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Nano Spray Drying as an Innovative Technology for Encapsulating Hydrophilic Active Pharmaceutical Ingredients (API)

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Abstract

The vibrating mesh spray technology implemented in the Nano Spray Dryer B-90 was evaluated for drug delivery applications by spray drying solutions containing different functional polymers to structure the respective encapsulating matrices (Arabic gum, cashew nut gum, sodium alginate, sodium carboxymethyl cellulose and Eudragit RS100) and a specific model drug to be encapsulated (vitamin B12). A systematic study investigated the influence of feeding liquid stream properties such as viscosity, conductivity and surface tension respectively on particle size distribution, specific surface area and morphological aspects. The encapsulating efficiency and the release kinetics of the different systems were evaluated considering *in-vitro* experiments characterized by different pH conditions that respectively simulate the gastric (acid) and enteric conditions (alkaline). The performance of each formulation was evaluated by considering the intrinsic properties of the materials used and also the spray dryer operating conditions.

Keywords: Spray drying; Drug delivery; Nanoparticle; Controlled release

Introduction

Spray Drying represents a single-step, continuous and scalable process dedicated for converting liquid streams (solutions, emulsions, suspensions, slurries, pastes or even melts) into dry free-flowing powders which enables the production of particles with controlled size and morphological aspects. It also allows the encapsulation of active agents thus opening a wide spectrum of opportunities in the field of particle engineering in pharmaceutical, materials and food science [1]. The recent rise of nanotechnology has increased the pressure on existing spray dryer systems to produce nanoparticles with a satisfactory yield and controlled size distribution.

Nanoparticles have proved to be a feasible technological solution to overcome limitations such as reduced dissolution rates because of their reduced size and hence larger specific surface area thus representing a way of increasing the availability of poorly soluble compounds. Encapsulation technologies have demonstrated the possibility of engineering target delivery systems by ensuring the protection of the encapsulated agent against hazardous conditions or chemicals that may be present in the environment and enabling the specific-site controlled release via external stimuli (e.g. pH, temperature, among others). The concept of nanoencapsulation is thus gaining more and more attention. The potential of nanoparticle spray drying has not yet been fully exploited and represents a theme of interest because of several benefits that are inherent to the technique [2].

The conventional spray drying process is limited for producing particles with characteristic dimension below 2 μm mainly because of the atomization technology commonly employed, which are based on pressure or centrifugal forces, and also due to the limited collection efficiency related to cyclone separators [3-7]. A new generation of bench scale spray dryers seems to alter this perspective of limitations once exploring an innovative concept within the spray drying technology. The production and collection of submicron particles from a solution turns out to be possible by simultaneously exploring a piezoelectric driven vibrating mesh atomizer and a high-efficiency electrostatic dry powder collector. A laminar drying air flow inside the spray chamber also provides instant drying of the aerosol at mild conditions. Up to date the new Nano Spray Dryer technology has been successfully employed for a variety of drug delivery applications including the use of Arabic gum, whey protein, polyvinyl alcohol, modified starch and maltodextrin as different polymeric wall material for encapsulation. In a complementary way the nano spray drying process has also been successful applied to perform decomposition, crystallization, drying and crystal shape control in just one process step [7-13]. In this work the vibrating mesh spray technology implemented in the Nano Spray Dryer B-90 was evaluated for drug delivery applications by spray drying solutions containing different functional polymers to structure the respective encapsulating matrices (Arabic gum, cashew nut gum, sodium alginate, sodium carboxymethyl cellulose and Eudragit RS100) and a specific model drug to be encapsulated (vitamin B12).

Experimental Section

Materials

Arabic gum (Purity Gum 1773), cashew nut gum (kindly provided by UFCE), sodium alginate (Keltone® LVCR), sodium carboxymethyl cellulose (Denvercel PH) and ammonium methacrylate copolymer (Eudragit® RS100) were selected as encapsulating agents to be tested in the present work. Vitamin B12 was selected as a hydrophilic model drug to evaluate the encapsulation efficiency of the referred systems.

Sample preparation

Each encapsulating agent (EA) was dissolved using MilliQ water as a common solvent to respectively produce 0.1, 0.5 and 1.0% (w/w)

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solutions. Sodium hydroxide (NaOH) or ammonium hydroxide (NH4OH) were added to adjust the pH if necessary to ensure the complete dissolution of a specific polymer. After that, each model drug (MD) was co-dissolved by direct addition under stirring to accomplish EA:MD ratios of respectively 9:1 and 8:2.

