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*Research Article*

# A Statistical Approach to Optimize the Spray Drying of Starch Particles: Application to Dry Powder Coating

**Luca Bilancetti,[1] Denis Poncelet,[1] Catherine Loisel,[1] Stefania Mazzitelli,[2] and Claudio Nastruzzi[2,3]**

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***Abstract.*** This article describes the preparation of starch particles, by spray drying, for possible application to a dry powder coating process. Dry powder coating consists of spraying a fine powder and a plasticizer on particles. The efficiency of the coating is linked to the powder morphological and dimensional characteristics. Different experimental parameters of the spray-drying process were analyzed, including type of solvent, starch concentration, rate of polymer feeding, pressure of the atomizing air, drying air flow, and temperature of drying air. An optimization and screening of the experimental parameters by a design of the experiment (DOE) approach have been done. Finally, the produced spray-dried starch particles were conveniently tested in a dry coating process, in comparison to the commercial initial starch. The obtained results, in terms of coating efficiency, demonstrated that the spray-dried particles led to a sharp increase of coating efficiency value.

**KEY WORDS:** dry coating; microparticles; spray drying; starch.

## INTRODUCTION

In the last decade, the coating process with polymer in dry powder state (usually called "dry powder coating") has been developed as innovative technology, alternative to the traditional coating, with organic polymeric solutions or aqueous polymeric dispersions (1–5). Dry powder coating usually involves the use of one or more polymers, as dry powder, fed directly into a drum coater or into the fluidized bed chamber, with the simultaneous or alternate application of relatively small amounts of liquid plasticizers (generally comprised between 10% and 30%, with respect to the powder weight), such as triethyl citrate (1–4) or water-based mixtures (2,3).

The dry powder coating technology presents important advantages over conventional coating processes, including avoidance of organic solvents, associated with environmental, toxicological, and safety-related issues, also impacting the manufacturing costs (6,7). In addition, the dry powder coating technology is generally timeless and costless also when compared to coating processes based on aqueous polymeric dispersions (8).

To achieve reasonable shell formation in dry powder coating processes, particle size of the coating polymer represents a crucial parameter. Micronized particles (ranging between 1 and 10 μm in size) are indeed generally preferred (4,9). The selection of an appropriate method, to obtain dry powders with a controlled mean size and a determined size distribution, appears crucial for the development of a high efficiency of dry powder coating processes.

In this respect, spray drying could represent one of the methods of choice for the production of fine powders (usually with a dimensional range comprised between 1 and 30 μm) for pharmaceutical and food applications (10–12). The spray-drying approach is suitable for a large array of products including heat-sensitive or heat-resistant and water-soluble or water-insoluble materials, as well as to low and high molecular weight compounds, including a variety of polymers (12).

Other advantages offered by the spray-drying technology reside in the fact that it is a simple and rapid process; it can be easily scaled up after a "good" solvent, for a particular material, has been identified.

Spray drying is based on the atomization of a polymeric solution (eventually containing an active ingredient, in the form of solution or suspension) within a drying chamber. A stream of heated air (usually in coflow with the atomized polymer) transforms the small droplets in solid microparticles by a rapid evaporation of the solvent. Finally, the formed microparticles are separated from the heating air by a cyclone separator and conveniently collected.

Previous studies describing coating approaches based on dry powder coating technology were focused on the use of two main classes of coating material: semisynthetic cellulose derivates (e.g., hydroxypropyl methylcellulose succinate,

[1] ENITIAA, UMR CNRS GEPEA 6144, route de la Geraudiere BP 82225, 44322, Nantes Cedex 3, France.
[2] Department of Chemistry and Technology of Drugs, University of Perugia, via del Liceo 1, 06123, Perugia, Italy.
[3] To whom correspondence should be addressed. (e-mail: nas@unipg.it; URL: www.biomaterials.it)

 

ethyl cellulose) (1) and acrylic and methacrylic polymers (e.g., Eudragit RS) (2,3). In order to find alternative materials suitable for dry powder coating processes, in the current paper, the production of a spray-dried modified starch (Lycoat© RS 780 product bulletin, http://www.readilycoat.com) powder and its use as coating layer ("guest") for microcrystalline cellulose pellets (used as model internal core "host") in dry powder coating approach, are described.

Starch and its derivates are particularly attractive as possible coating material since they represent a class of additives largely employed for pharmaceutics as well as food applications. Starch is one of the largest naturally existing substances, and it can be used as film-forming polymer being natural and biorenewable.

Applications of starch films and coatings, by conventional spray coating processes, are commonly used since they are edible, odorless, tasteless, colorless, nontoxic, and biodegradable (13,14).

Summarizing, this paper describes (a) the production of modified starch particles by spray-drying technique; (b) the evaluation of the influence of different operating parameters on particle characteristics, namely, dimension, morphology, and recovery; and finally (c) the validation of the produced spray-dried starch particles in a dry powder coating process.

## MATERIALS AND METHODS

### Materials

Lycoat© RS 780, a modified starch derivative (hydroxypropyl pea starch) was a kind gift from Roquette (Roquette, Lestrem, France; Lycoat© RS 780 product bulletin, http://www.readilycoat.com); microcrystalline cellulose pellets (CELLETS® 1,000–1,400 μm) were purchased from IPC Process-Center GmbH and Co. (KG, Dresden, Germany); triethyl citrate (Merck KGaA, Darmstadt, Germany) and glycerol (Acros Organics, Geel, Belgium) were used as plasticizers. All other chemicals and reagents were of the highest purity grade commercially available.

### Choice of Solvent

The solubility of hydroxypropyl starch (Lycoat© RS 780) was determined as follows: up to 200 mg of polymer was added to 1 ml of solvent or solvent mixture at room temperature and maintained under stirring for 2 h. The following solvents or mixture of solvents were considered: (a) pure water, (b) pure ethanol, (c) pure acetone, (d) water/ethanol (95:5, 90:10, 80:20 *v*/*v*), (e) water/acetone (95:5, 90:10, 80:20 *v*/*v*).

### Production of Starch Particles by Spray Drying

Starch particles were produced using a spray drier ("Mini Spray Dryer" Model B-290, Buchi, Laboratoriums Technik AG, Flawil, Germany; see scheme in Fig. 1).

A starch solution (15–25%, *w*/*v*) was transferred through a peristaltic pump and feed to the spraying nozzle (0.7 mm i.d.), into the drying chamber of the apparatus. A flow of heated air, aspirated by a pump, induces the quick evaporation of the solvent from the drops, leading to the formation of solid particles. The obtained powder, after separation from the exhausted air by a cyclone, was settled into the product collection vessel and was kept under vacuum up to the final use.

