) was used and the samples were fixed on an indium support. The area analysed consisted of a circular region of 1 mm^2 and the kinetic energy of the heart electrons coming from the first atomic layers of the solids is measured through hemispherical analyser with an energy of analysis of 50 eV. The results were expressed as spectrums of counts/s at the detector versus binding energy, and the surface atomic concentrations of the elements carbon (C), oxygen (O), and silicon (Si) were calculated.

3. Results

3.1. *Nanocapsules preparation*

Table 2 presents the mean values of particle sizes and zeta potentials of the preparations as used and after washing operations. NC preparations consisted in homogenous populations of particles with acceptable diameters (below 300 nm), exhibiting a negative charge regarding zeta potential (−27.9 mV). The particle sizes and their zeta potential were not affected after one and two washing operations with demineralised water.

3.2. *Suspensions rheology*

The viscosities of different silica suspensions are presented in Fig. 1. For these preparations containing only silica, it is evident that the viscosity is function of the silica concentration. The suspension containing 1.5% silica is the least viscous and the measurement could be performed only at high shearing-rate. The increase in silica proportion leads to an increase in the consistency of the suspension and thus the minimal shearing-rate to obtain valid measurements decreases. Suspension containing 10% silica exhibits a shear-thinning at low shearing-rates preceding a plateau profile. This plateau profile occurs moreover at high shearing-rate for all preparations and, no destabilising effect was observed in the measurement field applied.

Table 2
Characteristics of PCL nanocapsules as obtained (1), after one washing (2) and after two washings (3) ($n = 3$)

Preparation	Particle size (nm) ± S.D.	Zeta potential (mV) ± S.D.
NC (1)	285.2 ± 10.1	−27.9 ± 1.0
NC1 washing (2)	281.2 ± 2.2	−32.6 ± 1.5
NC2 washing (3)	271.8 ± 1.5	−29.7 ± 0.2

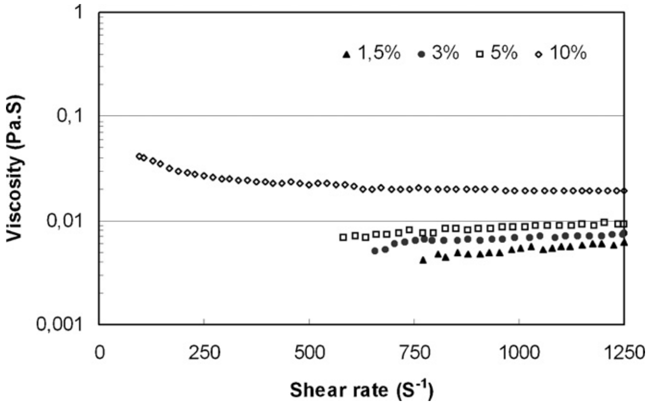

Fig. 1. Data for suspensions in water containing different concentrations of colloidal silica (% w/v). Viscosity is plotted as a function of shear rate.

The association of NC and silica leads to particular profiles as shown in Fig. 2a–c. With 1.5% silica concentration, the presence and the increase in NC proportion did not change the rheological profile although a slight increase in the shear rate range (Fig. 2a). Oppositely, a dramatical change characterised by a significant increase in viscosity is observed when using 3% silica and NC yielding in profiles similar to that obtained with 10% silica suspension, presenting a shear-thinning at low shearing-rate followed by a plateau profile (Fig. 2b). The increase in viscosity of the mixed preparations is more sensitive to silica concentration compared to that of NC and, is proportional to the silica content (Fig. 2c). These findings support the hypothesis of interactions between the two components leading to a new microstructure organisation.

3.3. *Spray-drying nanocapsules*

Table 3 presents different feed formulations spray-dried, outlet temperatures recorded and primary powders characteristics. With 1% NC in the preparation, the minimal silica concentration required to produce powders was 1.5% (sample 1). Below this proportion, NC strongly adhere leading to film formation on the cyclone wall and no powder is formed. With this 1.5% silica concentration or beyond that, the adhesion on the cyclone glass is counteracted and powders are accumulated in the collector vessel. When the NC proportion in the feed was increased dramatically at low silica concentration, the powders prepared primarily accumulated on the cyclone wall (sample 5). This adhesiveness is cured by increasing silica concentration (sample 6). These results show the importance of the two components quantities control in the feed submitted to spray-drying process. The outlet temperatures recorded were all around 100 °C and the collected spray-dried powders presented moisture contents in the same range, between 2.1 and 2.5%. These mixed spray-dried powders were recovered with 60–70% yield. The increase in silica proportion is not always accompanied by the same tendency in the yield. The upper yield was obtained with