The Nano Spray Dryer B-90 was operated in open loop with in-house pressurized air at a flow rate of 130 L/min. The spray drying experiments were performed by setting an inlet temperature (Tin) of 120°C using different spray meshes with 4.0 and 7.0 µm aperture size. The outlet temperature (Tout) varied between 50 and 60°C and was only registered for monitoring purposes.

Sample characterization

Liquid stream (Before Drying): The pH and conductivity were determined using a MP220 Series pHmeter and a MC226 Series conductivimeter (Mettler Toledo). The viscosity was evaluated using a DV-III Ultra rotational rheometer (Brookfield). The small sample adapter and a spindle SC16 were used to perform a single-point measurement once setting the rotational speed to 60 rpm. The surface tension was evaluated using a DCAT-11 digital tensiometer (Dataphysics).

Spray-Dried nanoparticles (After Drying): The particle size distribution of the spray dried powders was evaluated using a Beckman Coulter LS-230 laser diffraction instrument. The samples were resuspended in ethanol and sonicated during an 8 min interval prior to the analysis in order to ensure the deagglomeration procedure. The sample concentration necessary for the analysis was set considering 8% obscuration or 40% PIDS intensity. The particle morphology of the spray dried powders was determined with a QUANTA FEG 3D high-resolution scanning electron microscope (FEI Instruments) operating in a secondary electron imaging and high vacuum mode. The samples were fixed on self-adhesive tapes on an aluminum stub and sputtered with Au-Pd. The specific surface area of the spray dried powders was evaluated using a Gemini V Series 2380 instrument (Micromeritics) by B.E.T method. Nitrogen was used as the common adsorbate for all the experiments. The samples were pretretaed under high vacuum and ambient temperature during a 15 h period and also under high vacuum and 120°C temperature during a 2 h period before the experiments to ensure the removal of physically adsorbed water or any residual solvent.

Spray Solution	Viscosity (cP)	Surface Tension (mN/m)	Conductivity (µS/cm)
CMC (1.0%)	54	73	167
CMC (0.5%)	19	72	92
CMC (0.1%)	8,3	72	19
ALG (1.0%)	16,6	70	2030
ALG (0.5%)	9,5	71	23
ALG (0.1%)	6,3	70	11
EUD (1.0%)	9,2	40	3000
EUD (0.5%)	8,5	46	2060
EUD (0.1%)	7,5	61	63
AG (1.0%)	6,9	51	95
AG (0.5%)	6,7	57	53
AG (0.1%)	6,3	69	13
CNG (1.0%)	8,6	71	164
CNG (0.5%)	8,6	67	108
CNG (0.1%)	6,5	65	58

CMC=sodium carboxymethyl cellulose; ALG=sodium alginate; EUD=Eudragit RS100; AG=Arabic gum; CNG=cashew nut gum.

Table 1: Viscosity, conductivity and surface tension of spray solutions containing different polymers (encapsulating agents) at three concentration levels ranging from 0.1 to 1.0% (w/w).

Polymer	Viscosifier	Surfactancy	Ionic Strength Enhancer
CMC	XXX	0	0
ALG	XX	0	XXX
EUD	0	XXX	XXX
AG	0	XX	0
CNG	0		0

XXX=Intense; XX=Moderate; 0=Negligible

Table 2: Classification of the tested polymers according to the resulting properties inherent to the obtained solutions by considering the effect of the variable concentration.

Dissolution studies (Controlled Release Performance): The release kinetics of the encapsulated drugs was evaluated considering in-vitro experiments performed at different pH conditions to simulate specific desired applications. The experiments' temperature was set equal to 37°C and two buffer solutions were used to simulate different parts of the gastrointestinal tract (pH=8 (alkaline) to represent the intestine and pH=1 (acid) to represent the stomach). The samples were prepared by adding 2.5 mg of the spray dried powders to 50 mL of the respective buffer solutions. Several 125 mL Erlenmeyer flasks were used to store the samples and the environmental conditions were controlled using a lab-scale incubator. The sample withdrawal was performed by collecting aliquots of the supernatant at different time intervals: 1, 3, 5, 7, 10, 15, 20, 60 and 120 min. Quantitative analysis was performed by using UV-Vis spectrophotometric technique and prior experimentally determined calibration curves (not shown in the present text). A Cintra 10 (GBC) instrument was used to perform the experiments by considering the absorbance mode. Quantification of the dissolved amount of drug was carried out photometrically at 232 nm and 301 nm for the vitamin B12 samples.