Screening of the main parameters controlling the process was initially realized using a classical intuitive approach, "Changing One Separate factor a Time" (COST). The considered experimental parameters were the solvent employed for the solubilization of starch (Solv), the starch solution concentration (Conc), the rate of peristaltic pump for polymer feeding (Pump), the atomization gas pressure

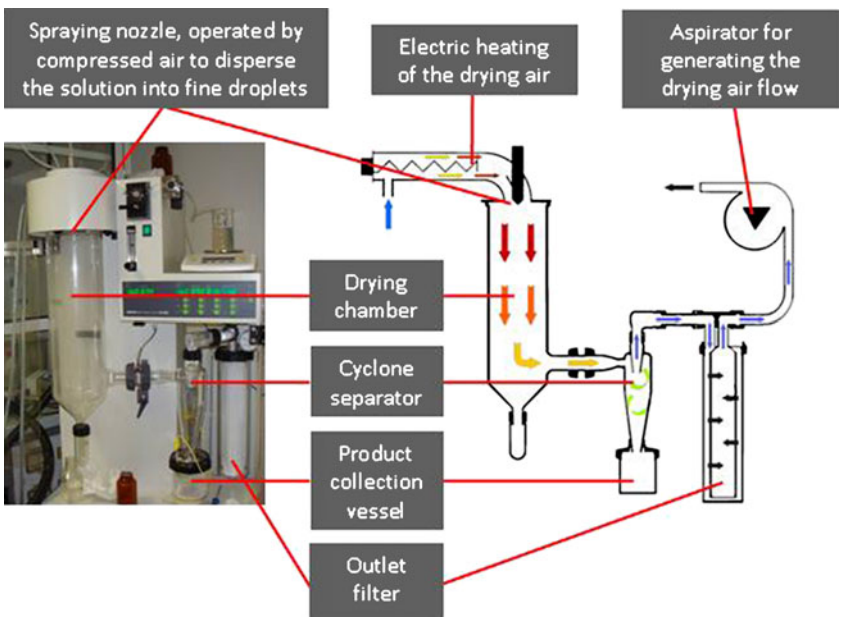


**Fig. 1.** Schematic representation of the spray-drying process

**Table I.** Solubility of Hydroxypropyl Pea Starch (Lycoat© RS 780) in Pure Solvents or Solvent Mixtures

| Solvent and solvent mixture | Ratio (%, *v*/*v*) | Solubility |
|---|---|---|
| Water[a] | – | Soluble[b] |
| Ethanol | – | Insoluble |
| Water/ethanol | 95:5 | Soluble[b] |
| Water/ethanol | 90:10 | Soluble[b] |
| Water/ethanol | 80:20 | Partially soluble[b,c] |
| Acetone | – | Insoluble |
| Water/acetone | 95:5 | Insoluble |
| Water/acetone | 90:10 | Insoluble |
| Water/acetone | 80:20 | Insoluble |

[a] The determination was performed at room temperature
[b] The determination of solubility was evaluated up to a starch concentration of 250 g/l
[c] Turbid fine dispersion

required to spray the solution (Spray), the flow rate of drying air (Air), and finally, the temperature of drying air (Temp). In Table I, the investigated experimental parameters and their range of variation are reported.

Taking into consideration the results obtained by this first approach that allowed the selection of the most critical parameters, the process optimization was performed by a second approach based on an experimental design and statistical analysis design of the experiment (DoE). A randomized central composite face-centered design (CCF), consisting of 16 runs, was used. The experimental design and the evaluation of the experiments were performed by the PC software MODDE 8.0 (Umetrics AB, Sweden), followed by multiple linear regression (MLR) algorithms.

### Size and Morphological Characterization of Spray-Dried Starch Particles

The morphology of spray-dried starch particles was evaluated by optical stereomicroscopy (Nikon SMZ 1500 stereo microscope, Tokyo, Japan). Samples of starch particles were dispersed, immediately after preparation, in cyclohexane, applied to a microscope slide, and examined microscopically. The morphology of starch spray-dried particles was also observed by scanning electron microscope (Cambridge S 360) after metallization by gold coating (Edwards Sputter coating S150). Starch particle size distribution was determined, in the dry form, by laser light diffraction (by volume; Mastersizer, Malvern, UK).

### Dry Powder Coating Process Using Spray-Dried Starch Particles

The dry powder coating process was conducted using a prototype pan coater device (manufactured in ENITIIA) that is schematized in Fig. 2. The characteristics of the pan coater were as follows: pan shape and dimensions, cylinder with 40-cm base diameter and 25 cm height; an air-compressed spray nozzle fixed at 20 cm from the "host" bed surface.

The entire dry powder coating procedure has been described elsewhere (15). Briefly, 400 g of microcrystalline cellulose pellets (used as "host") was charged in the pan coater. The speed of rotation was set at 35 rpm. The starch powder (used as "guest") was fed into the pan (at rate of 5 g/min), by a screw feeder (manufactured in ENITIIA), while the plasticizer was simultaneously sprayed by an air-compressed atomization nozzle (at a rate of 2 ml/min). The atomization pressure was set to 0.3 bars.

The coating process efficiency (CE) was calculated by Eq. 1:

$$\mathrm{CE}(\%) = \frac{M_c - M_i}{M_{starch} + M_{plast}} \quad (1)$$

where $M_i$ and $M_c$ are, respectively, the weight of the initial (before coating process) particles (host microcrystalline cellulose pellets) and coated particles; $M_{starch}$ is the weight of the guest starch powder, and finally, $M_{plast}$ is the weight of the plasticizer.

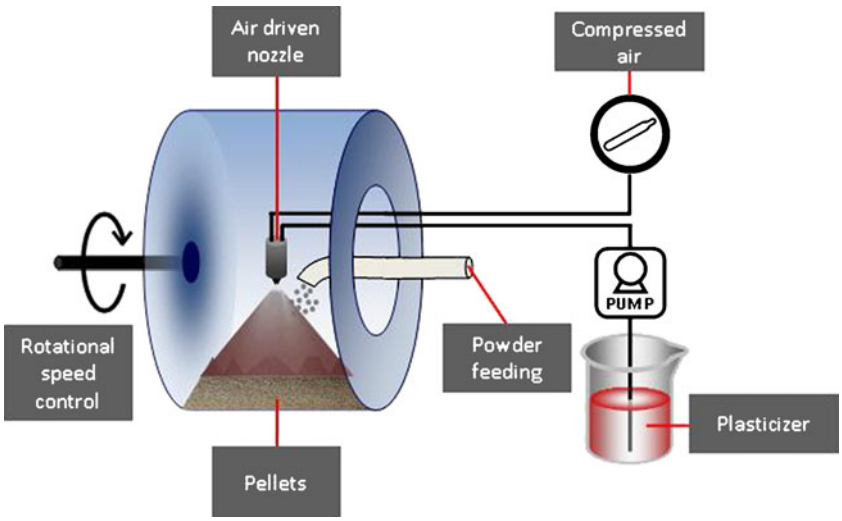


**Fig. 2.** Schematic representation of the pan coater device (manufactured in ENITIIA) for the dry powder coating process