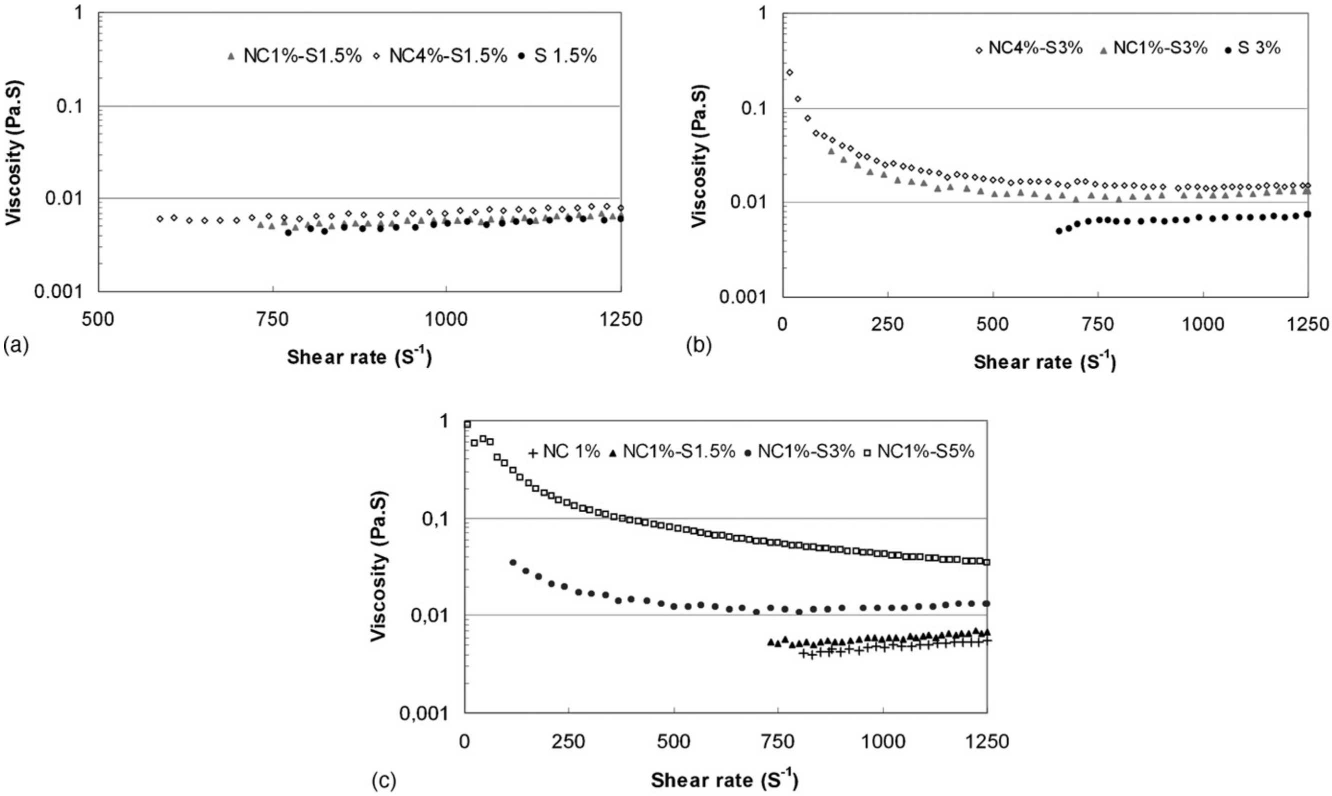

Fig. 2. Effect of the NC and silica concentrations on the rheology of mixed suspensions. (a) Influence of the NC concentration added to 1.5% silica; (b) influence of the NC concentration added to 3% silica; (c) influence of the silica concentration mixed with 1% NC.

3% silica formulations (both NC1 and 4%) and the lower with NC1% + S5% formulation.

As comparison, spray-drying colloidal silica was realised with three different concentrations (samples 7–9). The powders prepared were accumulated in the collector vessel without adhesion on the cyclone wall, and no difference was observed in terms of outlet temperature and moisture content. However increasing concentration led to the increase in the operation's yield.

3.4. Spray-dried powders characterisation

3.4.1. Morphological analysis

The shape and the surface morphology of spray-dried powders are presented in Fig. 3a–d. According to this SEM analysis, the morphology of the spray-dried particles is strongly dependent on both NC and silica concentrations. Spherical well-separated microparticles of various sizes were obtained with a mixture containing NC1% + S1.5% (Fig. 3a). The surface of particles appears rough with a porous shell consisting in silica particles. When the silica proportion varies from 1.5% to 3%, no change on the external morphology is observed (Fig. 3b). On the other hand, fused agglomerated particles with irregular shapes constituted by primary spherical particles were obtained with preparations containing NC4% + S1.5% (Fig. 3c). The primary particles are varied sizes and present at their rougher surface structures of about 300 nm and some cavities. The increase in silica concentration (NC4% + S3%) leads to well-separated particles with a porous external shape (Fig. 3d).

Table 3
Feed preparations spray-dried, outlet temperatures recorded and recovered powders characteristics

Samples	Preparation content (% w/v)		Outlet temperature (°C)	Moisture content (%)	Yield (%)	Powder adhesion[a]
	Nanocapsules	Silica				
1	1.0	1.5	103 ± 3	2.20 ± 0.10	68.3 ± 0.5	+
2	1.0	2.0	103 ± 2	2.32 ± 0.41	63.2 ± 0.9	−
3	1.0	3.0	104 ± 1	2.49 ± 0.38	69.5 ± 1.2	−
4	1.0	5.0	102 ± 2	2.36 ± 0.49	62.5 ± 2.0	−
5	4.0	1.5	98 ± 2	2.28 ± 0.29	65.9 ± 1.7	++++
6	4.0	3.0	101 ± 3	2.14 ± 0.24	72,3 ± 0.9	−
7	0	1.5	100 ± 2	2.25 ± 0.19	60.4 ± 1.9	−
8	0	3.0	99 ± 1	2.41 ± 0.12	71.8 ± 0.7	−
9	0	5.0	101 ± 1	2.34 ± 0.25	76.8 ± 4.1	−

[a] Adhesion to cyclone and receptacle glass walls: (−) no adhered powders, (+) very slight adhesion, (++++) intensive adhesion ($n = 3$).