Results and Discussion

Once considering that one of the aspects desired with the present work is to evaluate the influence of the feeding liquid stream properties on the spray dried powders obtained thereof, it is suggested, as a first approach, the presentation of the results relative to the liquid stream characterization just after the dissolution of different polymers (encapsulating agents). Table 1 illustrates the effect of the polymer concentration over physico-chemical properties of the solutions such as viscosity, conductivity and surface tension.

The results presented in Table 1 indicate that the viscosity of the solutions tend to increase as a function of the polymer concentration when considering the sodium carboxymethyl cellulose and the sodium alginate. This kind of behavior was already expected once the CMC and the ALG are known in the art to act as viscosifiers when present in solution. Despite of the fact that for both polymers Na^+ is the counter-ion that neutralizes the anionic functional groups distributed along the macromolecule, the effect tends to be more pronounced for the CMC probably because of the higher molecular weight of the present sample. For all other polymers tested herein the influence is almost negligible and the resulting viscosity doesn't exceed 10 cP even when considering 1.0% (w/w) polymer concentration.

Once analyzing the resulting surface tension (Table 1) it is evidenced that some of the polymers tested herein provide surfactancy properties, especially the Eudragit RS100 and the Arabic gum, resulting in a significant decrease of the surface tension by simply increasing their concentration. For all others the influence is almost negligible

and the resulting surface tension remains practically unchanged when compared to the surface tension of the water (~73 mN/m).

When considering the ionic strength resulting from the dissociation of functional groups or even dissolution of residual species, here simply expressed by the conductivity, the data presented in Table 1 evidences that the sodium alginate and the Eudragit RS100 are the ones which promote the most significant changes when present in relatively high concentrations.

The selected polymers (encapsulating agents) thus provide a portfolio which can be sub-categorized in at least five groups as described in Table 2.

As evidenced in Table 2 the sodium carboxymethyl cellulose (CMC) represents an intense viscosifier which doesn't alter significantly the resulting surface tension and conductivity. The sodium alginate (ALG) alters significantly the ionic strength and moderately enhances the resulting viscosity once the surface tension remains almost unaltered. The Eudragit RS100 (EUD) also alters significantly the ionic strength but simultaneously reduce the resulting surface tension once the viscosity remains almost unaltered. The Arabic gum (AG) only moderately reduces the surface tension whilst the viscosity and conductivity remain almost constant. The cashew nut gum (CNG), last but not least, represents the fifth group for which all three evaluated properties are not significantly altered because of the presence of the solute.

Spray Solution	Aperture Size (4.0 μm)	Aperture Size (7.0 μm)
CMC (1.0%)	Fail	Fail
CMC (0.5%)	Fail	Fail
CMC (0.1%)	Success	Success
ALG (1.0%)	Fail	Fail
ALG (0.5%)	Fail	Fail
ALG (0.1%)	Success	Success
EUD (1.0%)	Success	Success
EUD (0.5%)	Success	Success
EUD (0.1%)	Success	Success
AG (1.0%)	Success	Success
AG (0.5%)	Success	Success
AG (0.1%)	Success	Success
CNG (1.0%)	Success	Success
CNG (0.5%)	Success	Success
CNG (0.1%)	Success	Success

Table 3: Categorizing the status of the atomizing procedure as 'Fail' or 'Success'.

Spray Solution	D[4,3] (μm)	D[0,10] (μm)	D[0,50] (μm)	D[0,90] (μm)
CMC (1.0%)	N/A	N/A	N/A	N/A
CMC (0.5%)	N/A	N/A	N/A	N/A
CMC (0.1%)	5.49	1.00	3.65	12.98
ALG (1.0%)	N/A	N/A	N/A	N/A
ALG (0.5%)	N/A	N/A	N/A	N/A
ALG (0.1%)	9.84	0.84	5.51	34.23
EUD (1.0%)	3.95	1.23	2.68	9.25
EUD (0.5%)	2.52	0.70	1.73	5.58
EUD (0.1%)	Product was soluble in ethanol			
AG (1.0%)	2.019	0.758	1.763	3.660
AG (0.5%)	2.906	0.788	2.488	5.676
AG (0.1%)	3.480	0.822	2.589	7.386
CNG (1.0%)	6.723	0.858	3.282	20.37
CNG (0.5%)	2.961	0.698	2.556	5.827
CNG (0.1%)	Complete agglomeration			

Table 4: PSD data experimentally determined using the laser diffraction technique.