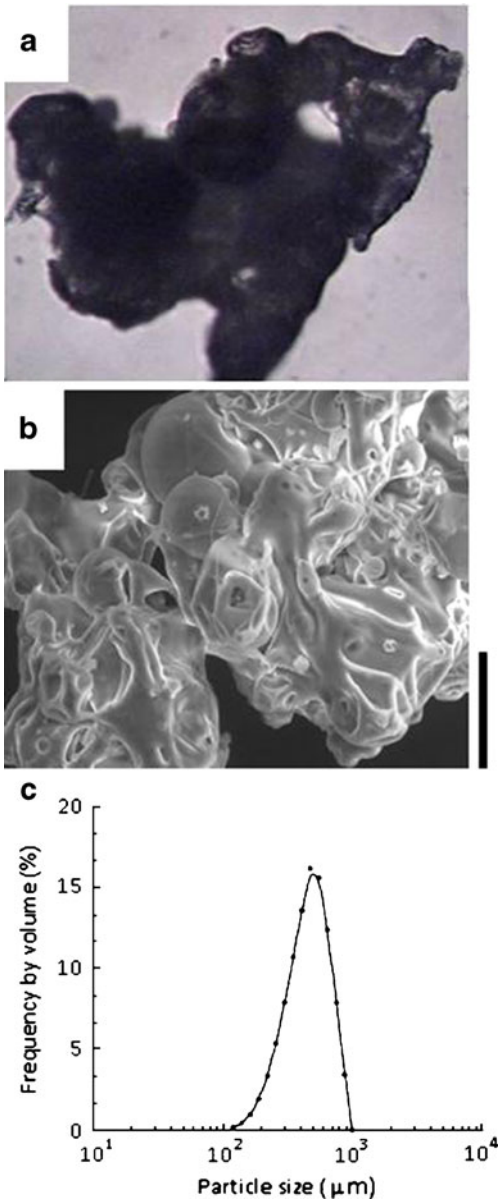


**Fig. 3.** Morphological and dimensional characterization of the model coating ("guest") material. Optical (**a**) and scanning electron (**b**) photomicrographs of native hydroxypropyl pea starch (Lycoat© RS 780) before spray drying. **c** Size distribution analysis (by volume) as determined by laser light diffraction. The *bar* corresponds to 50 and 30 μm, in **a** and **b**, respectively

To evaluate the quality of the coating, coated particles were sieved on a stainless steel sieve with 80-μm opening. The sieving was performed in order to estimate the possible friability of the coating layer (that would release guest particles) as well as the presence of free (not deposited onto the surface of host pellets) aggregates. The coating efficiency after sieving ($CE_{sieve}$) is given by Eq. 2:

$$CE_{sieve}(\%) = \frac{M_{cs} - M_i}{M_{starch} + M_{plast}} \quad (2)$$

where $M_{cs}$ is the weight of coated particles after sieving.

**Table II.** Production of Spray-Dried Hydroxypropyl Pea Starch (Lycoat© RS 780) Particles

| Parameter | Abbreviation | Range |
|---|---|---|
| Type of solvent | Solv | Water, water/ethanol, 95:5; water/ethanol, 90:10; water/ethanol, 80:20; |
| Starch concentration | Conc | 15–25%, *w/v* |
| Feeding rate | Pump | 5–10 ml/min |
| Atomizing gas pressure | Spray | 250–550 mbar |
| Drying air flow | Air | 28–35 $m^3$/h |
| Temperature of drying air | Temp | 100–160°C |

Investigated experimental parameters and their range of variation

## RESULTS AND DISCUSSION

As stated in the introduction, dry coating procedures would require "guest" powders with a number of specific requisites, such as shape, size distribution, and a dimensional range possibly comprised between 1 and 10 μm (4,9,15). In this respect, we started a series of experiments aimed to the production of starch particles by spray-drying technique.

### Characterization of the Commercial Starting Starch

As model coating ("guest") material, a modified starch was selected. This particular polymer is marketed by

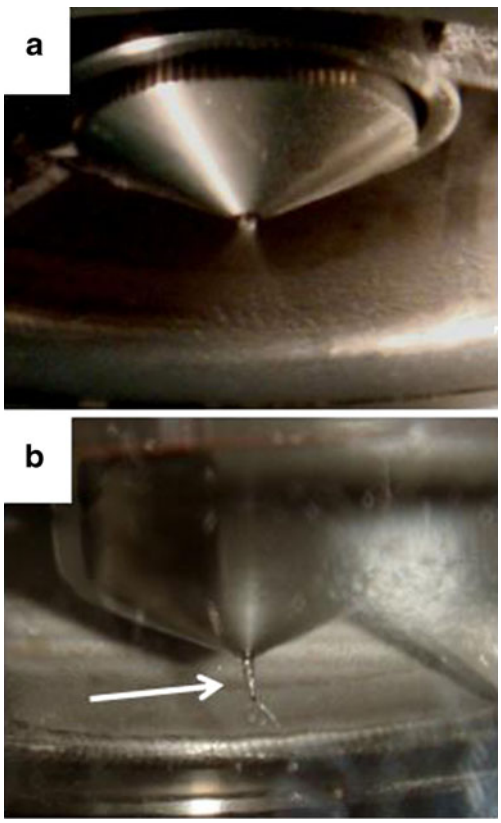


**Fig. 4.** Effect of the starch concentration (in water/ethanol 90:10, *v/v*) on spray pattern. Starch was solubilized at 20% (**a**) or 25% (**b**) *w/v*. *Arrows* indicate the large droplets formed due to the excessive viscosity of starch solution, resulting in low recovery percentages