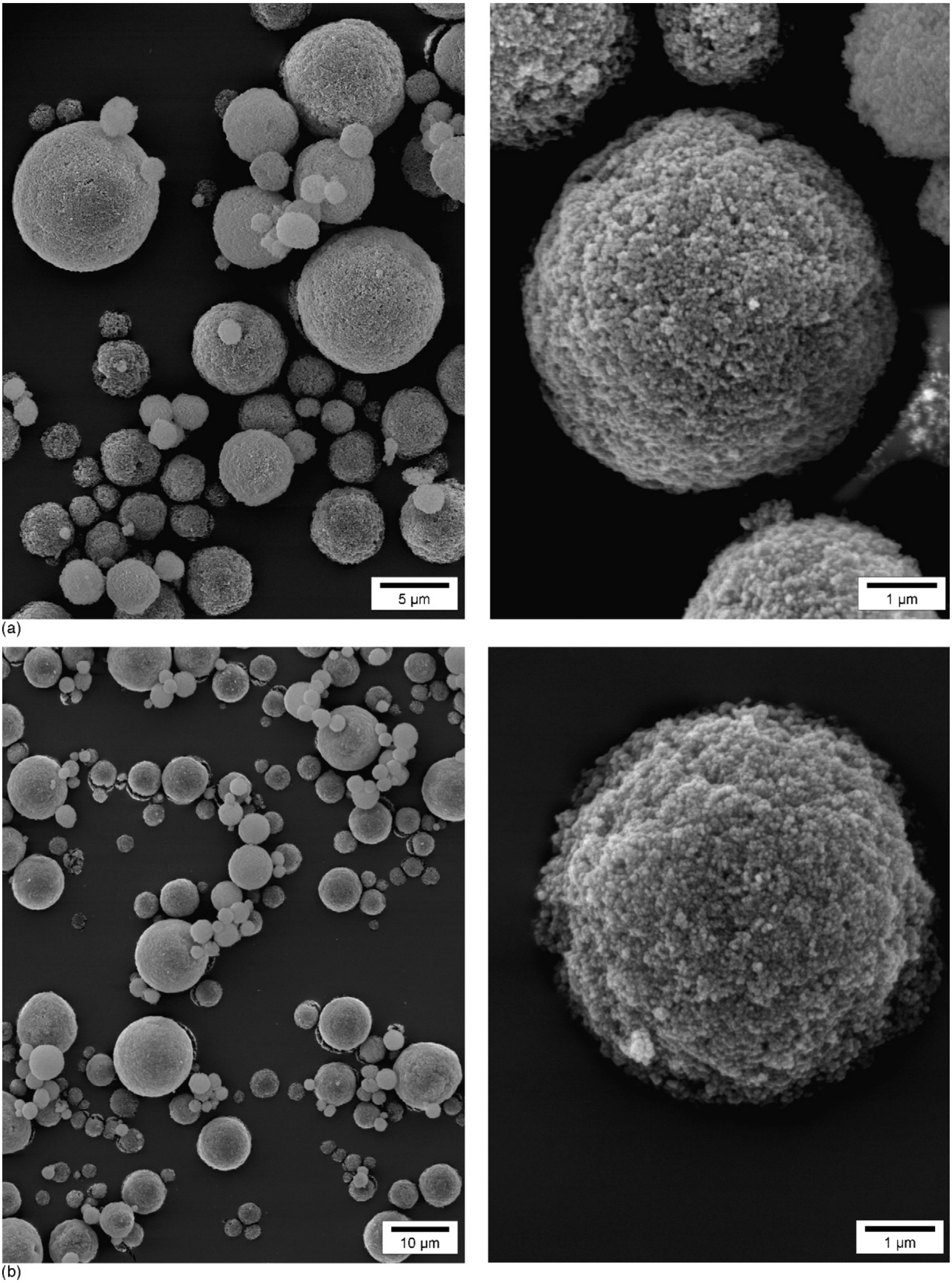

Fig. 3. SEM photographs of spray-dried powders exhibiting overall view (left) and high enlargement (right) for the different formulations: (a) NC1% + S1.5% (scale bars: left 5 μm, right 1 μm); (b) NC1% + S3% (scale bars: left 10 μm, right 1 μm); (c) NC4% + S1.5% (scale bars: left 10 μm, right 5 μm); (d) NC4% + S3% (scale bars: left 5 μm, right 2 μm).

