

# Bioencapsulation Innovations

May 2015

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**EDITORIAL**

## INTEGRATING RESEARCH TRAINING POWTECH IN PARTICLE & POWDER TECHNOLOGY

Even if BRG does not have authority to take up projects, it encourages collaborative initiatives. In the past, we supported two European COST actions. Do not hesitate to request our support if you build a project but also to use this newsletter to report advance done through actions.

The objective of PowTech ITN is to integrate inter-sectorial and multidisciplinary research in particle and powder technology into the training of 15 young researchers, to strengthen the competitiveness of food and pharmaceutical industry and to strengthen the European Research Area. The PowTech ITN started on 1 March 2011 and employed 14 PhDs and 1 Postdoc selected from around 200 applicants. There is a good gender and geographic distribution of the ESRs.

The ESRs have been trained by the PowTech Graduate School to develop research in close collaboration with industry with focus on opening their minds to innovation and the factors that influence the transformation of 19 research ideas into commercial reality.

The research activities of the network were structured in three network teams:

- **Powder Formation** Three types of nanocarriers (biodegradable polymeric nanoparticles, liposomes, polyelectrolytes nanoparticles) were developed and characterized in terms of physicochemical properties, release profile and antimicrobial performance, leading to better design of equipment and optimize formulation.
- **Powder Modification** CFD model was developed and successfully validated by comparing the particle

velocity field by positron emitting particle tracking. Small cellulose particles were coated with talc using high rotating mixers. Ultrathin aluminium oxide coating was realized using the gas-phase coating technique called Atomic Layer deposition at ambient temperature. It was also shown that it is possible to mix small amounts of water in powders by a new developed methodology.

- **Control of Powder Processing** Two projects aimed to develop modeling tools for high shear granulation or spray drying and three projects focused to develop knowledge on control of mixing, crystallization and flowability through systematic experimental design.

In April 2015, the ETN led to 2 patents. 3 PhD thesis were defended (10 more will be very soon).

21 articles (+20 submitted, 10 in preparation), 14 congress proceedings manuscripts (39 congress participations) have been submitted for publication.



This newsletter reports some of the projects realized over the course of Powtech.

More information of the project at <http://powtech.sik.se/>  
 Project reference: 264722 ;  
 Funded under: FP7-PEOPLE

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# STRUCTURE OF SPRAY DRIED EMULSION PARTICLES

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## INTRODUCTION

The protection and vectorization of active molecules requires their entrapment in a structured liquid or solid matrix. For lipophilic compounds (antioxidants, fatty acids, vitamins), their encapsulation in dry particles produced by spray drying oil-in-water (o-w) emulsion is widely used. Further to bringing protection, it allows the physical stabilization of the emulsion and the modification of its handling properties when producing the powder form.

Spray drying consists of the atomization of the initial o-w emulsion in liquid drops (20-80  $\mu\text{m}$ ) into a hot air flow. The drying of each liquid drop when in contact with hot air leads to solid particles (10-50 $\mu\text{m}$ ) wherein oil droplets ( $\leq 5\mu\text{m}$ ) containing active molecules are dispersed and protected by the solid matrix. The structure of the dry particles produced is built under mechanical, thermal and water constraints at play during processing (emulsification, atomization, drying) and depends on the initial liquid emulsion properties. The production of particles with tailored properties therefore requires a good knowledge of the process-structure relationship.

The influence of atomization on the oil droplet size distribution in sprayed o-w emulsion was investigated for two atomizers (bi-fluid nozzle, rotary wheel) and several emulsion size and viscosity. The constituent distribution (oil, emulsifier, support material) in the spray dried solid particles (surface, core) was obtained combining analytical methods.

## MATERIAL & METHODS

Initial liquid emulsions were prepared using maltodextrin DE12 (Glucidex®, Roquette, Fr) as wall material (support) in combination with acacia gum (Instantgum AA, Nexira, Fr), which also brings emulsifying properties (weight ratio 3:2). Sunflower oil was used as a model for lipophilic compounds.

Five emulsions were prepared with different oil droplet size (0.15 and 1.6  $\mu\text{m}$ ), oil content (3.3 to 8.6 %wt) and dry matter content (33 to 48 %wt). The coarse ones were homogenized using a rotor-stator (AXR, Silverson Machines Ltd, Fr) at 3500 rpm for 20 min. Submicron emulsions was obtained by further high pressure homogenization (Rannie Slow 22-50, APV, UK) at 300 bar for 4 min with re-circulation. The viscosity (20°C) of sunflower oil  $\eta_{\text{oil}}$  was 0.64 Pa.s and the viscosity of the continuous phase of the different emulsions  $\eta_c$  was comprised between 0.1 and 0.95 Pa.s (Couette rheometer, MCR 3001, Anton Paar, Fr). The interfacial tension  $\sigma$  between oil and aqueous phase (20°C) was between 55 and 68 mN.m<sup>-1</sup> (pendant drop technique, Tracker, Teclis-IT concept, Fr).

Initial liquid emulsions were atomized using a bi-fluid nozzle with external mixing (970-S3, Schlick, Ge) and a rotary atomizer with a 5 cm wheel (24 vanes). The liquid flow rate was varied from 5.10<sup>-4</sup> to 16.10<sup>-4</sup> kg.s<sup>-1</sup>, the rotational speed of the rotary atomizer from 3200 to 35000 rpm and the air flow rate in the bi-fluid nozzle from 4.10<sup>-4</sup> to 11.10<sup>-4</sup> kg.s<sup>-1</sup>. The oil droplet size distribution in emulsions before and after atomization was measured by laser light diffraction (MasterSizer 2000, Malvern, Fr).

Spray drying trials were performed in a

Niro Minor pilot spray dryer with the rotary atomizer. Inlet and outlet air temperature were 220 and 130°C respectively with an air flow rate of 100kg.h<sup>-1</sup> and a liquid flow rate of 33g.min<sup>-1</sup>.

## RESULTS & DISCUSSION

### Atomization

During the atomization of o-w emulsions, the shear stress applied at the air-liquid interface to disperse the liquid feed into drops can also cause deformation and breaking of oil droplets inside the emulsion.

In this study, a wide range of shear rate [between 10<sup>3</sup> and 10<sup>6</sup> s<sup>-1</sup>] was investigated. By comparing the oil droplet size distribution and median diameter  $d_{50}$  of the initial and sprayed emulsions, three behaviours were distinguished: no modification of both the oil droplet size distribution and  $d_{50}$ ; small decrease of  $d_{50}$  while keeping a monomodal oil droplet size distribution (monomodal breakup of oil droplets), significant decrease of  $d_{50}$  with a second peak appearing in the oil droplet size distribution (bimodal breakup) (Fig.1).

Oil droplet breakup occurs when the external forces, applying at the oil-aqueous phase interface due to the surrounding aqueous phase flow, overcome the internal forces due to interfacial tension  $\sigma$ . For a laminar

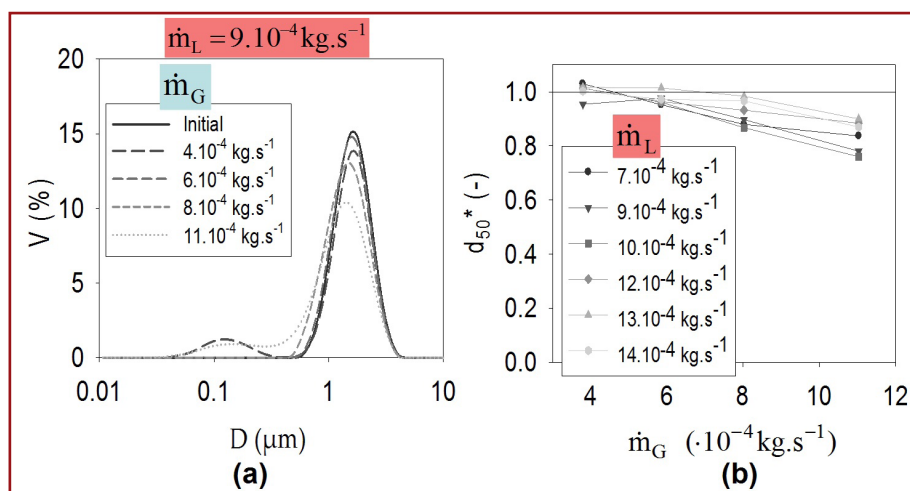


Fig 1: Example of the modification of the oil droplet size distribution (a) and normalized median diameter  $d_{50}^* = d_{50\text{final}}/d_{50\text{initial}}$  (b) during atomization with the bi-fluid nozzle for different gas flow rate and emulsion feed rate ( $d_{50\text{initial}} 1.6 \mu\text{m}$ ,  $\eta_c 0.3 \text{ Pa.s}$ ).