**Table III.** Production of Starch Particles by Spray Drying: Analysis of the Experimental Parameters by COST approach

| Batch | Solvent water/ethanol (%, *v/v*) | Conc (%) | Spray (mbar) | Pump (ml/min) | Air ($m^3$/h) | Temp (°C) | Recovery (%) |
|---|---|---|---|---|---|---|---|
| Effect of type of solvent | | | | | | | |
| LSDP-01 | 100:0 | 20 | 400 | 7.5 | 32 | 130 | 19 |
| LSDP-02 | 95:5 | 20 | 400 | 7.5 | 32 | 130 | 24 |
| LSDP-03 | 90:10 | 20 | 400 | 7.5 | 32 | 130 | 27 |
| LSDP-04 | 80:20 | 20 | 400 | 7.5 | 32 | 130 | 10 |
| Effect of the starch concentration | | | | | | | |
| LSDP-05 | 90:10 | 15 | 400 | 7.5 | 32 | 130 | 14 |
| LSDP-03 | 90:10 | 20 | 400 | 7.5 | 32 | 130 | 27 |
| LSDP-06 | 90:10 | 25 | 400 | 7.5 | 32 | 130 | 8 |
| Effect of the atomization gas pressure required to spray the solution | | | | | | | |
| LSDP-07 | 90:10 | 20 | 250 | 5.0 | 32 | 130 | 9 (10.2)[a] |
| LSDP-08 | 90:10 | 20 | 400 | 5.0 | 32 | 130 | 23 (7.4)[a] |
| LSDP-09 | 90:10 | 20 | 550 | 5.0 | 32 | 130 | 30 (3.9)[a] |
| Effect of the rate of peristaltic pump for polymer feeding | | | | | | | |
| LSDP-08 | 90:10 | 20 | 400 | 5.0 | 32 | 130 | 23 |
| LSDP-03 | 90:10 | 20 | 400 | 7.5 | 32 | 130 | 27 |
| LSDP-10 | 90:10 | 20 | 400 | 10.0 | 32 | 130 | 18 |
| Effect of the flow rate of drying air | | | | | | | |
| LSDP-11 | 90:10 | 20 | 400 | 5.0 | 28 | 130 | 11 |
| LSDP-08 | 90:10 | 20 | 400 | 5.0 | 32 | 130 | 23 |
| LSDP-12 | 90:10 | 20 | 400 | 5.0 | 35 | 130 | 28 |
| Effect of the temperature of drying air | | | | | | | |
| LSDP-13 | 90:10 | 20 | 400 | 5.0 | 32 | 100 | 12 |
| LSDP-08 | 90:10 | 20 | 400 | 5.0 | 32 | 130 | 23 |
| LSDP-14 | 90:10 | 20 | 400 | 5.0 | 32 | 160 | 26 |

Data represent the average of three independent determinations
[a] Particle size in microns, as determined by optical stereomicroscopy and SEM

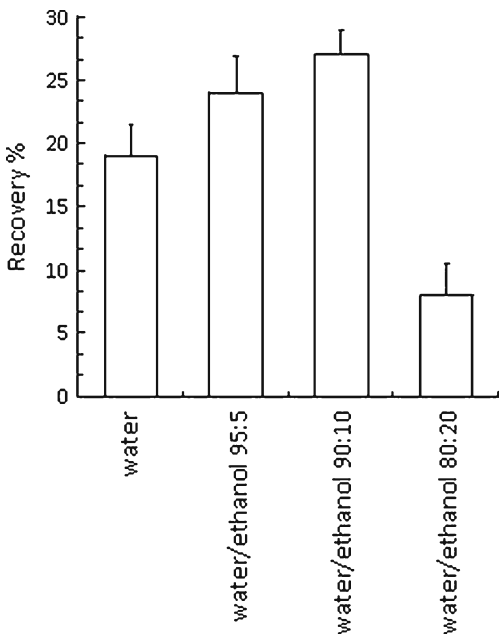


**Fig. 5.** Effect of solvent and solvent mixtures on starch recovery. Data represent the percentage of the recovered spray-dried starch particles, with respect to the initial weight of the dry starch before solubilization. Starch was solubilized in pure water (LSDP-01); water/ethanol 95:5, *v/v* (LSDP-02); water/ethanol 90:10, *v/v* (LSDP-03); and water/ethanol 80:20, *v/v* (LSDP-04). The experimental conditions employed for the production of the different batches are reported in Table III

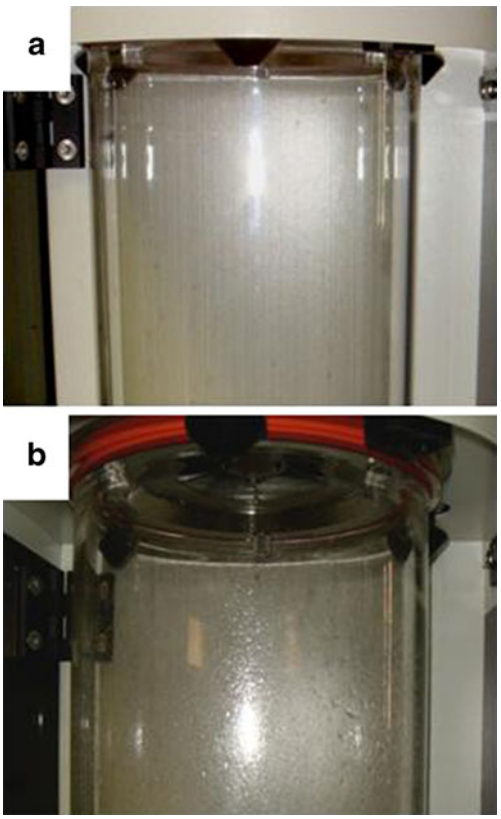


**Fig. 6.** Effect of rate of polymer feeding on particle recovery. The photographs show the wall of drying chamber during the spray drying at a feeding rate of 7.5 ml/min (**a**) and 5.0 ml/min (**b**)

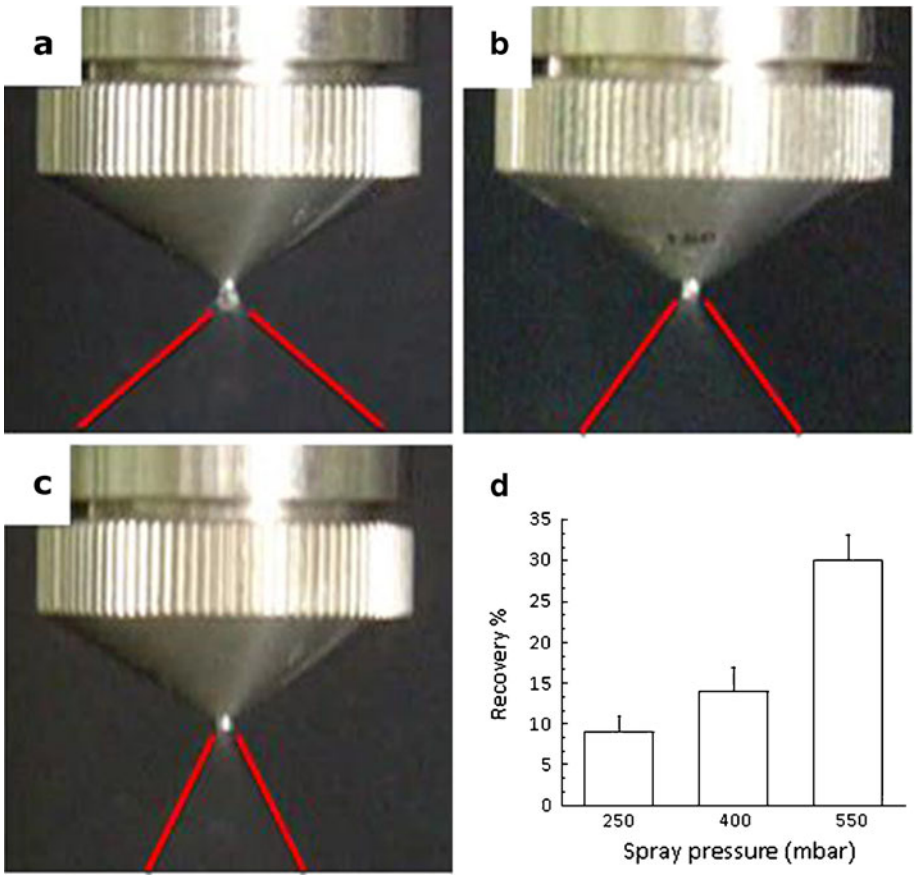


**Fig. 7.** Effect of the atomizing gas pressure on spray pattern and particle recovery. **a–c** Photographs of spray pattern at 250 (**a**), 400 (**b**), and 550 mbar (**c**). **d** Starch particle recovery at the indicated spray pressures