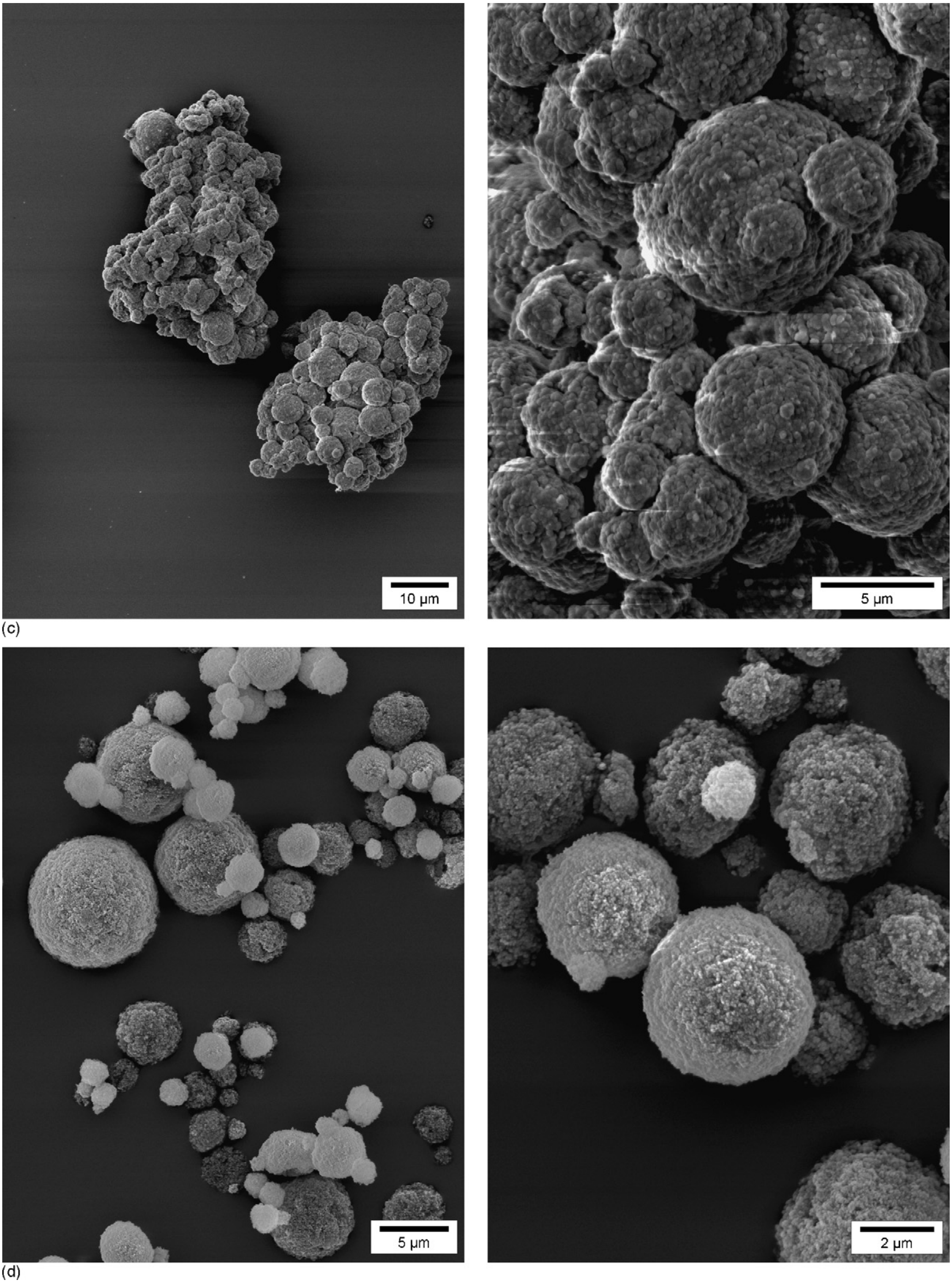

Fig. 3. (*Continued*).

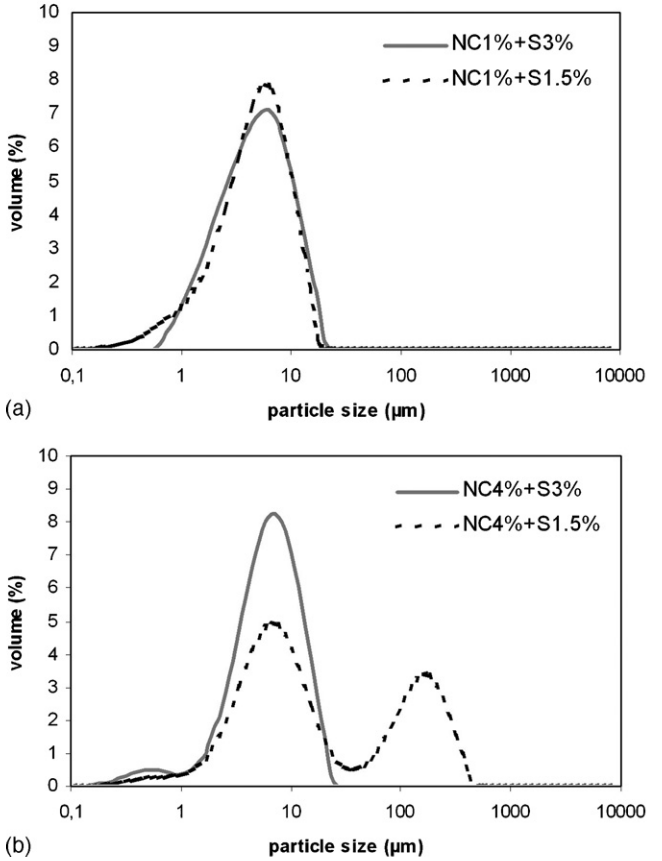

Fig. 4. Volume particle size distribution of spray-dried powders. Influence of the silica concentration on the size distribution of preparations containing (a) 1% nanocapsules and (b) 4% nanocapsules.

3.4.2. *Particles size distribution*

Fig. 4 presents the size distribution of the collected powders and the influence of their composition. The preparation containing NC1% + S1.5% is characterised by a monomodal distribution, and the increase in the silica concentration (NC1% + S3%) results in particle size distribution looking nearly similar (Fig. 4a). Oppositely, the preparation containing NC4% + S1.5% exhibits a bimodal distribution of particles. In this case agglomerates were not totally disrupted even when higher dispersing pressure was applied (data not shown). Increase in the silica concentration (NC4% + S3%) leads to a monomodal distribution close to the first peak of the bimodal distribution (Fig. 4b). Just as for well-separated particles, the size distributions are broads and these results are in accordance with the SEM observations.

3.4.3. *Powder density*

The bulk and tapped densities were determined on two batches for each spray-dried NC formulation and compared to spray-dried 3% (w/v) silica (Table 4). According to tapped density value, preparations can be classified in two groups: powders having a tapped density lower than 0.17 g/ml and powders with a tapped density higher than 0.22 g/ml. This separation is related to NC concentration, the lower the tapped density is the lower is the NC concentration. The highest density (0.250 g/ml) was obtained with formulation containing NC4% + S1.5% while powder prepared with formulation NC1% + S1.5% presented a tapped density value below that of silica. Carr index also varies depending on the preparation's formulation, from 15.5% to 34.12%. The higher the silica concentration is, the higher is the Carr index value.

The mean pycnometric density of the spray-dried colloidal silica particles was 2.3995 g/ml (Table 4), a value characterising high particulate density compounds. The presence of NC changes the solid matrix content and as result lower particulate density values are obtained. The higher density was obtained with NC1% + S3% formulation and the lower with NC4% + S1.5% formulation. The higher is the NC concentration the lower is the particulate density.

3.4.4. *Surface characterisation*

Both colloidal silica and NC are likely to adsorb at the surface of the microparticles prepared as evidenced by the SEM analysis, although it was not possible to evaluate the proportions of each component. The atomic surface composition of the spray-dried NC powders was thus analysed by ESCA and the surface proportions of the different species were calculated. As comparison untreated colloidal silica and PCL granules were analysed. The ESCA spectra recorded exhibit 3 peaks among which two from the 1s electron of O and C, and the last from the 2p electron Si (data not shown). The Si peak was unequivocally indicative of the presence of SiO_2 in the outer 10 nm of the spray-dried particles surface, whilst that of C and O were used to detect the presence of PCL or others NC ingredients (oil or surfactants). The ratios O/C and Si/O were also of interest in this characterisation.