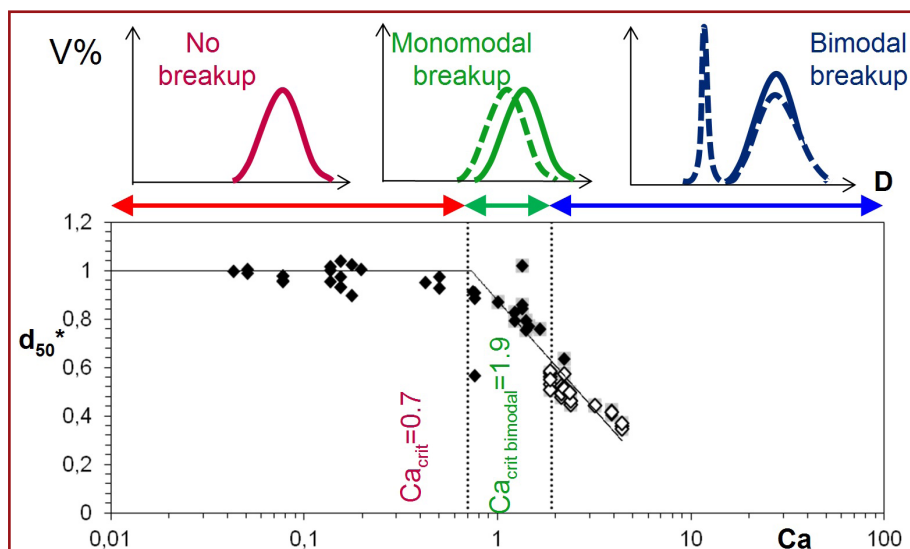


Figure 2: Determination of the critical values of capillary number from the modification of the oil droplet size distribution and  $d_{50}$  after atomization with rotary atomizer.

flow, the capillary number

$$Ca = \eta_c \dot{\gamma}_r / \sigma$$

represents the ratio of external disruptive stress to internal cohesive stress. Droplet breakup is therefore expected to occur above a critical value of  $Ca$  (Grace, 1982). Plotting the ratio  $d_{50}^*$  of final  $d_{50}$  to initial  $d_{50}$  as a function of  $Ca$ , it was possible to identify a couple of critical values of capillary number for each type of atomizer corresponding respectively to the transition from non breakup to monomodal breakup regime (about 0.7 for rotary atomizer and 1.3 for bi-fluid nozzle) and from monomodal to bimodal breakup regime (1.9 and 2.7) (Fig.2) (Munoz-Ibanez et al., 2015).

From the calculation of  $Ca$ , it is possible to define atomization conditions and emulsion formulation to keep ( $Ca < Ca_{crit}$ ) or to modify ( $Ca > Ca_{crit}$ ) the size distribution of oil droplets. Key parameters are atomizer type, atomization force (shear rate), viscosity of the continuous phase and oil droplet size.

### Particle structure

To study the impact of oil droplet breakup on the spray dried particle microstructure, powders were produced from the same initial emulsion (1.6  $\mu\text{m}$ ) but fixing conditions for the atomization leading (30 000 rpm) or not (3000 rpm) to breakup. Particles were observed with a Low-Vacuum Scanning Electron Microscope (LVSEM) (XL 30

Series, FEI, Fr). Backscattered images of both series of particles giving material contrast near the surface showed a higher concentration of oil droplets (in dark grey) close to the surface when breakup occurred (Fig.3a). This was confirmed on images obtained by confocal Raman microscopy (alpha300, WITec, Ge) giving the constituents distribution inside the particles (Fig.3b). Oil droplets (yellow) can be clearly seen dispersed within the solid matrix and at the particle surface in the case of breakup. Some segregation between maltodextrin and acacia gum also occurred during drying with a layer of acacia gum (red) forming at the particle surface. Surface oil extraction following the Niro Analytical Method n°A10a using petroleum ether, led to small non encapsulated oil contents, slightly lower when no breakup occurred (1.1%wt of total oil instead of 3.4%wt).

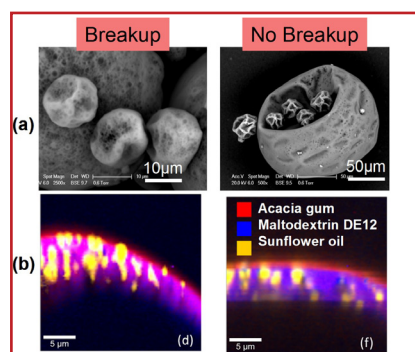


Fig 3: LVSEM (BSE) (a) and Confocal Raman microscopy (b) images of spray dried particles with and without oil droplet breakup.

## CONCLUSIONS AND PERSPECTIVES

The use of capillary number for the choice of conditions for atomization is a useful tool to control the dry emulsion structure that will remain in the reconstituted emulsion. Avoiding oil droplet breakup also permits to limit the oil content at the particle surface (non-encapsulated). Confocal Raman microscopy is a promising technique for the determination of constituent distribution in dry particles, but with limitations due to the resolution.

## ACKNOWLEDGEMENTS

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# INFLUENCE OF POWDER PROPERTIES ON THE MIXTURE QUALITY OF SPICE POWDER MIXES

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## INTRODUCTION

Dry powder mixing is widely used throughout different industries. It is crucial that satisfactory mixture quality (MQ) is achieved and maintained. There are many factors that influence MQ including mixer parameters and properties of the dry powders. This paper focuses on the influence of powder properties and presents some results from a project within an EU funded network called "PowTech" (Shenoy et al., 2014 & 2015).

## METHODOLOGY

Binary powder mixtures were produced by mixing two powders, one being common salt, in a 2L paddle mixer. The two powders were mixed in equal proportions by weight. The mixing was carried out for 150s and samples were withdrawn from pre-defined specific points across the mixer at fixed time intervals during mixing. Salt concentration in each of the samples was measured using an electrical conductivity method. The MQ was assessed by evaluating the co-efficient of variation (CoV) of salt between the samples. A CoV of 6% or less represents good mixing.

To investigate the influence of differences in powder densities (bulk and particle) on the mixing of the powders, trials were conducted with 7 binary mixes containing powders with similar sizes but different densities, as pres-

ented in Table 1. The powders were a number of salts with different sizes, sugar, paprika, onion, black pepper, oregano and thyme. The particle size ratios (higher / lower) were less than 1.3, except for D6 at 1.61. There was a large variation in the poured bulk density ratios ranging from 1.5 to 16.4, while the particle density ratios had much less variation, ranging from 1.36 to 1.77.

**Table 1 : Influence of the density ratio on CoV at 150 s**

Trial n°	Ration (higher/lower)			CoV (%) at 150 s
	Bulk density	Particle density	Particle size	
D1	1,5	1,36	1,24	2
D2	2,0	1,43	1,20	1
D3	3,5	1,61	1,26	2
D4	6,25	1,68	1,15	13 ± 2
D5	6,9	1,70	1,25	14 ± 1
D6	16,1	1,77	1,61	14 ± 6
D7	16,4	1,76	1,10	21 ± 5

Table 1 shows the influence of differences in densities between the two components (or density ratios) on the MQ (MQ) at the end of mixing, as represented by the CoV at 150s. The difference in bulk density (bulk density ratio) has a strong influence on MQ. For the lower bulk density ratios, less than 3.5 (D1, D2, D3 in Table 1), very good MQ was achieved as CoV is less than 6%. However, for the higher ratios, > 6.2 (D4 to D7), unsatisfactory MQ was achieved. These results show that dif-

ferences in bulk density may have an impact on MQ, especially when the bulk density ratio exceed a value of 6.

In trials D4 to D7, oregano or thyme were mixed with salts. The poor mixing was due to segregation based on the denser salt particles sieving downwards through the large void spaces that exist in the low bulk density oregano and thyme. The large voidage is most likely due to the irregular shapes of the thyme and oregano. Images of the shapes of salt, oregano and thyme are presented in Figure 1. The oregano has a leafy type shape and the thyme has a needle type shape. It is believed that the shapes of the oregano and thyme resulted in the high voidage which allowed the salt to sieve downwards causing segregation and poor mixing with the salts.

## PARTICLE SIZE

To investigate the effect of particle size on the MQ of binary powder mixtures, trials were performed using paprika and potato starch with salts of different particle sizes. Ideally, in trials like these, it is desirable to have powders with identical densities, however salt is used in all trials and it is much denser than all of the other powders. Thus, 8 trials were selected, such that the bulk density ratios of the component powders were similar, as presented in Table 2. These values were well within the range of ratios that achieved good mixing in the previous section. The particle density ratios

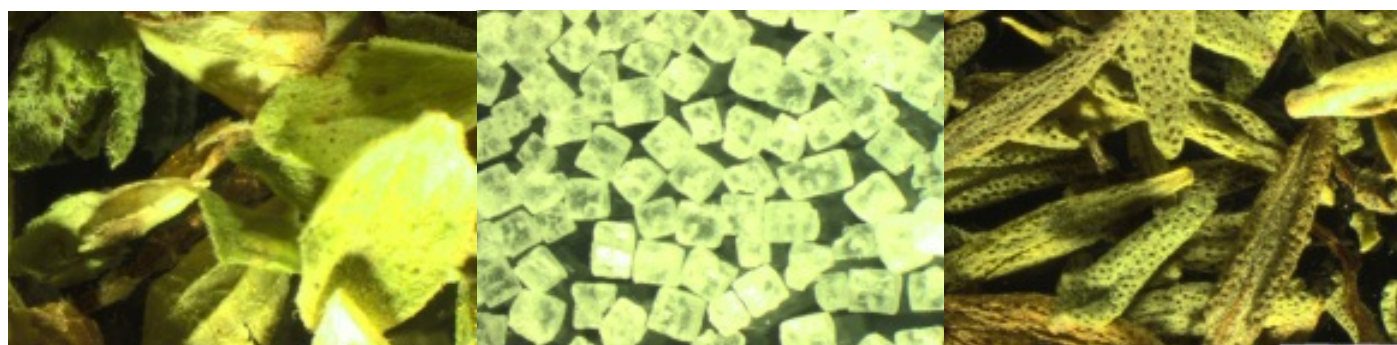


Figure 1: Images of oregano, salt and thyme.

## ARTICLE

were all very similar in the range of 1.49 to 1.59.