Roquette under the registered trade name of Lycoat© RS 780 (product bulletin, http://www.readilycoat.com). This starch is characterized by a rapid dissolution at room temperature, using traditional mixing equipments, as indicated by the producer. Film coatings, applied with conventional procedure, will not impair either the flavor or the color of tablets (Lycoat© RS 780 product bulletin, http://www.readilycoat.com). The starting starch particles (as provided by the producer in the commercial product) have been characterized by optical (Fig. 3a) and scanning electron microscopy (Fig. 3b). The microphotographs show that the commercial starch particles are characterized by a rather irregular shape and surface, as well as a high porosity. Figure 3c reports the size distribution analysis of the starch particles, as determined by laser light diffraction granulometer. The mean diameter was evaluated equal to 510±47 μm (±SD).

**Table IV.** Experimental Design Matrix and Results of the DoE Approach

| Run number | Spray (mbar) | Pump (ml/min) | Temp (°C) | Recovery (%) |
|---|---|---|---|---|
| 1 | 250 | 5.0 | 100 | 6 |
| 2 | 250 | 5.0 | 160 | 12 |
| 3 | 250 | 7.5 | 130 | 3 |
| 4 | 250 | 10.0 | 100 | 0 |
| 5 | 250 | 10.0 | 160 | 0 |
| 6 | 400 | 5.0 | 130 | 20 |
| 7 | 400 | 7.5 | 100 | 20 |
| 8 | 400 | 7.5 | 130 | 29 |
| 9 | 400 | 7.5 | 130 | 30 |
| 10 | 400 | 7.5 | 160 | 27 |
| 11 | 400 | 10.0 | 130 | 20 |
| 12 | 550 | 5.0 | 100 | 35 |
| 13 | 550 | 5.0 | 160 | 52 |
| 14 | 550 | 7.5 | 130 | 30 |
| 15 | 550 | 10.0 | 100 | 35 |
| 16 | 550 | 10.0 | 160 | 45 |

All runs were performed with an initial starch concentration of 20% *w/v*

**Table V.** Coefficient List for Lycoat Spray-Dried Particles

| Recovery | Std. err. | *P* | Conf. int(±) |
|---|---|---|---|
| Constant | 2.3317 | 1.69437e−005 | 4.41755 |
| Spray | 1.72318 | 2.08439e−005 | 3.26466 |
| Pump | 1.72318 | 0.242423 | 3.26466 |
| Temp | 1.72318 | 0.0489305 | 3.26466 |
| Spray × spray | 3.32907 | 0.266314 | 6.30714 |
| Pump × pump | 3.32907 | 0.880028 | 6.30714 |
| Temp × temp | 3.32907 | 0.400611 | 6.30714 |
| Spray × pump | 1.92657 | 0.619723 | 3.65 |
| Spray × temp | 1.92657 | 0.235533 | 3.65 |
| Pump × temp | 1.92657 | 0.461727 | 3.65 |

All runs were performed with an initial starch concentration of 20% *w/v*

### Selection of the Solvent Composition

To run smoothly and efficiently, a spray-drying process, the solvent (or solvent mixtures) has to respect some conditions.

1. High polymer solubility reduces process time and limits solvent evaporation energy.
2. The polymer concentration should be sufficiently high to result in the formation of particles with a relatively high density and thus with good mechanical characteristics.
3. The viscosity of the initial solution should be relatively low to allow its homogenous atomization.
4. A solvent with low boiling point and especially low evaporation enthalpy reduces energy cost and speed up the drying process.
5. For pharmacy and food applications, the solvent should be possibly approved by the respective control agencies.

Water is the most obvious solvent for starch. However, starch aqueous solutions are often quite viscous (especially for high molecular weight starch), and their evaporation