For untreated colloidal silica, the corresponding relative % atomic concentrations of C, O and Si are 1.7, 66.1 and 32.2, respectively (Table 5) results comparables with the theoretical values of 66.6 and 33.3 for O_2/Si_1 (Merck Index, 1989). The surface layer of PCL is composed of 73% C and 27% O, also in close agreement with the theoretical values of 75% and 25%, respectively (Iroh, 1999).

Table 4
Apparent and particulate densities of the spray-dried products (mean ± S.D.)

	NC1.0% + S1.5%	NC1.0% + S3.0%	NC4.0% + S1.5%	NC4.0% + S3.0%	S3.0%
Bulk density (g/ml)	0.100 ± 0.007	0.117 ± 0.002	0.211 ± 0.011	0.167 ± 0.004	0.093 ± 0.002
Tapped density (g/ml)	0.125 ± 0.002	0.167 ± 0.001	0.250 ± 0.000	0.222 ± 0.005	0.142 ± 0.008
Carr index (%)	20.0 ± 0.8	30.24 ± 0.9	15.50 ± 4.4	24.77 ± 0.70	34.12 ± 2.55
Particulate density (g/ml)	1.5979 ± 0.0019	1.7669 ± 0.0021	1.2068 ± 0.0003	1.3648 ± 0.0011	2.3995 ± 0.0420

Table 5
Surface atomic composition determined by ESCA for untreated colloidal silica, untreated PCL and spray-dried nanocapsules

Samples	Formulations	Atomic concentrations (%)			Elemental ratios	
		O 1s	C 1s	Si 2p	O/C	Si/O
1	SiO_2	66.1	1.7	32.2	38.9	0.49
2	PCL	27.0	73.0	–	0.37	–
3	NC1.0%–S1.5%	44.7	36.2	19.1	1.23	0.43
4	NC1.0%–S3.0%	45.9	32.4	21.7	1.42	0.47
5	NC4.0%–S1.5%	20.8	76.5	2.7	0.27	0.13
6	NC4.0%–S3.0%	36.6	49.6	13.9	0.74	0.38

The silica augmentation from 1.5% to 3% in the spray suspension containing 1% or 4% NC produces changes in the three elemental (1s, 2p)-electron peaks levels. The relative % atomic concentrations of Si and O increase whilst that of C decreases. The composition of the microparticle surface at high silica content (NC1% + S3%) is 21.7% Si and 45.9% O and the ratio Si/O is 0.47 a value nearest 0.5 corresponding to the SiO_2 stochiometry. For this sample, the 1s-electron O peak is essentially inducted by the silica's oxygen. The preparation containing NC4% + S1.5% presented the lowest Si % at the surface of microparticles (2.7%) indicating the very weak proportion of colloidal silica in the outer layer. Moreover, the value of the ratio O/C (0.27) is comparable to that of PCL (0.37). In all cases the 1s-electron of C was detected and the highest percentage was related to the lowest silica proportion (1.5%) added to 4% NC.

4. Discussion

4.1. Nanocapsules preparations

Spray-drying is a great raw material consumer even for a laboratory apparatus like Büchi B191. The pilot employed allowed the preparation of PCL blank NC at great quantities with the same characteristics, moreover the different batches exhibited a good reproducibility. Regarding particle size and zeta potential values before and after washing operations, NC are unchanged. The using of co-surfactants is favourable to a very good stabilisation of the NC by anchoring surfactant molecules in the wall, resulting in better protection from particle aggregation as previously shown (Mosqueira et al., 2000). Since NC prepared are intended to dilution and/or mixing with another preparation before spray-drying, it is of importance to verify their stability and ensure that this process will not cause degradations nor aggregations following surfactant removal.

4.2. Nanocapsules/silica interactions

The rheological measurements were used to characterise preparations submitted to spray-drying process. Since these preparations are complex formulations consisting in water-suspended particles of various compositions, sizes and shapes, it is of interest to investigate the colloidal state and interactions developed when NC and silica are mixed. Due to the colloidal nature of the two components, this mixture could lead to new interactions (solid/solid, solid/liquid).

It is known that the rheological behaviour of colloidal suspensions is determined by several factors as the nature and magnitude of the interparticle interactions, the size and shape of particles, the volume fraction, the suspending media, to name a few (Yziquel et al., 1999). Colloidal silica used in this study is prepared by the flame hydrolysis process of silicon tetrachloride, which generates hydroxyls groups (silanols) on the silica surface, and irreversible fractals aggregates formed by the fusion of primary particles (Raghavan and Khan, 1997; Yziquel et al., 1999). When dispersed in a polar liquid, the interactions between the surface hydroxyls of aggregates and the suspending medium through hydrogen bonding dominate particle/particle interactions (Yziquel et al., 1999). A solvation layer is thus formed on the silica surface and gives rise to a short-range non-DLVO repulsions, solvation forces that stabilise the silica particles in a non-flocculated suspensions exhibiting low viscosity (Raghavan et al., 2000). However, at high volume fraction level, these solvation forces could be outclassed by hydrogen interparticles bonds, leading to a three-dimensional network and thus a significant increase in viscosity as shown by the suspension containing 10% silica. Because hydrogen bonds (about 8–40 kJ) are moderately weak compared to covalent liaisons (360 kJ) (Saint-Michel et al., 2002), they could be easily broken by the hydrodynamic forces during shearing, explaining the significant decrease of viscosity. After shearing has ceased, the hydrogen bonds will reform on standing leading to viscosity increase. For silica beforehand dispersed in water, these major risks are being left: (i) a non-reproducible mixture of the two components, (ii) solid/solid interactions between NC and silica surfaces.