After preparing and characterizing the polymer solutions the natural second step should be to test the atomization performance of the different formulations in order to evidence if there is any limitation related to the use of the vibrating mesh spray technology. Table 3 summarizes the obtained results by simply categorizing the status of the atomizing procedure as 'Fail' or 'Success'.

The results presented in Table 3 indicate that the major limitation of the system is related to pump and atomize viscous solutions such as the ones obtained when preparing 0.5% and 1.0% (w/w) sodium carboxymethyl cellulose or sodium alginate solutions. By considering that these two polymers represent intense and moderate viscosifiers (as proposed in Table 2) they impose technical restrictions to be atomized when considering the vibrating mesh spray technology. Increasing the aperture size from 4.0 μm to 7.0 μm corresponds to a strategy that enables the atomization of the 0.5% (w/w) sodium alginate solution but doesn't solve the restriction evidenced to the 1.0% (w/w) sodium alginate solution and also to the 0.5% and 1.0% (w/w) sodium carboxymethyl cellulose solutions. For all other tested polymers and respective solutions, despite of the solute concentration, no restriction regarding the atomization step was evidenced even when considering 1.0% (w/w) solutions (note: the tests were performed using both the 4.0 μm and the 7.0 μm size mesh aperture size).

The particle size distributions of the spray dried powders were determined and the results presented here are respectively expressed by the mean volume diameter (D[4,3]), 10% percentile (D[0,10]), median (D[0,50]) and 90% percentile (D[0,90]). Table 4 summarizes the obtained results.

The obtained results do not support the premise of sub-micron sized particles production employing the vibrational mesh spray technology. As a matter of fact, agglomeration of spray dried powders is a common phenomenon inherent to the drying process itself. In other words, the experimentally determined particle size distributions may undercover agglomeration aspects hindering the primary particle size determination. As a complement, morphological aspects, homogeneity and agglomeration (aggregation) state of the spray dried powders were evaluated using the high-resolution scanning electron microscopy technique. Figure 1 shows several micrographs registered at different magnifications for direct comparison purposes.

The micrographs evidence that the primary particles have almost spherical shapes and are sub-micron sized contradicting the PSD results obtained with the laser diffraction technique. A detailed observation on surface aspects of the particles enables the identification of "physical bridges" or "necks" responsible for the agglomeration mechanism established with the drying process therefore increasing the mean diameter of the particle size distribution.

Another aspect of fundamental importance is the performance of the different systems with respect to the release kinetics of the encapsulated active agent once exposed to different pH conditions. By considering that the desired major application is related to pH-sensitive controlled release and in order to simulate the gastric (acid) and the enteric (alkaline) conditions two different pH were tested. The obtained results are presented in the Figures 2 and 3.

The results presented in Figure 2 indicate that the different tested polymers (encapsulating agents) pose different behaviors and related performance regarding controlled release applications when