**Table 2 : Influence of the density ratio on CoV at 150 s**

Trial n°	Ration (higher/lower)			CoV (%) at 150 s
	Bulk density	Particle density	Particle size	
S1	0,5	2,79	1,58	2
S2	2,0	2,83	1,59	3
S3	2,5	1,81	1,49	3
S4	3,1	2,60	1,58	3 ± 1
S5	4,5	2,34	1,56	3
S6	6,6	2,39	1,56	6 ± 1
S7	9,9	1,84	1,50	6 ± 1
S8	15,7	1,69	1,49	8 ± 4

The influence of size ratio on MQ for all 8 trials is presented in Table 2. For the first 5 trials (S1 to S5), where the size ratio is less than 4.5, very good MQ was achieved, with CoV values of 3% or less. As the size ratio increased in trials S6 to S8, MQ disimproved to 6% and 8%. However, even at the very large size ratio of nearly 16 the CoV of 8% was not too much outside the satisfactory upper limit of 6%, and was much better than the poor bulk density ratio trials (D4 – D7). Overall, Table 2 shows that difference in particle size can influence MQ. Very good MQ was achieved at size ratios below 4.5. At higher size ratios the influence is not as large as might have been expected, particularly at the size ratio of nearly 16. One of the effects that may occur at high size ratios is the coating of larger particles by smaller particles due to cohesive attractions and the large specific surface area of the small particles. This can be seen in Figure 2 for paprika – salt medel (size ratio = 6.6), where the small paprika particles are coating the large salt particles. This effect may help in counteracting a segregation tendency due to large differences in particle size.

## WATER & COHESION

To study the effect of higher water content in paprika and oregano, the powders were pre-conditioned at different humidities ranging from 40 to 94% RH. The conditioned powders

were mixed with salt in the paddle mixer and the MQ evaluated. The flowability of the conditioned powders was also measured using a Brookfield powder flow (PFT) tester. For paprika powders, varying water activity ( $a_w$ ) values in the range of 0.4 to 0.75 had little effect on MQ. However, at  $a_w = 0.9$  the MQ was affected, as the MQ improved more slowly over the mixing time than the other mixes, although it did move towards the same final values of the other mixes. The rationale for this behaviour is most likely due to the increased cohesion due to major uptake of water by the paprika powder at  $a_w = 0.9$ . Water sorption isotherm data showed that the water content of paprika at  $a_w = 0.9$  is around 30% while it is around 15% at  $a_w = 0.75$ . The PFT tester confirmed that the paprika had moved from being an easy flow powder



**Figure 2: Image of mixture of paprika and salt medel (size ratio = 6.6).**

to being very cohesive at  $a_w = 0.9$ .

A similar set of mixing trials were carried out with oregano and salt, which were previously shown to mix poorly. The influence of  $a_w$  on the MQ was quite different to paprika / salt, in so far as increasing  $a_w$  caused an improvement in MQ, especially at the higher  $a_w$  values of 0.82 and 0.94. The improvement in mixing at higher  $a_w$  was due to moisture sorption by the oregano particles which made them more cohesive and sticky. Water sorption isotherm data showed that the water content of oregano at  $a_w = 0.9$  is around 20% while it is around 10% at  $a_w = 0.5$ . The PFT tester confirmed an increase in cohesiveness. Visual inspection showed the oregano particles coated by many salt particles at  $a_w =$

0.82 and 0.94.

## CONCLUSIONS

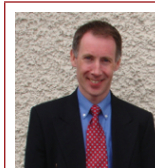
Difference in bulk density between the salt and other powders displayed a very big influence on the MQ of the binary mixes. Differences in particle size had an effect on MQ but it was not as large as initially expected. This may be due to finer particles coating the larger particles. Increasing cohesiveness may reduce the MQ of easy to mix powders, but may improve the MQ of segregating mixes.

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John Fitzpatrick's research interests are in food particle & powder technology and sustainability & environmental protection. He has been involved in research projects in powder flowability and caking; protein precipitation and sugar crystallisation; dry powder mixing and rehydration of food powders.

# COMPOSITE SURFACE CHARACTERIZATION

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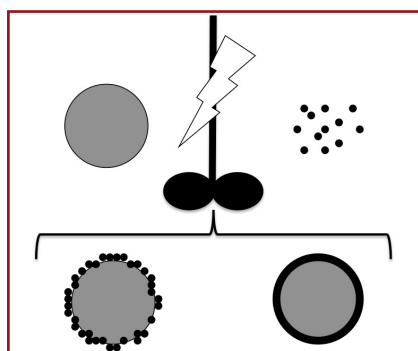
## INTRODUCTION

Generating quantitative data is one of the first steps in developing models or predictive tools for industry and improve fundamental knowledge. In dry coating this information is usually obtained from theoretical assumptions or determined qualitatively (Ottles, 2009). The reason for this situation is partly because the coating information has to be determined by complex, expensive and time-consuming techniques. This methodology also requires the use of further automated image analysis routines.

In this publication development of different visualization techniques allowing for better characterizing of surface structures of dry coated powders will be discussed. Presently the available techniques can be complex and require, lots of time to set up and run properly.

## DRY COATING

Dry coating is a simple innovative eco-friendly process, which can create value-added new composite materials. The principle is to «attach» small guest particles onto larger host particles (10 to 100 times bigger) using mechanical forces (Figure 1). According to the operating conditions, the used process (generally a high energy mixing device) and the properties of the used materials, discrete coating, continuous porous coating, filming or



**Figure 1: Dry coating principle: large particles (host) are mechanically mixed with smaller particles (guest).**

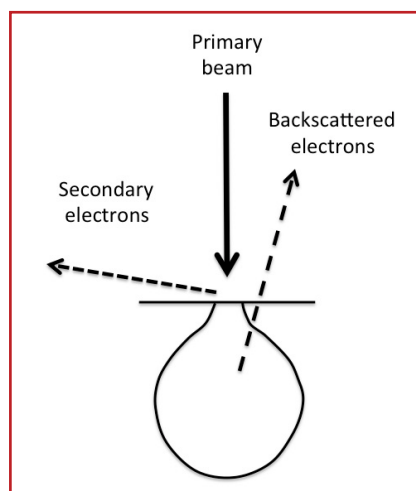
**Table 1 : Charcaterization techniques**

Technique	ESM	EDS	Raman
Principle	Electro scattering	Energy dispersive x-ray spectroscopy	Light inelastic scattering
Imaging specification based on	Atomic number (BSE) or Tomography	Elemental analysis	Material Raman spectrum

multilayering can be achieved (Figure 1). This work mainly focused on discrete coating (Figure 1, left).

## MATERIALS & METHODS

The dry coating operation was carried out with the hybridization system NHS-0 from Nara machinery, Japan. The volume capacity is 0.5 L. The ope-



**Figure 2: Backscattered (BSE) or secondary electrons (SE) in ESEM.**

rating conditions were chosen to avoid breakage of the powders. The processing time has been set arbitrarily to 6 minutes.

The host particles are PMMA (ca. 160µm). They have an ideal spherical shape. The guest particles are talc of ca. 10µm. Their shape is like platelets (Figure 2).

## CHARACTERIZATION

Three different visualization techniques were tested in this work and are highlighted in Table 1.

The Environmental Scanning Electron Microscopy (ESEM Philips XL 30) is a versatile tool for characterizing the surface morphology of particles with huge magnifications allowing visualizing structures down to angstrom. The reconstruction of the images is obtained from detectors of electrons that have interacted with the sample. Two major modes (Figure 2) are possible based on backscattered electrons (BSE) or secondary electrons (SE). For the BSE, the contrast depends on atomic number. A large number leads to brighter pixels in the image. For the SE, the contrast depends on topography. Sharp edges leads to brighter pixels in the image.

The preparation of the sample, was straightforward, as the environmental microscope doesn't require any metallization of the sample surface.

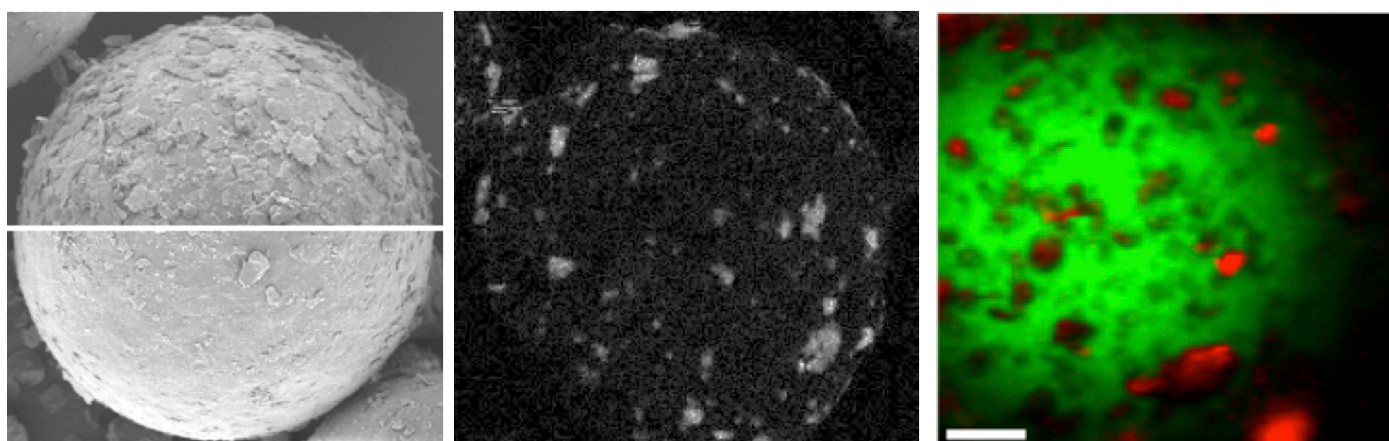
In addition, the ESEM can be coupled to an energy dispersive X-ray spectrometer to realize an elemental atomic analysis of the surface. This allows the user to scan at one point of the image, or to perform a full imaging of a selected surface, which enables discrimination of the guest and host particles if they differ by one atomic element.

Raman imaging spectrometry (AFM Witec Alpha 300R) provides for chemical mapping of the surfaces based on the Raman inelastic light scattering phenomenon. To discriminate the guest particles from the host particles, the materials have to be Raman active. Greater difference in the spectra enables easier determination of differentiation.