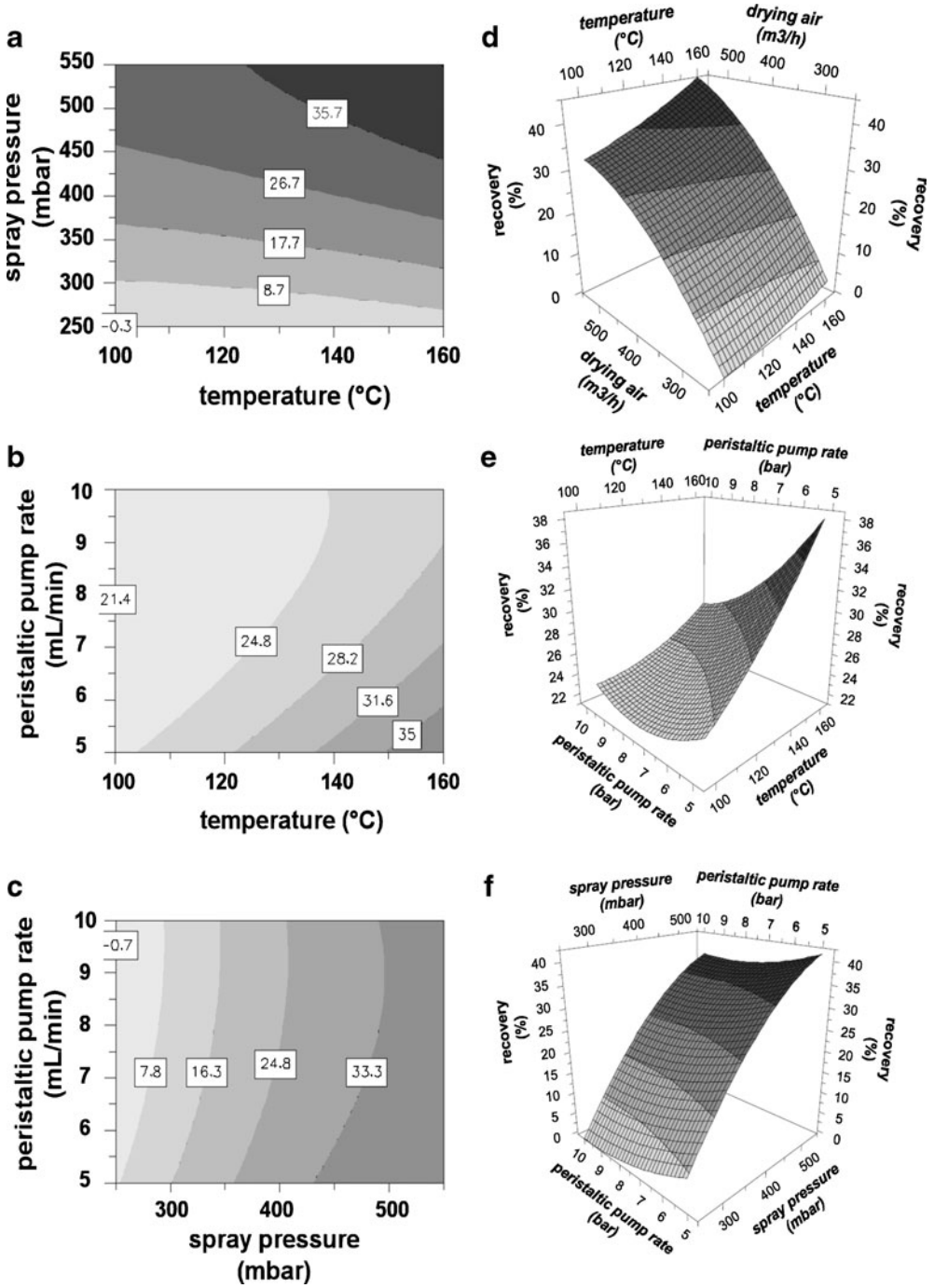


**Fig. 8.** DoE analysis for the production of starch (Lycoat© RS 780) spray-dried particles. Contour plots (**a**–**c**) and the corresponding response surface plots (**d**–**f**) of the response "recovery" for the interaction between the variables: "Temp" *vs.* "Spray" (**a**, **d**); "Temp" *vs.* "Pump" (**b**, **e**), and "Spray" *vs.* "Pump" (**c**, **f**)

enthalpy is high. Therefore, as preliminary study, the solubility of the starch in various solvents or solvent mixtures was investigated. As reported in Table II, water, ethanol, acetone, and their mixtures were considered. Good solubility (up to 250 g/l) was achieved for water and the water/ethanol mixtures. On the contrary, starch was insoluble in pure ethanol and acetone and in water/acetone mixtures. Starch concentrations higher than 250 g/l were not considered, since the solution became too viscous and therefore almost impossible to be homogeneously atomized. For instance, a 25% of Lycoat© RS 780 in water has a viscosity of 380 mPa s (Lycoat© RS 780 product bulletin, http://www.readilycoat.com). Taking into consideration what is stated above, all spray-drying experiments were performed using only water/ethanol mixtures.

## Influence of Operating Conditions on the Production of Starch Particles: Intuitive COST Approach

In the first part of the study, aimed to the optimization of spray-dried starch production, a classical intuitive approach, COST, was performed. This strategy allowed defining the critical parameters influencing the process, especially considering particle dimension, morphology, surface characteristics, and percentage of particle recovery.

Following this approach, a number of experimental parameters (listed in Table II) were selected and varied one by one, while all the others were maintained constant. The considered parameters were type of solvent, starch concentration, rate of polymer feeding, pressure of the atomizing gas, flow, and temperature of drying air.

### *Effect of Solvent and Starch Concentration on Spray-Dried Starch*

As previously stated, starch solution, at concentrations higher than 20%, *w/v* (i.e., 25%, *w/v*), generated spray patterns with a significant proportion of large droplets, as shown in Fig. 4. This fact resulted in a drastic decrease of the recovery percentage that passed from 27% (obtained with a 20% *w/v* starch concentration) to 8% (Table III).

As solvent, water/ethanol mixtures were preferred to pure water due to two main considerations: firstly, the presence of the organic solvent facilitates the evaporation process and therefore reduces the time and energy required for particle production; secondly, the use of ethanol in mixture with water could also have a positive effect on the percentage of particle recovery. In fact, as reported in Fig. 5 and Table III, the use of water/ethanol mixtures at 90:10 volume ratio led to the highest recovery (27%), with respect to all other batches of spray-dried starch. This result was tentatively interpreted due to the faster evaporation of the solvent from the sprayed droplets, with a consequent reduction of the number of droplets colliding and thus sticking to the wall of drying chamber. We also tested the possibility of increasing the percentage of ethanol, performing a number of spray-drying tests with starch solutions in water/ethanol mixture at 80:20 (%, *v/v*). Unfortunately, as reported in Table I, the starch is only partially soluble in water/ethanol at 80:20, and therefore, the use of such mixture results in the

**Table VI.** Optimized Parameters Selected for Spray-Dried Starch Particle Production

| Parameter | Abbr. | Range |
|---|---|---|
| Type of solvent | Solv | Water/ethanol, 90:10 |
| Starch concentration | Conc | 20%, *w/v* |
| Feeding rate | Pump | 5 ml/min |
| Atomizing gas pressure | Spray | 550 mbar |
| Drying air flow | Air | 35 $m^3$/h |
| Temperature of drying air | Temp | 160°C |

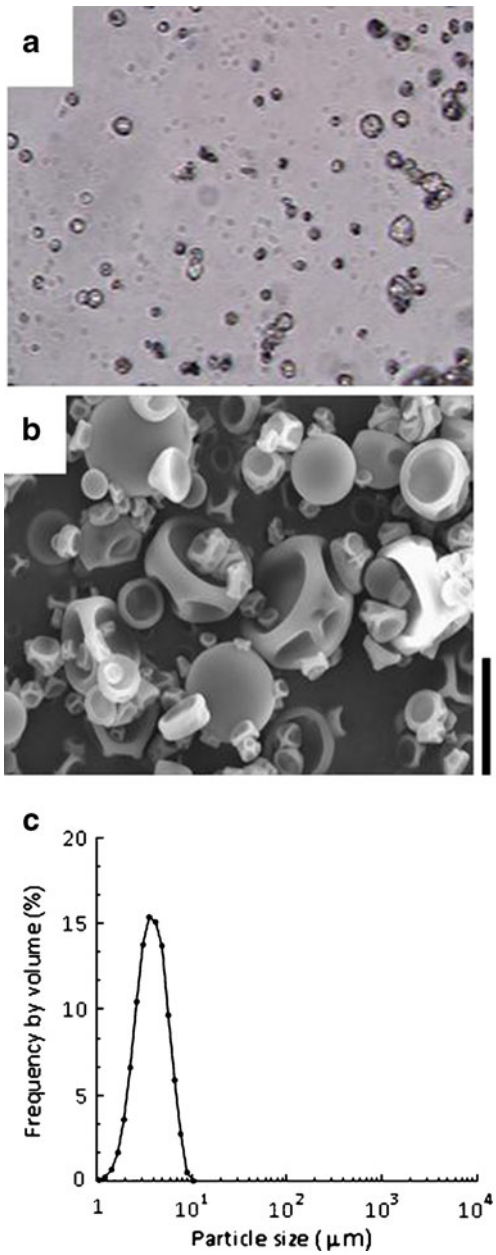


**Fig. 9.** **a** Optical photomicrograph of the optimized spray-dried starch particles (see experimental parameters in Table VI). **b** Scanning electron photomicrograph of spray-dried starch. The *bar* corresponds to 50 and 30 μm, in **a** and **b**, respectively. **c** Size distribution analysis (by volume) as determined by laser light diffraction

formation of a turbid dispersion containing small undissolved starch particles. This features resulted in a highly inhomogeneous atomization of the starch dispersion, often resulting in a partial/complete clogging of the spraying nozzle with a drastic drop of the recovery value (8%).