With respect to this feed preparation method, it was expected that the free hydrophilic moieties of surfactants surrounding NC will interact with the solvation layer around silica aggregates when mixing the two components, so no stronger interaction is supposed to be developed or at most moderate interactions which favour a stabilised mixed suspensions without flocculation and/or sedimentation phenomena. NC suspensions in the absence of silica present a rheological profile similar to that of water (Fig. 2c). Thus the significant increase in viscosity of the mixed suspensions prepared with 3% and 5% silica is pertinent with the formation of new arrangements, which span the effective volume fraction of the dispersed phase. Clusters of silica surrounding one or several NC are formed and support a three-dimensional network connexion leading to gel formation, event not possible with NC alones.

The shear rate range used in this study is very large compared to published data. In all cases, shear did not induce thickening which could be responsible of nozzle obstruction or net formation instead of droplets, nor destabilising phenomena in the microstructure organisation commonly associated to fractures in the viscosity evolution. So, these mixed preparations are well-suited for atomisation.

4.3. Spray-drying nanocapsules and powders characteristics

The choice of a drying method is usually determined by the ability of the preparation contents to resist against the drying stress as well as the final product functions of use. In the spray-drying NC case, these technical problems have to be solved: (1) the preservation of the particles integrity and (2) the promotion of dried particles with adequate sizes permitting separation from the drying fluid. NC are characterised by a great specific surface that require protection from the thermal stress during drying because of the polymer nature of the wall and the oil nature of the core. Thus, colloidal silicon dioxide appears as a candidate of choice to cover the NC surface and stabilise them within a solid matrix because it also develops a great specific surface and possesses a good thermal conductivity interesting for water removal. This silica is a biocompatible amorphous carrier largely used as tablets excipients, considered by the FDA and other regulatory agencies as a safe component for non-parenteral administration of drugs (Rowe et al., 2003).

Because NP preparations will develop different particle sizes, because for two batches of the same preparation the encapsulated quantity of drug could be different, find a mean to control the quantity of NC introduced in the feed preparation before spray-drying becomes essential. Our findings demonstrated that the minimal adjuvant concentration required is function of that of NC introduced in the feed preparation. With insufficient concentration of adjuvant spray-drying NC led to strong adhesive products onto the apparatus walls. This can be explained by the fact that the silica proportion is not suitable to protect well the NC from the drying stress. In the case of NC adsorption on the silica surface as hypothesized by the preceding studies (Müller et al., 2000; Pohlmann et al., 2002), there would be a formation of at least small quantities of the desired powders when silica concentration is not sufficient to interact with all NC, and only the excess of NC will adhere onto the cyclone wall. During these studies, the NC proportions in the preparation were not taken into account when explain the threshold of 3% (w/v) silica for the spray-drying success. Since spray-dried silica particles led to non-adhesive powders (samples 7–9 in Table 3), producing powders without strong adhesion on the walls seems to be related to NC cover by the silica particles. It is interesting to note that this difference in powder behaviour appears whereas the moisture contents are similar. In this context, the assumption of NC degradation and thus the oil escapement during drying can be advanced. NC/silica powders particles were recovered with acceptable yields for the spray-drying process. Increasing infinitely the silica proportion is not necessary because of the viscosity increase and as result a poor atomisation aptitude causing the yield reduction.

Spray-drying NC/silica mixtures resulted in spherical microparticles, and according to the proportions of the two components these primary particles are well-separated or fused agglomerated. The NC are in fact entrapped within solid dried matrixes following their interaction with silica particles in the feed before drying. After the liquid droplets releasing from the nozzle, they are exposed in hot air stream for drying. Therefore the solid concentration in droplets is significantly increased during drying. The viscosity is also increased and the bonds between silica particles act in favour of the droplet stabilisation preventing collapse. The clusters of silica surrounding one or several NC are thus consolidated at the water removal, and if an optimal mixing is achieved between the two components in the feed, silica can prevent NC aggregation within the microparticle matrix. The spherical appearance of particles is a characteristic researched by the spray-drying process and which usually confers to powders free flowing properties. It is related to the spherical aspects of droplets after atomisation and demonstrates the absence of destabilising effects on the droplet shape as sedimentation or droplet elongation leading to doughnut-shape structure formation during drying, phenomena previously described elsewhere (Luo and Nieh, 1996; Iskandar et al., 2003).

The particles surface is always rugged consisting in silica or a mixture of silica and NC. Indeed, silica and NC are both likely to accumulate at the surface of the microparticles formed. When the NC proportion is more important than that of silica, it is evident that NC are adsorbed at the peripheral of droplets and thus will accumulate at the powder surface. Because structures nearly 300 nm in size are present at the surface, it could be though that the agglomeration of primary particles and the adhesiveness of agglomerates on different supports are related to NC degradation.

The size distribution of the prepared powders was accessed in a dry state without particular treatment of samples, by applying compressed air for particles dispersion. The broad size distribution of the spray-dried particles, although homogenous preparations, is pertinent with microscopic observations and is representative of the atomised droplets size distribution. Indeed the nozzle atomisation system often produces droplets with a large distribution in sizes (Master, 1991). During drying if the droplets do not stick themselves, the same size distribution of initial droplets could characterise powder's particles. Fusion of primary particles could also takes place in the last stages of the process and thus leading to larger agglomerates as shown with NC4% + S1% preparation. For this last preparation, the first peak of the bimodal distribution is close to that of preparation NC4% + S3% (Fig. 4b). The global particle shape is thus explained by a conjunction of two phenomena, the aggregation of primary microparticles during drying following the fusion of the NC polymer walls, and the interparticle adhesion favoured by the oil core deployment through the microparticle matrix.

A great volume reduction under tapping is correlated with poor flow properties powders. It has been experimentally suggested that a material with a Carr's index above 25% has as a poor flow properties (Gabaude et al., 2001). Focusing on this parameter, spray-dried silica and powder containing NC1% + S3% have poor flow properties while NC1% + S1.5% and NC4% + S3% preparations exhibit passable flow properties (Table 4). This characteristic is related to the small particle size and the interparticle voids reduction upon tapping. Surprisingly, the powder containing NC4% + S1.5 exhibits good flowing property, although its great adhesive tendency, explained by the bigger particle size of the agglomerates and the interparticle adhesion. Nevertheless, this aptitude cannot be considered as an advantage since agglomerates formation is related to NC degradation.