## RESULTS & DISCUSSION

Figure 3 shows a series of characteristic visualizations performed on one





(a) ESEM, SE mode

(b) ESEM, EDX analysis

(c) RAMAN spectra analysis

Figure 3: Visualization of PMMA particle coated with talc particles,

particle of PMMA, which were dry coated with talc particles.

In Figure 3-a, the SE mode of the ESEM gives the surface aspect of the composite surface (top image) and of the initial PMMA surface (bottom image). On the top image, we clearly see platelets shaped talc particles deposited on the PMMA surface. But we also see fragments on the bottom image. As the initial surface of the host particle isn't completely smooth, the conclusion is that it is not possible to discriminate what is talc or PMMA from the top image. In order to be able to detect the talc, a possible solution is to use the ESEM-BSE mode which is sensitive to the chemical nature of the materials. From Figure 4, it is possible to detect the talc particles in white (larger average atomic number) on the grey homogeneous surface of PMMA (smaller average atomic number). Further automated image analysis can therefore be performed to quantify the coating coverage (Lecoq, 2015).

In Figure 3-b, the EDX analysis produces the Si elemental mapping image of the surface of the composite. We know that silicon (Si) is a structuring element of talc [ $Mg_3Si_4O_{10}(OH)_2$ ] and silicon is not present in PMMA. So when a pixel is white, it means Si is detected, hence the talc.

Figure 3-c represents a composite image where the PMMA is in green and Talc is red. The colorization was performed by choosing distinct characteristic spectra from two different materials. In one pixel of the surface, the spectral signature is either from PMMA or from talc. Consequently, it is therefore possible to quantify the coverage present.

## CONCLUSIONS

According to the chosen technique, its operating conditions and the materials, the visualization will give different information. If the guest and host powders are Raman active, the Raman spectroscopy could be used efficiently, as long as the Raman spectra have significant differences. Otherwise, it is impossible to differentiate.

When using the ESEM, the «chemical mode» (BSE) or the EDX spectroscopy is adapted when the host and the guest particles have different average atomic numbers or different atoms. Differentiation will therefore be visible on the reconstructed image showing different grey levels for the guest and the host. If this is not the situation (e.g. an organic powder on another similar organic powder), the chemical contrast will not give enough differentiation between the two materials. In this situation the ESEM could be used in topographic mode (SE). The differentiation will be possible if the topography of the composite surface is ideally a flat surface (initial host) on which the guest particles are deposited.

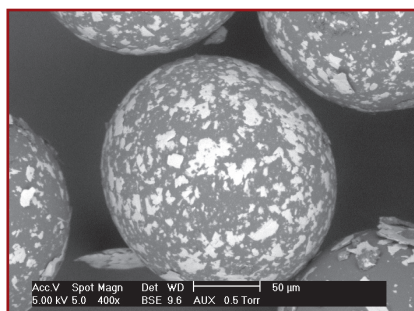


Figure 4: PMMA coated with talc in BSE mode.

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# DAIRY POWDERS: DRYING KINETICS AND MORPHOLOGY

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## INTRODUCTION

Spray drying is used to produce powders from a liquid feed. The liquid feed is atomized in a hot air stream and transformed into a powder in a single operation in a very short time. Spray drying is very common in food industry on account of its ability to handle heat-sensitive foods with maximum retention of their nutritive content. It is used for production of products such as instant coffee, tea, and soup and dairy powders. Operating conditions of spray dryers are wide-ranging; each product and chamber design demands unique settings in order to achieve specific properties of the final product. In fact, depending on the characteristics of the feed, the type of atomiser and processing conditions during spray drying powder particles with different size and morphology are created (Walton, 1999). In order to control properties of final powders and to reduce time and cost of designing and scale-up of the spray drying process simulation modelling tools are implemented.

The goal of this project is to build a validated model for describing drying kinetics of a single particle and agglomerate from a dairy product. The model is used to predict surface condition of the spray dried particles. This will allow a multi-scale analysis of regions of co-

alescence and stickiness of individual particles when occurs in real-time in a spray dryer.

In this paper morphology changes of dairy powders during drying are investigated, in order to assess their influence on drying rate and on the effective diffusivity of water.

The presented work is a summary of two articles published in the Journal of Food Engineering (Malafronte, 2015; Malafronte, accepted).

## METHODS

### Drying kinetics measurements

A single drop drying kinetics device was used to record the weight, temperature and size change during convective drying. Drying experiments were performed on four different types of fresh milks and three different creams. Products were selected to cover a large range of fat content.

### Confocal Laser Microscopy (CLSM)

CLSM was used to locate fat and proteins on the surface and inside the dried particle, and to investigate the morphology of powder particles.

### Evaluation of effective diffusion coefficient of water

Effective diffusivities of water in dairy products were calculated using a parameter estimation method suggested by Malafronte et al. (2015). The method compares the experimental data obtained using the drying kinetics device with the results of the distributed drying kinetics model to estimate the effective diffusion correlation. The effective diffusion coefficient is considered a function of water content and temperature.

## MODEL

### Drying kinetics model

The drying kinetics model consists of a fully coupled distributed parameter which is able to simulate simultaneously water content and temperature profiles within a spherical particle. In this model physical properties are considered as a function of the local temperature and the moisture content. A modified Fick's second law describing mass transport in terms of effective diffusivity is used.

## RESULTS

### Drying kinetics

Drying kinetics was measured for all products at three different air temperatures (50, 70 and 90 °C). Comparison of low fat content products (skim milk, light milk, medium milk, whole milk, diluted coffee creamer) with products with a high fat content (coffee creamer, medium cream, heavy cream) shows that when fat content increases drying time increases.

### Morphology of dairy powder

In Figure 1, micrographs of the four representative products — light milk, whole milk, coffee creamer, and heavy cream — are shown. From a macro-

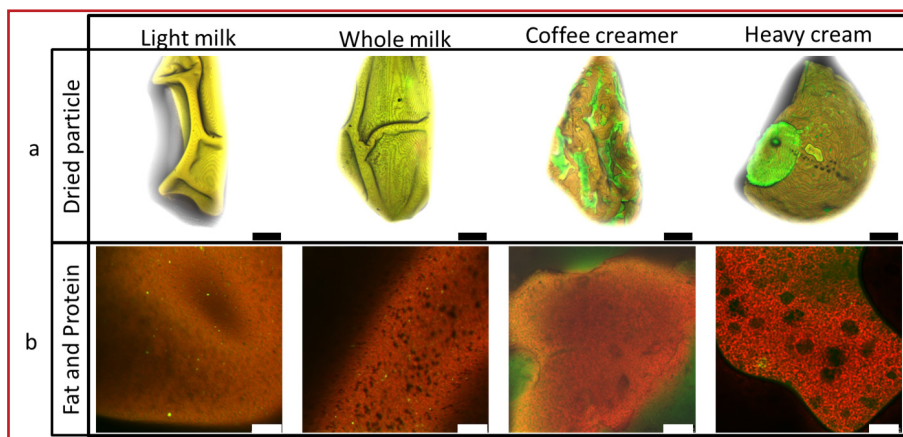


Figure 1. CLSM micrographs of the four dairy powder particles. Overlay of the fat (green), the protein (red) structures and the particle shape. The scale bars represent (a) 250  $\mu\text{m}$  and (b) 25  $\mu\text{m}$ .



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copic point of view (Figure 1a), the pictures show that the dried dairy products have different morphologic characteristics after drying: light milk and whole milk particles are shrivelled, the coffee creamer is partially inflated, and the heavy cream is spherical. In particular shrivelling of powder particles reduces when the fat content increases and the initial water content decreases and is due to the lower flexibility of the external skin. From a microscopic point of view all products exhibit a porous protein matrix (Figures 1b), in which the fat phase is entrapped (low fat products) or there is a porous protein matrix embedded in a fat phase (high fat products). The pore size of the protein matrix seems to increase with increasing fat content in the dairy products. In addition, the coffee creamer and the heavy cream show fat domains separated from the protein matrix, indicating that phase separation occurred between the protein and fat phase.

## Morphology and drying rate changes

Figure 2 shows the drying rates of skim milk, light milk, medium milk, whole milk, diluted coffee creamer, coffee creamer, and heavy cream. Results show that drying rate decreases when initial water content decreases and fat content increases: the higher the fat content the higher the drying time. For most of the products two falling drying periods can be distinguished, except for heavy cream, which exhibit only one falling drying period. It is possible to observe that for skim milk, light milk, medium milk, whole milk, and diluted coffee creamer the drying rate reduces faster at low water content than at high water content, and differences in slopes decrease when fat content increases. Differences in drying rates among the products could be ascribed to differences in fat content. When increasing the fat content more fat is confined in the protein network, which hinders diffusion of water near the surface and, as a consequence, evaporation. In the case of coffee creamer the opposite happens: drying rate decreases faster at high water content than at

low water content. The different behaviour shown by coffee creamer may be an effect of phase separation (Figure 1), during which fat leaves the protein network and agglomerate allowing the remaining water to diffuse more freely.

Comparison of the drying rate with changes in morphology during drying shows that during the first falling drying period drops of light milk, whole milk and coffee creamer shrink but retain a spherical shape, while during the second falling period shrivelling occurs. Shrivelling of particles may be due to the formation of a soft skin at the end of the first falling drying period, and differences in shrivelling of different products may be ascribed to the amount of fat confined in the protein network. In the case of heavy cream, which shows only one falling drying period, drops slightly shrink during drying and a vacuole is formed. The presence of a vacuole could be due to dissolved air entrapped in the fresh heavy cream.