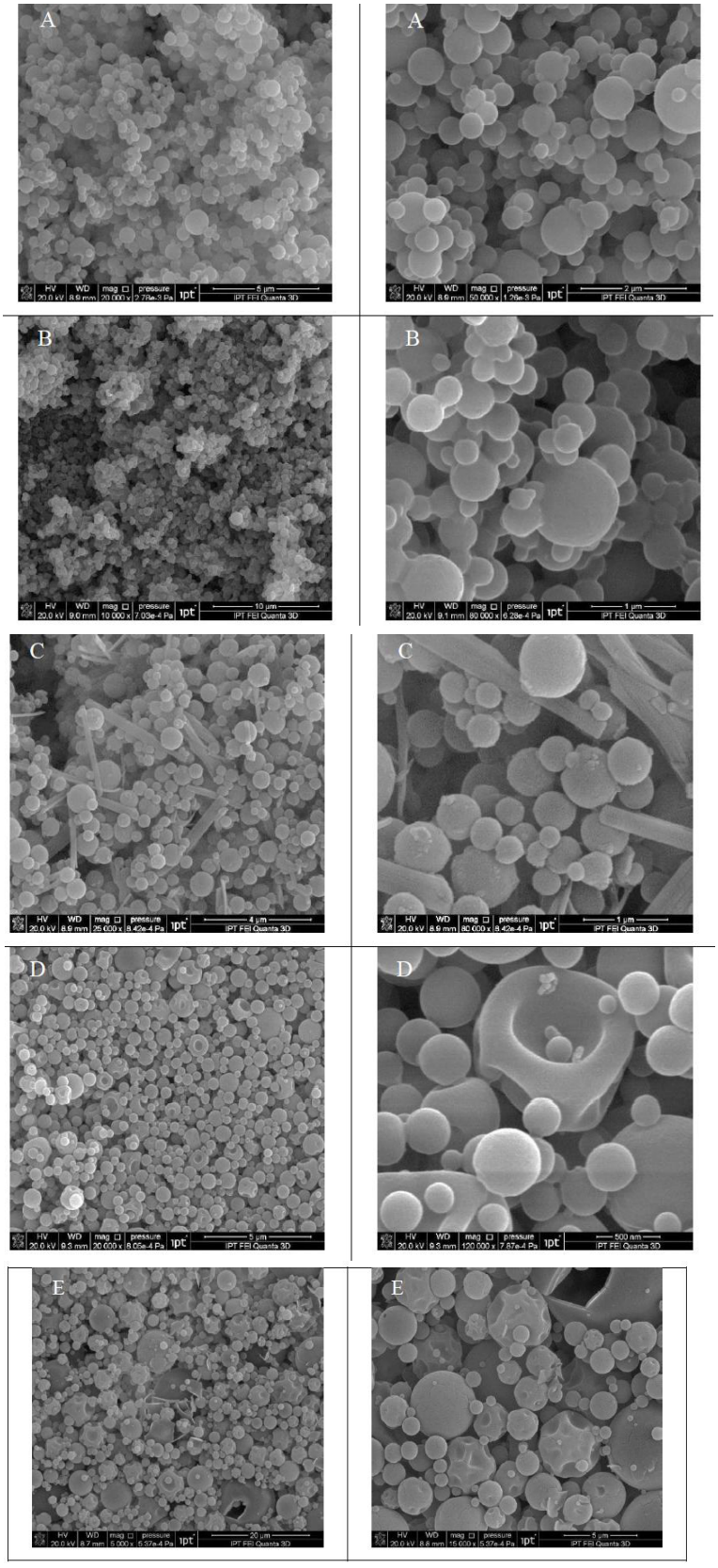

Figure 1: SEM micrographs (A – CMC; B – ALG; C – EUD; D – AG; E - CNG).

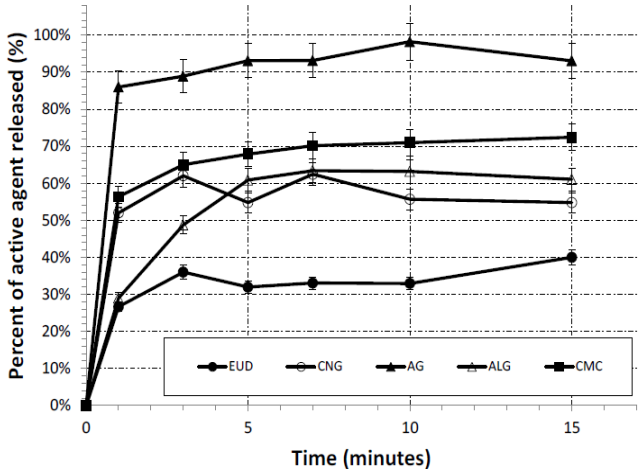

Figure 2: Controlled release kinetics experimentally determined over a 15 minutes period (in-vitro experiments) at an acidic pH condition (pH=1).

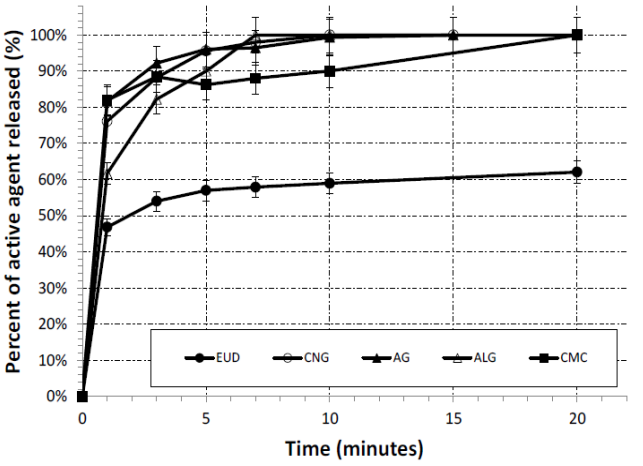

Figure 3: Controlled release kinetics experimentally determined over a 20 minutes period (in-vitro experiments) at an alkaline pH condition (pH=8).