An increase in NC proportion leads to a significant decrease in the particulate density. This observation is explained by the voids reduction within the matrix and at certain point by the formation of non-porous shells following NC fixation at the peripheral of the microparticles as shown by SEM observations. Colloidal silica is well known as spray-drying adjuvant mainly for increasing particles densities (Palmieri et al., 1994). Since the spray-dried microparticles appeared porous according to the SEM analysis, increasing the silica proportion in the feed was expected to increase the particulate density. In addition, with 1% NC in the feed, the augmentation of the silica proportion from 1.5% to 3% leads to density increase without change in the particle size distribution. This means that reorganisation occurs in the feed and more silica is entrapped within the microparticles.

A particular feature of this work is the use of the reliable ESCA technique to characterize the surface layer of the spray-dried particles. By analysing the surface relative % atomic concentrations of the elements Si, C and O, we determined the surface composition of the spray-dried microparticles containing NC and silica. It was assumed that the elements found in the surface layers of spray-dried particles are elements presents in the two pure components to which we can add surfactants and oil core elements. We did not measure the ESCA spectra of polysorbate 80 and miglyol 810, which are liquid at room temperature and cannot be held at the high vacuum necessary in the sample chamber of the apparatus.

At a given NC concentration, the increase in silica proportion leads to silica augmentation at the surface. This observation indicates that at ideal concentrations, the NC are covered by silica in the dried state. Tacking into account that an elemental surface composition in Si of 32.2% corresponds to 100% of SiO_2 at or near the surface, NC were well protected by silica and keep away from the outer surfaces in the cases of these preparations, from the best at least, respectively, NC1% + S3%, NC1% + S1.5% and NC4% + S3%. It is interesting to note that even with small silica content compared to NC (NC4% + S1.5%), silica was detected at the powder surface but the Si/O ratio is much lower than that corresponding to silica (0.13/0.5). The particularity of this preparation was the high atomic percentage of C greater than that of PCL, result indicative of the presence of another component at the surface. Since this preparation was difficultly held in the vacuum because of important degasification, we can conclude that the oil core was deployed to the entire matrix following NC disintegration during drying.

The carbon atom was detected in the surface layer of microparticles whatever the composition of the spray-dried NC. Some hypotheses are plausible: (i) the shell porosity and (ii) the surfactant adsorption. Because of a non-continue surface layer of silica as revealed by SEM analysis, underline NC and thus polymer wall could be easily accessible to the X-ray beam. Polysorbate 80 surfactant is known to adsorb at the surface of spray-dried particles containing soluble compounds (Adler et al., 2000). Since the theoretical % relative atomic concentrations of C and O in the polysorbate 80 molecule are 71.1% and 28.9%, respectively, for C_{64}/O_{26} (Rowe et al., 2003), the adsorption of this molecule at the surface will essentially increase the % of C atom.

Because silica is hydrophilic, it is expected that the spray-dried particles will disintegrate and release the NC in aqueous medium. When the proportions of the two components are adjusted to obtain separated microparticles, the powders presented good wettability and the dispersion reconstitution in demineralised water under moderate agitation was easy. From these results we assumed that the NC integrity is preserved since the fused agglomerated particles were not disintegrated in the same conditions. The particle size measurements were performed and the mean results were 1043 ± 64, 607 ± 46 and 852 ± 70 nm, respectively, for the reconstituted dispersions of the following formulations NC1% + S1.5%, NC1% + S3% and NC4% + S3%. These results are intermediate between the mean size of the original NC and the mean size of the dry powder. This is indicative of the presence at the same time in the dispersion medium of the released NC, the NC/silica and silica aggregates, because of the difficulties arising for the separation of NC from silica as also observed in the original feed. A refining is thus needed as well for the re-dispersion method as for the separation of the two components when they are present in a mixed suspension.

5. Conclusion

The main object of this work was to prepare dried solid forms of interest containing NC. The mixing protocol, the concentrations of both NC and silica are crucial parameters that affect the feed behaviour and the spray-dried particles characteristics. Shape and morphology, size distributions, apparent and particulate densities, and surface composition of the powders were investigated furnishing information surely useful for the development of this application.

Interactions occurring in the feed are directed by hydrogen bounds and were more sensitive to the silica concentration. The NC incorporation into separated microparticles was achieved following the association of NC and silica at adequate concentrations in the feed before spray-drying. Using the ESCA technique, we demonstrated the evidence of NC exclusion from the particle's surface to obtain powders suitable for good handling as intermediary pharmaceutical products.

References

Adler, M., Unger, M., Lee, G., 2000. Surface composition of spray-dried particles of bovine serum albumin/trehalose/surfactant. Pharm. Res. 17, 863–870.

Allémann, E., Gurny, R., Doelker, E., 1993. Drug-loaded nanoparticles—preparation methods and drug targeting issues. Eur. J. Pharm. Biopharm. 39, 173–191.

Bodmeier, R., Chen, H., 1988. Preparation of biodegradable poly(±)lactide microparticles using a spray-drying technique. J. Pharm. Pharmacol. 40, 754–757.

Briançon, S., Fessi, H., Lecomte, F., Lieto, J., 1999. Study of an Original Production Process of Nanoparticles by Precipitation, 2nd ed. European Congress of Chemical Engineering, Montpellier, France.

Broadhead, J., Edmond Rouan, S.K., Rhodes, C.T., 1992. The spray drying of pharmaceuticals. Drug Dev. Ind. Pharm. 18, 1169–1206.

Chasteigner, S., Fessi, H., Cave, G., Devissaguet, J.P., Puisieux, F., 1995. Gastro-intestinal study of a freeze-dried oral dosage form of indomethacin-loaded nanocapsules. S.T.P. Pharma. Sci. 5, 242–246.