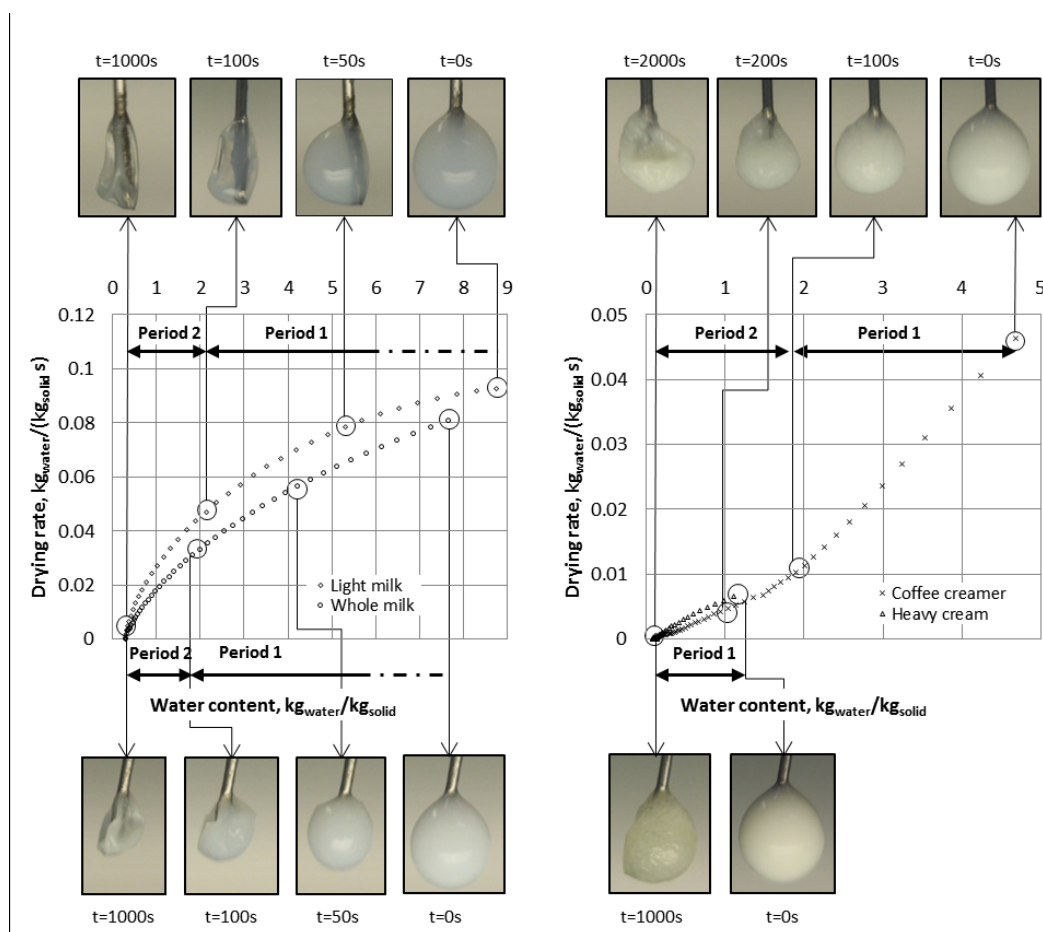


Figure 2. Comparison of the drying rates with morphological changes for single drops of light milk, whole milk, coffee creamer and heavy cream dried at 70 °C.

## Effective diffusivity of water in dairy products

Effective diffusivities were calculated for light milk, medium milk, whole milk, diluted coffee creamer, and coffee creamer, since they showed a final shrivelled and partially inflated morphology such as skim milk. A strong dependency of the effective diffusion coefficient of water in dairy products on fat content could be observed at fat content higher than 0.3 kgfat/kgsolid. Results of effective diffusivities are in agreement with the results of experimental drying kinetics: the higher the fat content the longer the drying time and as consequence the lower the effective diffusion of water in the product.

## CONCLUSION

The effect of the composition of commercial dairy products on drying kinetics and morphology of powders was investigated. Results showed that fat content plays an important

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role on drying kinetics and final morphology of particles: higher fat content results in longer drying times and less shrivelled particles. Changes in morphology and the drying rate seem to be related. Two falling drying periods were observed for most of the products. During the first period the drops shrink spherically, while during the second period shrivelling occurs. The effective diffusivity of water shows that high fat contents lead to a lower diffusivity of water in the products.

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Industrial PhD candidate from August 2011 until November 2015 (expected). The PhD project is in collaboration with TetraPak Processing System and it has been part of the EU Marie Curie project PowTech Initial Training Network (ITN). Her research focus on developing a validated model to predict drying kinetics and stickiness of dairy products during spray drying. MSc in Food Engineering at University of Salerno.

## DIVERSIFIED NEWS



No need to wait for long hours sandman to join the arms of Morpheus!

**French brand Achel offers a new range of underwear called «Improved sleep»**

which combines aromatherapy and microencapsulation! To sleep better, of course.

Textile expert and strong know-how made in France (First North company to benefit from the label «Origine France Garantie»), the Lemahieu company has chosen to position itself in a niche market to respond to new uses and changing needs of consumers. Particularly those of older people.



This range of men and women's underwear promotes sleep and sleep with plant extracts (eg. Valerian) and essential oils (eg. Lavender).

**For more information**

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**MIT researchers reconfigure complex emulsions**

By Deanna Utroske, 02-Mar-2015  
Double emulsions can be made in large-scale quantities with mixing processes newly tested and refined by researchers at the Massachusetts Institute of Technology.  
<http://www.cosmeticsdesign.com/Formulation-Science/MIT-researchers-reconfigure-complex-emulsions>



**Capsulæ is developing an oral vaccine for salmon**

Salmon farming involves treatment of fish to avoid infections. The OVAS project (Oral Vaccination for Aqueous Species) initiated by Capsulæ and developed in a joint venture with Argentine biotechnology company aims to reduce the number, cost and time of vaccinations performed by injection for each salmon. Capsulæ then developed a microencapsulation technology allows the administration of oral vaccines in the form of particles incorporated in food granules. One of the main constraints is that the active ingredients must withstand highly degrading gastric conditions before release at the salmon intestine. A patent, which will retain Capsulæ industrial property and which for Arnaud Picot, Director General, «could eventually be applied to many other animal species», is pending.

**More information**

[http://www.asrc.fr/fr/wp-content/uploads/sites/2/2014/02/ASRC\\_360RetD\\_n8-decembre2014.pdf](http://www.asrc.fr/fr/wp-content/uploads/sites/2/2014/02/ASRC_360RetD_n8-decembre2014.pdf)



We invite you to contribute to Special Issue regarding the application of phytochemistry in nanomedicine: **Applications of Phytochemistry on Drug Delivery Nanosystems** It will cover topics related to drug delivery systems based on natural compounds, application of specially formulated medicinal plants in therapeutics and also in food sciences. The Special Issue is scheduled for publication in October 2015.

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Information collected by Victor Roulier, from Capsulæ

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CALENDAR

<b>PROGRAM 2015</b>	
<b>May</b>	 <p><b>Polymerix 2015 : Biosourced polymers</b>                  May 28 - 29, 2015                  Rennes, France  <a href="http://www.cbb-developpement.com/index.php?option=com_content&amp;task=view&amp;id=506&amp;Itemid=666">http://www.cbb-developpement.com/index.php?option=com_content&amp;task=view&amp;id=506&amp;Itemid=666</a></p>
<b>June</b>	 <p><b>7th International Symposium on Food Rheology and Structure (ISFRS 2015)</b>                  June 7 - 11, 2015                  Zurich, Switzerland  <a href="http://www.isfrs.ethz.ch">http://www.isfrs.ethz.ch</a></p>
	 <p><b>First International Convention IMMUNOPHARMACOLOGY - VACCIPHARMA 2015</b>                  Meliá Marina Varadero, Varadero Beach, Cuba - June 14-19, 2015  <a href="http://www.scf.sld.cu">http://www.scf.sld.cu</a></p>

<b>June</b>	 <p><b>Eudragit Advance Workshop</b>                  Tours, France - June 17-18 2015  <a href="https://e-lab.eudragit.com/login/login.jsp">https://e-lab.eudragit.com/login/login.jsp</a></p>
	 <p><b>18th Gums &amp; Stabilisers for the Food Industry Conference</b>  <b>Hydrocolloid functionality for affordable and sustainable global food solutions</b>                  Glyndwr Univ., Wrexham, UK                  June 23rd - 26th 2015  <a href="http://www.foodhydrocolloidstrust.org.uk">http://www.foodhydrocolloidstrust.org.uk</a></p>
<b>August</b>	 <p><b>23th annual «Advances in Tissue Engineering»</b>                  Rice University, Houston, Texas - August 12 -15, 2015.  <a href="http://www.tissue.rice.edu/">http://www.tissue.rice.edu/</a></p>
<b>October</b>	 <p><b>32th Club Emulsion meeting</b>                  October 1-2, 2015                  Pau, France  <a href="http://iprem-epcp.univ-pau.fr/live/clubemulsion2015">http://iprem-epcp.univ-pau.fr/live/clubemulsion2015</a></p>

<b>PROGRAM 2016</b>	
<b>April</b>	<p style="text-align: center;"><b>PBP</b></p> <p style="text-align: center;">WORLDMEETING</p> <p><b>10th World Meeting on Pharmaceuticals, Biopharmaceuticals and Pharmaceutical Technology</b>                  April 4-7, 2016                  Glasgow, UK  <a href="http://www.worldmeeting.org/home/">http://www.worldmeeting.org/home/</a></p>
	 <p><b>8th Training School on Microencapsulation</b>                  Cork Ireland                  April 12 -15, 2016.  <a href="#">More information very soon</a></p>
<b>April - May</b>	 <p><b>19th Microencapsulation Industrial Convention</b>                  April - May, 2016                  Frankfurt, Germany  <a href="#">More information very soon</a></p>
<b>September</b>	 <p><b>24th International Conference on Bioencapsulation</b>                  September, 2016                  Lisbon, Portugal  <a href="#">More information very soon</a></p>



**23TH INTERNATIONAL CONFERENCE ON BIOENCAPSULATION**



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[http://bioencapsulation.net/2015\\_Delft/](http://bioencapsulation.net/2015_Delft/)



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**Boston, USA**  
**October 1-3, 2015**  
<http://www.northeastern.edu/ims2015/>



# MECHANISTIC TIME SCALES IN ADHESIVE PARTICLE MIXING

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## INTRODUCTION

The mixing in which fine particles are attached onto the surfaces of carrier particles has successfully been employed to produce homogeneous pharmaceutical formulations, both in the case of very potent APIs and as regards dry powder formulations for inhalations (Vikas Anand Saharan, 2008). While the homogeneity of random mixing obeys the law of probability and is determined by a statistical distribution, the adhesive particle mixing poses different mechanisms governing the blending process due to complex interparticle interaction. Several such mechanisms have been documented in the literature, namely (i) Random mixing (ii) De-agglomeration (iii) Adhesion, and (iv) Redistribution and compression (Grasmeijer F, 2013).