considering *in-vitro* acidic pH condition (pH=1). The Arabic gum (AG) seems to be the less effective one once an amount of active agent released of approximately 90% is verified in an extremely short period of time (~1 minute). For the cashew nut gum (CNG), sodium alginate (ALG) and sodium carboxymethyl cellulose (CMC) the same trend of premature release is verified and the amount of active agent released over a 15 minutes period exceeds 50% for all three cases. For comparison purposes it is evidenced that over the same period of time only 40% of the active agent is released for the Eudragit RS 100 (EUD) case. The effective retention of the active agent and respective maintenance of the micro(nano)spheres integrity in acidic pH conditions are of crucial importance because of the fact that the bioabsorption itself only occurs in the enteric treat.

When considering *in-vitro* alkaline pH condition (pH=8) for all tested polymers, except for the Eudragit RS 100 (EUD), the amount of active agent released over a 10 minutes period of time exceeds 90%, thus indicating restrictions of the potential use of these polymers for pH-sensitive controlled release applications. Different from this kind of trend the Eudragit RS 100 (EUD) appears to be an effective choice when exploring this kind of release mechanism (pH shift) once the amount of active agent released doesn't exceed 60% even when promoting a 2-fold increase on the period of evaluated time. This kind of behavior is of extreme importance when designing extended release applications.

Once considering that the most promising results are the ones obtained for the Eudragit RS 100 (EUD) the focus of the present work will now be directed towards the direct comparison between a conventional spray-drying system (Mini Spray Drier Büchi B190) against the vibrating mesh technology (Nano Spray Drier Büchi B90).

As a strategy to overcome misunderstanding and potential incorrect interpretation of the results presented in Table 4 (PSD data) it is suggested, as an alternative, to analyze the effects over the specific surface area instead of mean diameter. Specifically for the Eudragit RS100 (EUD) samples, which were produced by feeding liquid streams with varying solute concentrations (0.1; 0.5 and 1.0%), the S_{BET} of the spray dried powders are compared directly with the same property of a sample obtained using a conventional spray-drying equipment (Mini Spray Drier Büchi B190), here considered as a 'reference'. Table 5 illustrates the obtained results indicating a 10-fold increase simply by substituting the conventional two-fluid nozzle (Mini Spray Drier Büchi B190) by the vibrating mesh (Nano Spray Drier Büchi B90) and setting all formulation parameters the same.

Another interesting aspect of the presented results is that the specific surface area tends to increase with the respective dilution of the feeding liquid stream. A 10-fold reduction on the solute concentration results in approximately 135% increase on the S_{BET}. The obtained results corroborate with the PSD data presented in Table 5 which evidences a significant decrease on the mean volume diameter (by discarding any porosity effects it can be assumed as a rule that the specific surface area is increased as the particle size becomes smaller).

As a complement, morphological aspects, homogeneity and agglomeration (aggregation) state of the spray dried powders were evaluated using the high-resolution scanning electron microscopy technique. Figure 4 shows several micrographs registered at different magnifications for direct comparison purposes.

The comparative controlled release kinetics of the spray-dried powders respectively obtained by a conventional spray-drying system (Mini Spray Drier Büchi B190) and by a vibrating mesh technology (Nano Spray Drier Büchi B90) is presented in Figure 5. As shown in Figures 2 and 3 the results presented herein are referred to two pH conditions (pH=1 and pH=8).

The obtained results demonstrate that the release rate behavior is almost the same for the two samples when considering acidic pH conditions, thus indicating that the protection efficiency imposed by the polymeric matrix is independent of the particle size once the solubility of the respective polymer is severely restricted. Once shifting the pH to alkaline conditions a differentiation regarding the release rate behavior of the two compared samples becomes evident. The

Sample Identification	Specific Surface Area S_{BET} (m^2/g)
EUD (1.0%) (Mini Spray Dryer Büchi B190)	0.308
EUD (1.0%) (Nano Spray Drier B90)	3.101
EUD (0.5%) (Nano Spray Drier B90)	5.903
EUD (0.1%) (Nano Spray Drier B90)	7.339

Table 5: Specific surface area data obtained by the B.E.T method.