Conte, U., Conti, B., Giunchedi, P., Maggi, L., 1994. Spray dried polylactide microsphere preparation: influence of the technological parameters. Drug Dev. Ind. Pharm. 20, 235–258.

Couvreur, P., Dubernet, C., Puisieux, F., 1995. Controlled drug delivery with nanoparticles: current possibilities and future trends. Eur. J. Pharm. Biopharm. 41, 2–13.

Damgé, C., Aprahamian, M., Balboni, G., Hoeltzel, A., Andrieu, V., Devissaguet, J.P., 1987. Polyalkylcyanoacrylate nanocapsules increase the intestinal absorption of a lipophilic drug. Int. J. Pharm. 36, 121–125.

European Pharmacopoeia, 2005. Méthodes de Pharmacotechnie, 5th ed. European Pharmacopoeia, Strasbourg, pp. 256–257.

Fäldt, P., Bergenstähl, B., Carlsson, G., 1993. The surface coverage of fat on food powders analyzed by ESCA. Food Struct. 12, 225–234.

Fessi, H., Puisieux, F., Devissaguet, J.P., 1988. Procédé de préparation des systèmes colloïdaux dispersibles d'une substance sous forme de nanocapsules. European Patent 0274961 A1.

Gabaude, C.M.D., Gautier, J.C., Saudemon, P., Chulia, D., 2001. Validation of a new pertinent packing coefficient to estimate flow properties of pharmaceutical powders at a very early development stage, by comparison with mercury intrusion and classical flowability methods. J. Mater. Sci. 36, 1763–1773.

Giunchedi, P., Conti, B., Maggi, L., Conte, U., 1994. Cellulose acetate butyrate and polycaprolactone for ketoprofen spray-dried microsphere preparation. J. Microencapsul. 11, 381–393.

Iroh, J.O., 1999. Poly(epsilon-caprolactone). In: Mark, J.E. (Ed.), Polymer Data Handbook. Oxford University Press, New York, pp. 361–362.

Iskandar, F., Gradon, L., Okuyama, K., 2003. Control of the morphology of nanostructured particles prepared by the spray drying of nanoparticle sol. J. Colloid Interf. Sci. 265, 296–303.

Kim, Y.I., Fluckinger, L., Hoffman, M., Lartaud-Idjouadiene, I., Atkinson, J., Maincent, P., 1997. The antihypertensive effect of orally administered nifedipine-loaded nanoparticles in spontaneously hypertensive rats. Br. J. Pharmacol. 120, 399–404.

Kreuter, J., 1994. Nanoparticles. In: Kreuter, J. (Ed.), Colloidal Drug Delivery Systems. Marcel Dekker, New York, pp. 219–342.

Luo, P., Nieh, T.G., 1996. Preparing hydroxyapatite powders with controlled morphology. Biomaterials 17, 1959–1964.

Magenheim, B., Benita, S., 1991. Nanoparticle characterization: a comprehensive physicochemical approach. S.T.P. Pharma. Sci. 1, 221–241.

Maincent, P., Le Verge, R., Sado, P., Couvreur, P., Devissaguet, J.P., 1986. Disposition kinetics and oral bioavailability of vincamine-loaded polyalkyl cyanoacrylate nanoparticles. J. Pharm. Sci. 75, 955–958.

Master, K., 1991. Spray Drying Handbook. Longman Scientific and Technical, New York.

Merck and Co., 1989. The Merck Index, 11th ed. Merck and Co., Rahway.

Mosqueira, V.C., Legrand, P., Pinto-Alphandary, H., Puisieux, F., Barratt, G., 2000. Poly(D,L-lactide) nanocapsules prepared by a solvent displacement process: influence of the composition on physicochemical and structural properties. J. Pharm. Sci. 89, 614–626.

Müller, C.R., Bassani, V.L., Pohlmann, A.R., Michalowski, C.B., Petrovick, P.R., Guterres, S.S., 2000. Preparation and characterization of spray-dried nanocapsules. Drug Dev. Ind. Pharm. 26, 343–347.

Palmieri, G.F., Wehrlé, P., Stamm, A., 1994. Evaluation of spray-drying as a method to prepare microparticles for controlled drug release. Drug. Dev. Ind. Pharm. 20, 2859–2879.

Palmieri, G.F., Bonacucina, G., Di Martino, P., Martelli, S., 2001. Spray-drying as a method for microparticulate controlled release systems preparation: advantages and limits. I. Water-soluble drugs. Drug Dev. Ind. Pharm. 27, 195–204.

Pohlmann, A.R., Weiss, V., Mertins, O., Pesce da Silveira, N., Guterres, S.S., 2002. Spray-dried indomethacin-loaded polyester nanocapsules and nanospheres: development, stability evaluation and nanostructure models. Eur. J. Pharm. Sci. 16, 305–312.

Raghavan, S.R., Khan, S.A., 1997. Shear-thickening response of fumed silica suspensions under steady and oscillatory shear. J. Colloid Interf. Sci. 185, 57–67.

Raghavan, S.R., Walls, H.J., Khan, S.A., 2000. Rheology of silica dispersions in organic liquids: new evidence for solvation forces dictated by hydrogen bonding. Langmuir 16, 7920–7930.

Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients, 4th ed. Pharmaceutical Press, London.

Saint-Michel, F., Pignon, F., Magnin, A., 2002. Rhéométrie et structure des dispersions de silices nanométriques dans du polyol. Rhéologie 2, 31–38.

Schmidt, C., Bodmeier, R., 1999. Incorporation of polymeric nanoparticles into solid dosage forms. J. Contr. Rel. 57, 115–125.

Staniforth, J.N., 1988. Pharmaceutical technology. In: Aulton, M.E. (Ed.), Pharmaceutics: The Science of Dosage Form Design, 1st ed. Churchill Livingstone, Edinburgh, pp. 600–615.

Yziquel, F., Carreau, P.J., Tanguy, P.A., 1999. Nonlinear viscoelastic behavior of fumed silica suspension. Rheol. Acta 38, 14–25.