Although the effects of material properties on the adhesive mixing process have been well documented, the mixing dynamics have not yet received much attention (de Boer et al., 2012). There is a need to investigate mixing mechanisms and dynamics, in order to provide better understanding of the overall process. The aim of this work is thus to estimate the time scale of the mechanisms governing the mixing process as well as their relative importance as regards achieving a homogeneous mixture.

## MATERIAL & METHODS

### Material

Spherical mannitol pellets with a median diameter just above 200 $\mu$ m and micronized lactose monohydrate with a median size of 4  $\mu$ m were selected for the mixing experiments.

### Mixing experiments

The mixing experiments were performed

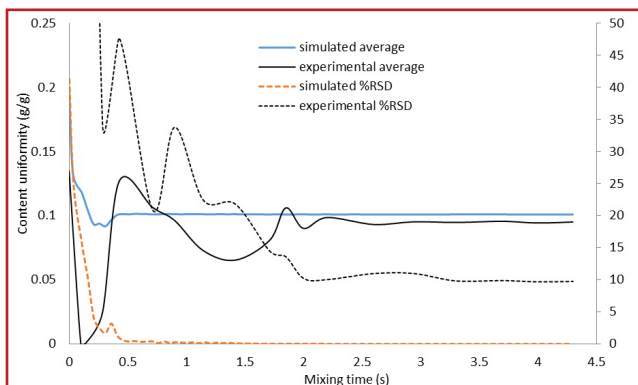


Figure 1. Random mixing dynamics.

med in a MiPro high shear granulator (Procept, Belgium) installed with a 1.9 litre vessel and a 3 bevelled-blades impeller. A moderate impeller speed of 500rpm was used in all experiments. A total of 260g of material with 5% w/w of fine-particle agglomerates was loaded in each experiment. The mixer was stopped at several time points to withdraw samples for analysis.

### Fines content assessment

As the carrier and fines widely differ in particle size, the content of fine particles in a blended sample can be assessed from the bimodal particle size distribution, provided that agglomerates are fully disintegrated during the test. Sympatec HELOS with RODOS operated at 3.0 bar was found to be suitable for this. The relative standard deviation (RSD) of the fines content is used as the mixing index [RSD<5% is acceptable for the homogeneity].

### Agglomerate size assessment

To access the size of the fine-particle agglomerates, care must be taken not to disintegrate them during the analysis. To this end, the Sympatec QicPic equipped with the GRADIS gravitational powder feeder was employed. Both the original fine-particle agglomerates and the fines-carrier assemblies formed during mixing were measured.

### Mathematical modelling

The particulate flow is modelled using the Eulerian-Eulerian approach which

treats the discrete solid phase as a continuous medium with averaged properties. A general scalar transport equation is used to model the tracer distribution in the vessel to keep track of mixing behaviour.

$$\partial(\alpha_s \rho_s C) / \partial t + \nabla(\alpha_s \rho_s u_s C) = 0$$

## RESULTS & DISCUSSION

### Random mixing dynamics

The macro mixing dynamics can be observed in Figure 1. The simulated tracer distribution reaches the equilibrium state rapidly, i.e. %RSD was 0.1 after 0.5s of mixing. Experimental data shows that after 2.5s of mixing, the low fluctuation of the average and the %RSD of the tracer concentration indicates the existence of a random mixture. Therefore, the time required to obtain a random mixture described by mechanism (i) is fast and is of the same order as the time for flow development, i.e. a couple of seconds.

### De-agglomeration dynamics

The de-agglomeration kinetics is illustrated in Figure 2, in which different size fractions of agglomerates are plotted versus mixing time. The size fractions are normalized relative to the corresponding values at the 5s time point. The larger the agglomerates are, the faster is the de-agglomeration kinetics. For example, agglomerates larger than 1500 $\mu$ m are reduced dramatically af-

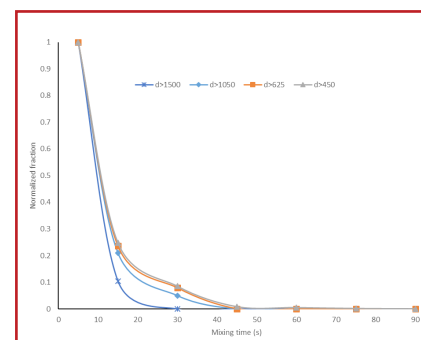


Figure 2. De-agglomeration rate.

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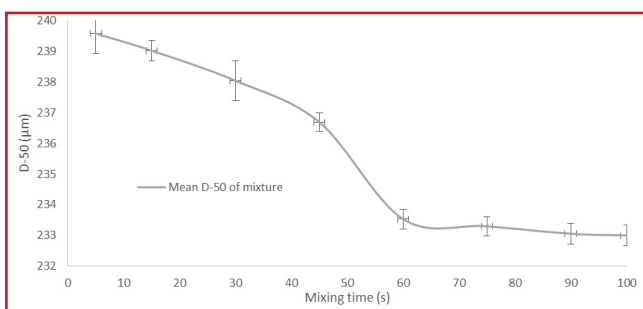


Figure 3. De-agglomeration dynamics.

ter 15s, and are no longer present after 30s. As for the size fraction larger than 450µm, 50s of mixing is needed to reach a stable level.

The levelling out of the overall particle size in Figure 3 can be taken as an indication that the mixing is ready. At even longer mixing times, re-distribution of the fine particles between the carriers can be expected (the last proposed mechanisms). However, the size change during this stage is not significant and will furthermore will not affect the homogeneity of the mixture (see next section). Therefore, the mixing experiments were finished after 100s in this work.

### Content uniformity dynamics

Figure 4 shows the evolution of the fines content and homogeneity when mixing 5% fine lactose of the size fraction 1.4- 2.0mm. The fines content was obtained by the analysis procedure described in the method section. At the very early mixing stage, fine-particle agglomerates were observed to float on the top of the powder bed, which resulted in a very high fine content. Not surprisingly, the mixture was strongly inhomogeneous, with an RSD of 24% at 5s. The fines content thereafter continuously decrease as agglomerates are broken up and distributed throughout the mixture. The progression

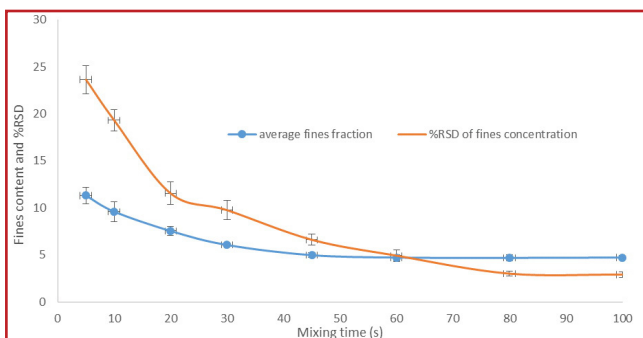


Figure 4. Content uniformity dynamics.

of mixing can be assessed by evaluating both the homogeneity and the average fines content. After 60s an RSD of 4.9% was reached, i.e. a value just below the limit of 5% which is often set as a criterion for acceptable blend uniformity. At longer blending times the uniformity is only slightly improved and the content remains at a constant level.

The overall homogeneity achieved in the current experiments is the combined result of all mechanisms, i.e. random mixing, de-agglomeration and adhesion, acting together. By comparing the time scale to achieve blend homogeneity with the time scale governing the different mechanisms, it is obvious that the mixing time required to produce a uniform formulation is determined by the de-agglomeration kinetics. In other words, once de-agglomeration of the fines-agglomerates is completed, a homogeneous mixture is achieved.

### CONCLUSIONS

A quantitative study of the mixing dynamics of adhesive mixtures was carried out to evaluate the importance of different mixing mechanisms. Overall, data were in agreement with the notion of four different mechanisms, i) random mixing, ii) de-agglomeration, iii) adhesion and iv) exchange and redistribution. Time scales for the first three of these could be established. A main finding was that the de-agglomeration of fine-particle agglomerates is the rate-limiting step as regards achieving satisfactory blend homogeneity, which is illustrated in Figure 5.

This study provided in-depth understanding of the early stages of adhesive mixing. The later stage mechanisms, i.e. exchange, re-distribution and compression of the fine particles, would also merit further investigation as these may affect key properties of adhesive mixtures, such as the dispersibility of fines in the case of adhesive mixtures for inhalation.