*Effect of Polymer Feeding Rate on Spray-Dried Starch*

The function of the peristaltic pump is to carry the starch solution to the nozzle. This parameter influenced the efficiency of the drying process; in fact, high pumping rates (10.0 ml/min) resulted in large volumes of sprayed solution to be dried. As a consequence, heated air was partially unable to instantaneously transform liquid droplets in solid particles.

Increasing the feed allows reducing the process time but with a risk of incomplete droplet drying. This phenomenon considerably reduced the final particle recovery efficiency (18%), principally due to the adhesion of a large percentage of droplets to the wall of the drying chamber (Fig. 6). Lowering the pumping rate at 7.5 or 5.0 ml/min had a positive effect on the starch recovery that increased up to 22% and 23%, respectively (Table III).

*Effect of Gas Flow on Spray-Dried Starch*

Gas flow of the spraying device is defined as the amount of atomization gas required to spray the liquid to be dried. This parameter greatly influences particle dimensions, and therefore, the effect of gas flow, on particle size, was determined. Different spray pressures were analyzed comprised between 250 and 550 mbar (Table III).

The obtained results demonstrated that the increase of the spray pressure had two main effects. Firstly, the increase of nitrogen pressure changes the spray pattern with a progressive reduction of spraying angle that passes from 105° to 55° (see Fig. 7a–c). This feature had a positive effect on particle recovery, since a smaller amount of droplets stuck on drying chamber wall resulting in higher recovery (Fig. 7d).

Secondly, the increase of nitrogen pressure had also a strong effect on particle dimension that is progressively reduced. In fact, the mean dimension of spray-dried starch particles decreased from 10.2±0.9 to 3.9±1.4 μm.

*Effect of Drying Air Flow on Spray-Dried Starch*

The flow of drying air influences the transformation of droplets in solid particles; an increase in flow led to a decrease of the transit time of starch droplet/particles through the spray drier. This feature reduces the contact time between drying air and sprayed droplets, representing an advantage for thermolabile compounds that remain in contact with hot air for a short time.

On the contrary, an increase in aspiration rate could be a disadvantage if the solvent evaporation (transforming liquid droplets to solid particles) requires longer time with respect to the permanence into the instrument. The analysis of the

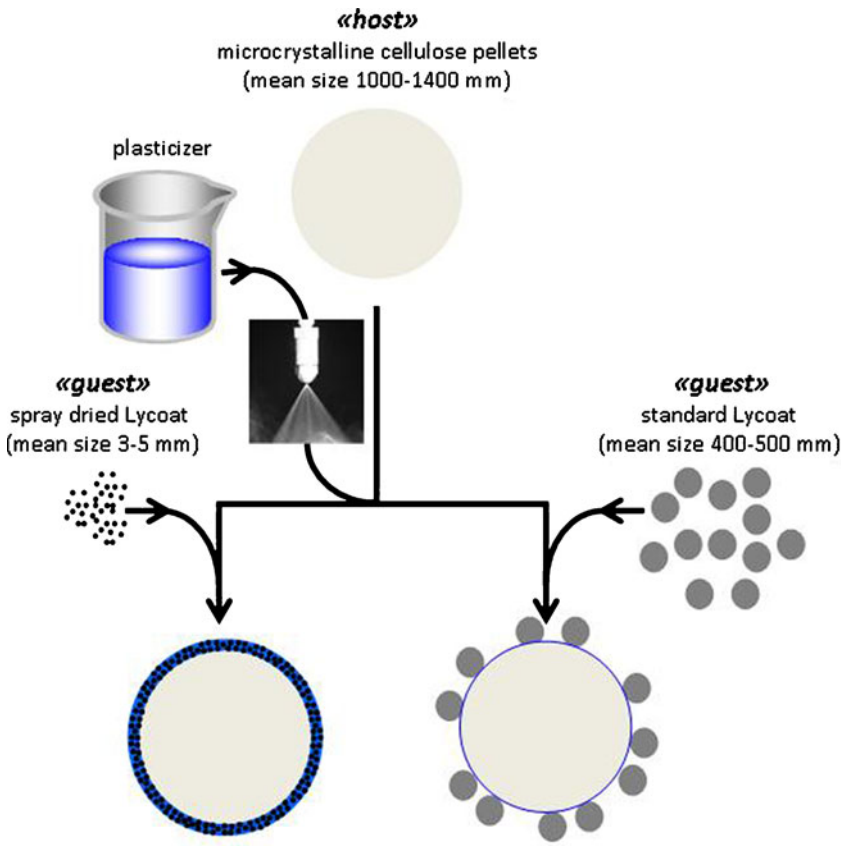


**Fig. 10.** **a** Schematic representation of dry powder coating process. **b** Dry coating process efficiency (CE) using different plasticizers

obtained data (reported in Table III) indicates that, as expected, particle recovery is dependent on aspirator values. The optimal value for the air flow was set at 35 $m^3$/h, which resulted in a recovery of 28%.

*Effect of Drying Air Temperature on Spray-Dried Starch*

Temperature of air drying is an important parameter especially for particle recovery and material stability. The air required to dry the sprayed droplets is carried inside the instrument with an aspirator. Aspiration makes a partial vacuum, allowing the inlet of hot air. The temperature employed in spray-drying preparations should not cause any thermal degradation of the material to be dried and an almost instantaneous evaporation of the solvent. Data reported in Table III indicate that a progressive increase of temperature (from 100°C to 160°C) had a positive effect on particle recovery that increases from 12% to 26%.

## Influence of Operating Conditions on the Production of Starch: DoE Approach

The results of COST approach were thereafter employed for optimizing and quantifying the interactions among experimental parameters by a DoE approach.

DoE offers a rational approach that enhances the value of the research, reducing the number of experiments, and providing much more information about the effects of different variables and their possible interactions (16).