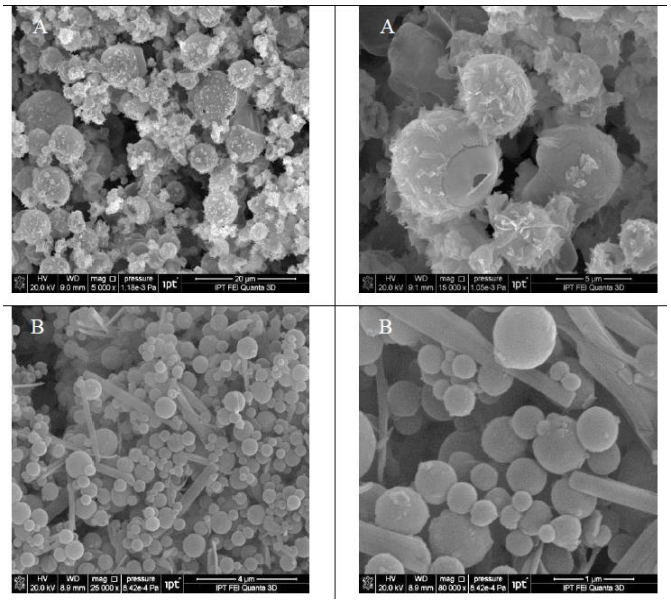

Figure 4: SEM micrographs (A – Mini Spray Drier Büchi B190; B – Nano Spray Drier Büchi B90).

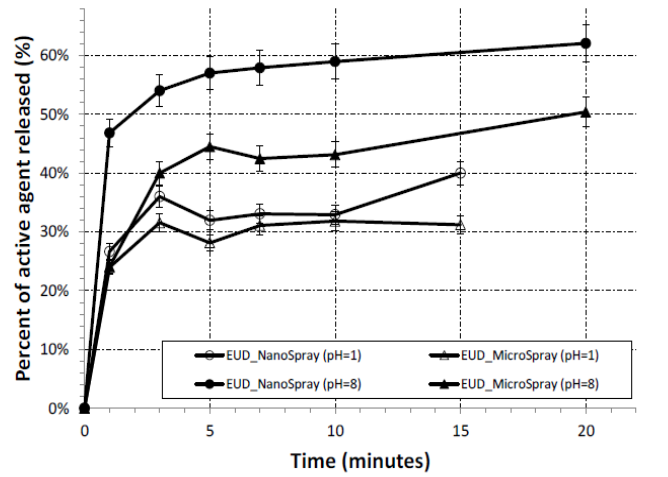

Figure 5: Controlled release kinetics experimentally determined over a 20 minutes period (in-vitro experiments) for spray-dried powders obtained via conventional two-fluid nozzle technology and vibrating mesh technology.

release rate kinetics is faster when considering the application of the vibrating mesh technology as evidenced in Figure 5. This behavior may be justified either as a consequence of the 10-fold increase registered for the specific surface area (Table 5) or any alteration regarding the crystallinity of the polymeric matrix which may improve its solubility in alkaline pH conditions (data not evaluated).

When considering in-vitro alkaline pH condition (pH=8) the amount of active agent released over a 20 minutes period of time equals approximately 50% and 60% respective for the samples obtained by a conventional spray-drying system (Mini Spray Drier Büchi B190) and by a vibrating mesh technology (Nano Spray Drier Büchi B90).

Conclusion

The vibrating mesh spray technology proved to be an effective tool for the production of submicron particles despite the elongated process time. The major limitation related to this new atomization concept was found to be related to highly viscous feeding streams which couldn't be sprayed even when substituting the 4.0 µm mesh by the 7.0 µm one. This restriction was particularly evidenced for the carboxymethyl cellulose once it corresponds to a strong viscosifier. Spray drying of highly diluted solutions favored the production of submicron particles despite of the side effect of significantly reducing the productivity.

By considering pH-sensitive controlled release applications and the five different polymer matrices tested herein, the Eudragit RS100 presented the most promising results. As a function of its pronounced pH-dependent solubility it was demonstrated the potential of controlling the release rate kinetics even in acidic or alkaline pH conditions. The direct comparison of two samples respectively obtained by a conventional spray drying system (Mini Spray Drier Büchi B190) and by a vibrating mesh technology (Nano Spray Drier Büchi B90) demonstrated that the reduction of the particle size and, as a consequence, the increment of the specific surface area both contribute to speed up the release rate kinetics.

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