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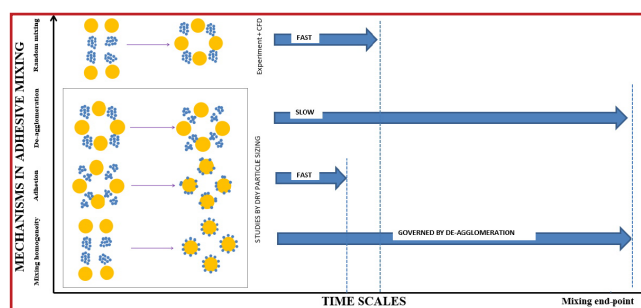


Figure 5. Adhesive mixing mechanistic time scales

R., 2012. A critical view on lactose-based drug formulation and device studies for dry powder inhalation: Which are relevant and what interactions to expect? *Advanced Drug Delivery Reviews*. 64, 257-274.

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Duy Nguyen is currently a PhD Student at Chalmers University of Technology. His research concerns mathematical modelling of fluid dynamics and particulate flow.

# PREPARATION AND SURFACE MODIFICATION OF MAGNETIC PLGA NANOPARTICLES FOR SUSTAINING NATURAL INTERFERON ALPHA RELEASE

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## INTRODUCTION

In The aim of work was to create nano-capsules for sustained and targeted drug delivery of natural interferon alpha (IFN- $\alpha$ ), which is an effective medicine mainly used to treat hepatitis viruses. The work discussed in this paper was performed as part of the "PowTech" FP7 Marie Curie Initial Training Network, and involved the co-encapsulation of natural interferon alpha and superparamagnetic iron oxide (magnetite,  $\text{Fe}_3\text{O}_4$ ) nanoparticles (NPs).

## PREPARATION OF NPS

Co-encapsulation of IFN- $\alpha$  and  $\text{Fe}_3\text{O}_4$  into a poly(lactic-co-glycolic acid) (PLGA) matrix (PLGA NPs) was carried out by double emulsion solvent evaporation method as shown in Figure 1 (Shubhra et al., 2014a). The effects of process variables were studied in order to obtain small sized NPs with high encapsulation efficiency, which could be sterilized by ultrafiltration. It was found that the magnetite/PLGA ratio, the PLGA concentration, the external aqueous/intermediate organic phase volume ratio, and sonication time proved to be statistically significant influences.

## PROCESS OPTIMIZATION

The reason behind the optimization was to find out suitable conditions (process variables) to get maximum encapsulation efficiency with a constraint of obtaining various mean particle sizes (Shubhra et al., 2014b). Because the required magnetic properties of the model drug loaded NPs may be different, and are influenced by the relative amount of  $\text{Fe}_3\text{O}_4$  nano-

particles applied in the organic phase, the optimization has been carried out at various magnetite/PLGA ratios. Process optimization was carried out by experimental design and statistical analysis.

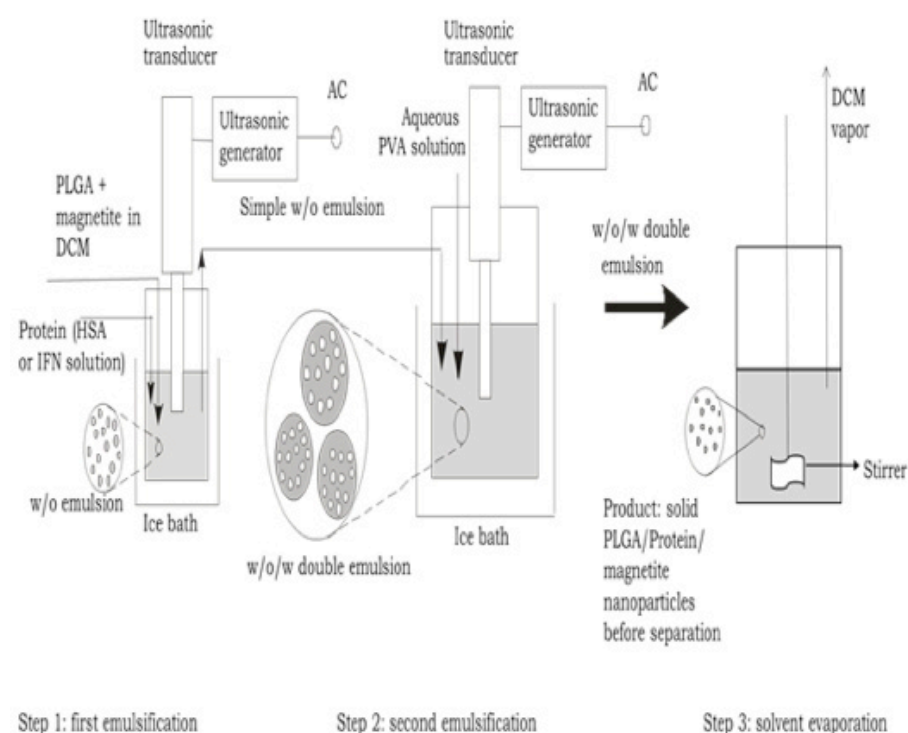
The mean hydrodynamic size and encapsulation efficiency of NPs ranged from 115-329 nm and 18 to 97%, respectively, depending on the process conditions (Shubhra et al., 2014b). Optimization resulted in high encapsulation efficiency for the model drug (92.3%) for relatively small sized PLGA NPs (155 nm).

Results of optimization with different combinations of process variables can be found in Figure 2. If we follow the

vertical line upward to the upper diagram at a given  $\text{Fe}_3\text{O}_4$ :PLGA ratio (in Figure 2, we have taken the example of  $X_{\text{Fe}_3\text{O}_4}=4.0\%$  wt/wt), it is seen that arriving at the point on the curve referring to the same mean particle size (155 nm in this case) will give EEHSA=92.3% which is the highest encapsulation efficiency achieved under these conditions (Figure 2, the horizontal dotted line of the upper diagram).

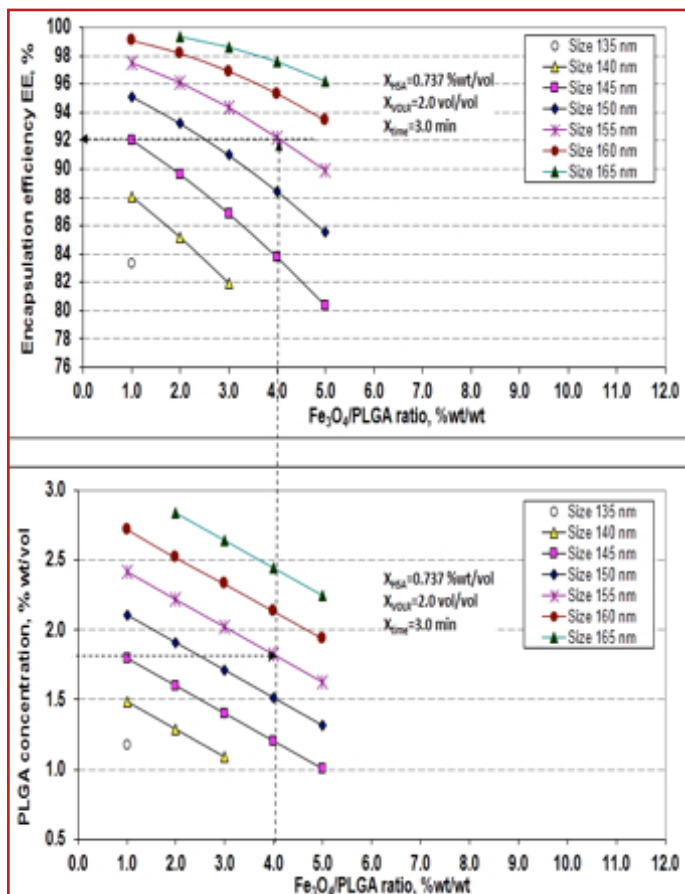
## SURFACE MODIFICATION

Nanocapsules prepared with a selected optimum condition were subjected to surface modification by using triblock copolymer poloxamer, in



**Figure 1: Schematic diagram of the double emulsion solvent evaporation method applied for preparation of PLGA nanoparticles with encapsulated HSA (model drug) or IFN and  $\text{Fe}_3\text{O}_4$  particles.**





**Figure 2: Optimization at different magnetite/PLGA ratio. At optimal values of other process variables, PLGA concentration and magnetite/PLGA ratio determines the achievable smallest mean particle size (lower diagram) and the highest encapsulation efficiency (upper diagram).**

and protect it from the quick degradation. Interferon release from poloxamer modified PLGA NPs was much slower than that for unmodified ones. The encapsulated magnetic nanoparticles allow targeting by external magnetic field.

## CONCLUSION

PLGA NPs co-encapsulating both natural interferon alpha and superparamagnetic iron oxide were prepared by double emulsion method. The process was optimization and the surfaces of NPs were modified by poloxamers. The concentration of PLGA in the intermediate organic phase and the duration of the second sonication af-

ected most strongly the mean hydrodynamic particle size. To achieve the smallest possible mean particle size, relatively low PLGA concentration, high dispersion energy and relatively small volume ratio of the intermediate organic/external aqueous liquid need to be applied. NPs with suitably modified surface showed 50 % less plasma protein adsorption. Surface modified PLGA NPs represented more sustained release of IFN- $\alpha$ , although at substantially lower concentration level, than unmodified NPs.