For the DoE analysis, three experimental parameters were selected as factors, namely, "Pump," "Spray," and "Temp," and tested at three levels (Tables IV and V). For three factors with three levels each, there are $3^3$ or 27 possible combinations in a full-factorial design. In our case, we selected 14 experiments by a randomized CCF, which requires fewer trials (17). CCF represents indeed one of the most used designs in pharmaceuticals (18,19). We also added two center points in order to have an estimation of the experimental error. In this way we obtained both a nonlinear response and a response surface modeling. The collected experimental data were fitted by an MLR model with which several responses can be dealt with simultaneously to provide an overview of how all the factors affect all the responses.

**Table VII.** Production of Dry Coated Particle with Hydroxypropyl Pea Starch (Lycoat© RS 780) in Standard and Spray-Dried Form

| Polymer | Particle size (μm) | Plasticizer | CE (%) | CE after sieving (%) |
|---|---|---|---|---|
| Lycoat | ~500 | TEC | 28.2±5 | 9.2±4 |
| Lycoat | ~500 | Glycerol/water | 22.7±6 | 11.1±3 |
| Lycoat | ~500 | Glycerol | 25.4±3 | 10.3±4 |
| Lycoat spray-dried | ~4 | TEC | 56.8±5 | 45.2±6 |
| Lycoat spray-dried | ~4 | Glycerol/water | 62.5±3 | 49.8±7 |
| Lycoat spray-dried | ~4 | Glycerol | 66.5±5 | 52.1±5 |

Data represent the average of five independent determinations
*TEC* triethyl citrate

The general MLR equation for the responses of the chosen model is reported below:

$$y_i = \text{Constant} + A_1F + A_2P + A_3H + A_4F^2 + A_5P^2 + A_6H^2 + A_7FP + A_8FH + A_9PH \quad (3)$$

where constant is the mean of the 16 runs and $A_i$ the regression coefficients of the factors and their interactions.

By examining the results of DoE, the main observation was that a change in "Temp" and "Spray" from low to high levels results in an increase of recovery. While "Pump" exerts an influence in its low level, causing the increase of the response (Tables IV and V). Both two-dimensional and three-dimensional graphs of the investigated factors are reported in Fig. 8, showing the influence of factors on particle recovery.

The validity and the significance of the model were estimated by analysis of variance. All the data obtained fitted

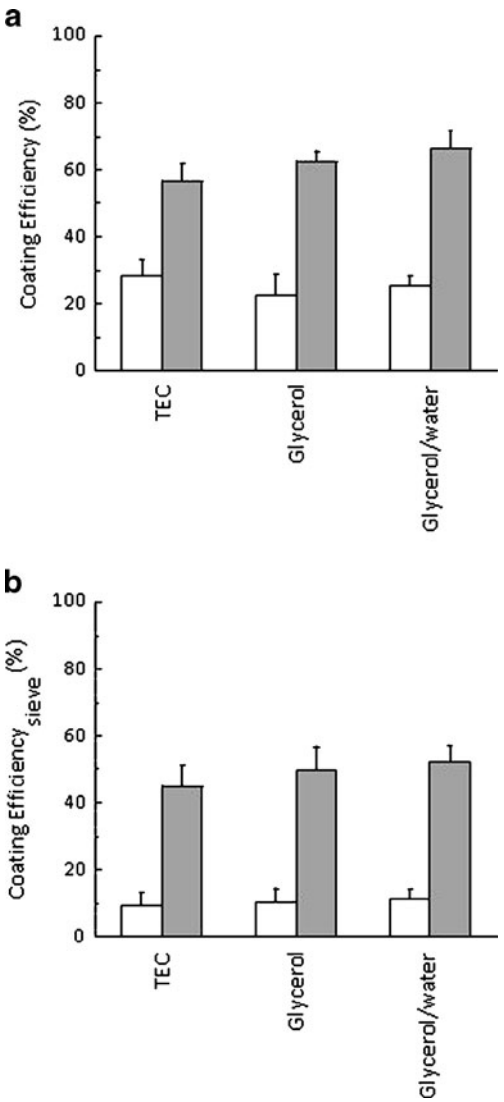


**Fig. 11.** Dry coating process efficiency before (CE) (**a**) and after sieving ($CE_{sieve}$) (**b**) using different plasticizers. *White bars* correspond to experiments conducted with standard starch particles and *gray bar* corresponds to experiments conducted with spray-dried starch particles and the best plasticizer

well, determining a good reproducibility of the studied model. We get a large regression coefficient $R^2$ (0.941) that is a necessary condition for a validity model with a significant power of prediction of the model $Q^2$ (0.714).

The optimized spray-dried starch particles were produced with the instrumental setup determined by COST and DoE approach, which is reported in Table VI. In addition, in Fig. 9 are shown the optical and scanning electron microscopic analyses and size distribution plot of the optimized spray-dried starch particles.

### Application of Spray-Dried Starch to Dry Powder Coating

The optimized spray-dried starch particles were validated in a dry powder coating process (schematized in Fig. 10), taking as reference materials the standard (commercial available) Lycoat© RS 780 particles, as supplied by the producer.

The dry coating process was performed with standard and spray-dried starch (as "guest") and different plasticizers, namely (a) triethyl citrate, (b) glycerol, and (c) a glycerol/water mixture (80:20, *v*/*v*).

The results of the experiments, reported in Table VII and Fig. 11, demonstrated that, in all cases, using standard starch, the coating process efficiencies, CE (Fig. 11a) and $CE_{sieve}$ (Fig. 11b), were relatively low, not exceeding 30% and 10%, respectively. On the contrary, the use of the spray-dried starch resulted in a substantial improvement of the coating process efficiency, as demonstrated by both CE and $CE_{sieve}$ parameters, which reached 60% and 50% values, respectively.

The improvement of coating process, obtained by spray-dried "guest" particles, could be explained by the effect of forces playing a role during the adhesion process.

The adhesion forces are the sum of Van der Waals, electrostatic, and capillary forces, where capillary force is the most important. If "guest" particles possess particular characteristics (in terms of size and size distribution), possibly (a) a mean diameter lower than 100 μm and (b) a homogeneous size distribution, the surface forces (interparticle attractions) are stronger than gravity force. In the case of commercial standard Lycoat, the particle diameter is relatively large (~510 μm); therefore, the adhesion forces between "host" core pellet and "guest" starch particles are weak; in consequence, the coating efficiency is very low, not exceeding CE<30%.

## CONCLUSIONS

In this study, a spray-drying technique for starch particle engineering is presented; the possibility to reduce particle size of Lycoat© RS 780 by spray-drying technique with a good process recovery is demonstrated.

The resulting powder particles exhibit a large surface area (due to a mean diameter comprised between 3 and 5 μm). These features allow the use of spray-dried particles to a dry powder coating processes, dramatically increasing the coating efficiency of the model core pellet of microcrystalline cellulose.

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