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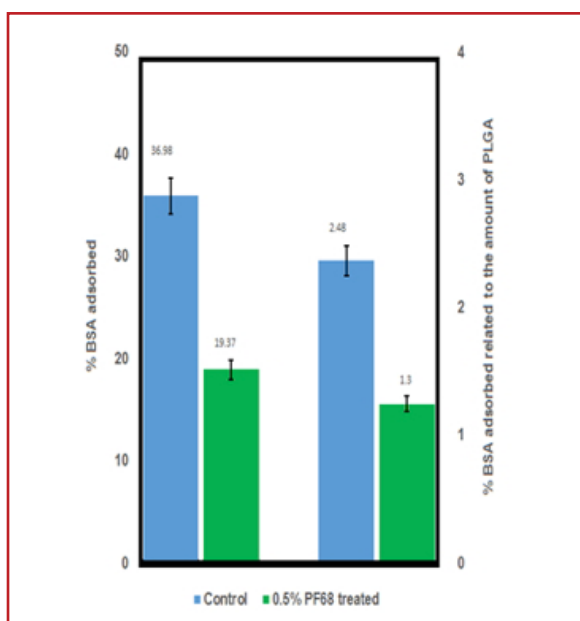
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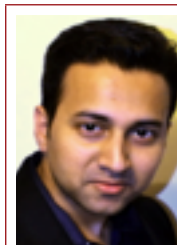
order to prolong their lifetime in the bloodstream (Shubhra et al., 2014c,d). Surface functionalization was verified by size increase, zeta potential and isothermal titration calorimetry. In blood serum protein adsorption measurements, bovine serum albumin tended to be adsorbed 50% less on the surface modified NPs in comparison to the unmodified ones (Figure 3) which was determined using UV/VIS spectrometry with the help of micro BCA protein assay kit at the wavelength of 562 nm.

In vitro IFN- $\alpha$  release study carried out using enzyme linked immunosorbent assay test showed that prepared PLGA NPs are capable to sustain the release of interferon,

duration of the second sonication af-



**Figure 3: Percentage of BSA adsorbed onto unmodified and modified PLGA NPs.**



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Dr. Shubhra carried out this PhD work under the supervision of Prof. János Gyenis and Dr. Tivadar Feczko which was in the frame of the "Pow-Tech" FP7 Marie Curie Initial Training Network. From this PhD work, 5 peer-reviewed journals have been published. He graduated from University of Pannonia, Hungary in October 2014. Currently he is a JSPS (Japan Society for the Promotion of Science) postdoctoral fellow and his main duty involves gene delivery to the brain to stop infarction.

# ENCAPSULATING PARTICLES WITH NANOSCALE PRECISION USING ATOMIC LAYER DEPOSITION

Van Ommen, J.R. (Delft University of Technology, the Netherlands); Goulas, A. (Delft IMP B.V., the Netherlands)

## INTRODUCTION

In most encapsulation processes, the coating is introduced via the liquid phase: either by dispersing the particles in a liquid, or by spraying a liquid onto the particles. An alternative is to use gas-phase coating. One way of doing this is with chemical vapor deposition (CVD): exposing the substrate to volatile precursors, that react at the surface to form a coating. Typically, two different precursors are being used. Although CVD is mostly used in the semiconductor industry for coating wafers, it is also used for coating particles. The typical coating thickness obtained with CVD is in the  $\mu\text{m}$ -range. Following Moore's law, there is an ongoing drive towards semiconductor components miniaturization, which also requires a coating technology that enables thinner films. This explains why atomic layer deposition (ALD) has become more popular in recent years: with this gas-phase coating technique, sub-nanometer precision can be achieved.

The difference in approach between CVD and ALD is that in the latter the gaseous reactants are added alternately. As a consequence, the coating chemistry is split into two half-reactions. Each of these reactions is self-limiting, such that at most a monolayer can be deposited. In this way, we have full control over the coating thickness: the number of times the alternating

feed of the two precursors is repeated determines the thickness of the achieved coating. For example, for an alumina coating, a precursor such as trimethyl-aluminium chemisorbs on a substrate by reacting  $n$  ( $1 \leq n \leq 2$ ) of its methyl-groups (ligands) with active sites (commonly hydroxyl-groups) at the surface, releasing methane (step 1). In step 2, the remaining ligands react with an oxidizer such as water releasing the other methyl-groups and repopulating the surface with hydroxyl groups (see Fig. 1.a.). After this second step, step 1 can be repeated. The formation of alumina is just one example: dozens of different inorganic materials can be made via ALD (Mikkulainen et al., 2013). Moreover, it is also possible to deposit organic films via an analogous mechanism (see Fig. 1.b); the method is then referred to as molecular layer deposition (MLD).

## ALD ON PARTICLES

Most research on ALD is aimed at depositing ultrathin films on wafers and other flat substrates. However, when carried out in a so-called fluidized bed, ALD is an attractive way of providing particles with an ultrathin coating. In a fluidized-bed ALD reactor, the particles are suspended in an upward nitrogen flow. The good mixing of the particles and the gas results in a very uniform coating of the particles. Moreover, this approach has an excellent scale-up potential: at the lab-scale we can coat

batches from less than 1g to more than 100g. However, in an industrial setting it would be rather straightforward to coat batches of several hundreds of kg. The size of the particles to coat is not limited to the  $\mu\text{m}$  range: ALD can also be applied to fluidized nanopowders. Nanoparticles – contrary to what is typically observed for micron-sized particles – are fluidized as very dilute agglomerates with distinctive fluidization characteristics. One of our research topics is understanding the fluidization of nanoparticles, and applying it as a tool for ALD on these particles. When working with powders of which the particle size is in the nanorange or just slightly larger (a few  $\mu\text{m}$ ), the particles often have a strongly cohesive behavior. In those cases, we work with assistance methods such as vibration or microjets to obtain smooth fluidization behavior (van Ommen et al., 2012).

## RESULTS & DISCUSSION

In the semiconductor industry, most ALD processes are carried out at vacuum. However, we operate our fluidized bed reactors typically at atmospheric pressure to facilitate scale-up. Normally, ALD processes are carried out between  $100^\circ\text{C}$  and  $300^\circ\text{C}$ , depending on the chemistry used. However, for several substrate particles – especially for materials of biological origin – this would be too high. Therefore, we recently investigated coating of titania nanoparticles with alumina at room temperature and atmospheric pressure using the coating chemistry given in Fig. 1.a. We found conformal, homogenous coatings (see Fig. 2.a). Moreover, the coating thickness linearly increases with the number of cycles applied (see Fig. 2.b), demonstrating the precise control over the thickness we can achieve (Valdesueiro et al., 2015).

As the precursors used in ALD are typically quite expensive, it is a prerequisite for economical process operation that they are efficiently used. We recently published a paper aimed at understanding and optimizing the precursor utilization efficiency using a multiscale modelling approach (Grillo et al., 2015). We showed that fluidized-bed ALD on high surface area powders is a forgiving process that can be

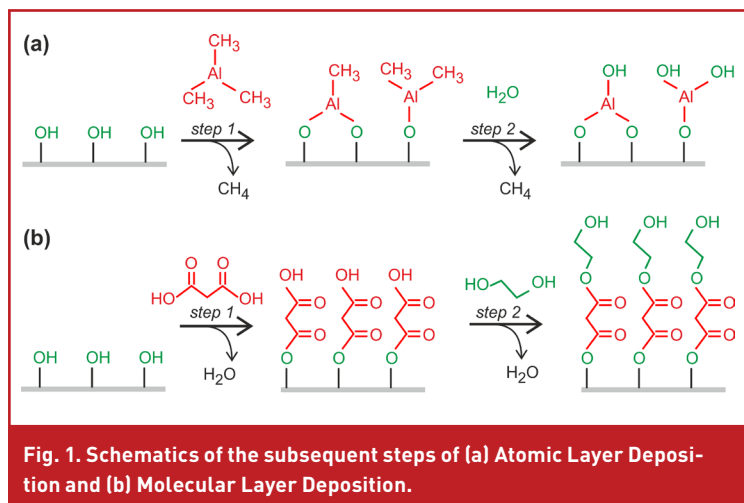
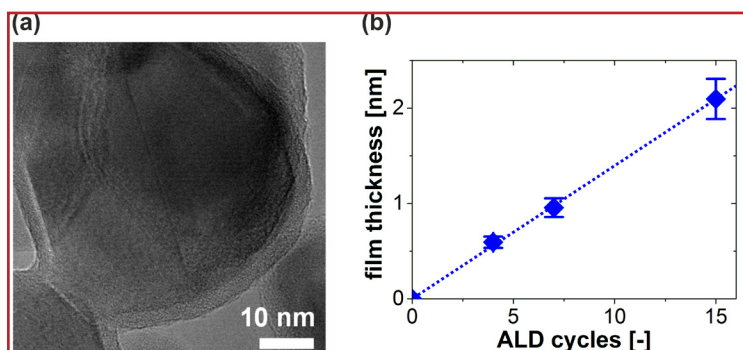


Fig. 1. Schematics of the subsequent steps of (a) Atomic Layer Deposition and (b) Molecular Layer Deposition.



**Fig. 2. Alumina coating of titania nanoparticles: (a) TEM picture of a particle coated with 15 ALD cycles; (b) film thickness as a function of the number of cycles.**

carried out with virtually no precursor wasting. For nanoparticles, the precursor will have to diffuse into the nanoparticle agglomerations. However, still more than 99% precursor efficiency can be achieved. In the case of porous micron-sized particles, typically used as carrier particles in the manufacturing of supported catalysts, this will be somewhat lower (~95%), but for the encapsulation of non-porous particles with a diameter in the micron-size range very high efficiencies of virtually 100% can be achieved. Another attractive feature of encapsulating micron-sized particles with this approach is that just very small amounts of coating material have to be used: on a 10  $\mu\text{m}$  particle, an alumina coating of 10 nm is just 0.6 vol% of the total particle. However, already such a thin film allows the formation of an extremely high barrier coating: it can reduce the water vapor transmission of a polymer substrate with more than a factor 100.

Like most conventional ALD reactors, fluidized-bed ALD reactors are operated in a temporal mode: the pulses of the different gaseous reactants are delivered subsequently in time. An alternative is to separate the administering of the reactants in space. We recently developed a spatial ALD reactor for particles. In this device, the particles are blown through the reactor with nitrogen as a carrier gas at atmospheric pressure: they are pneumatically transported. This pneumatic transport line consists of three parts: first the particles are heated, then reactant A is added and reacts with the particles, and subsequently reactant B is added and reacts with the particles. Our current test setup is laid-out for just a single ALD cycle. However, it is easy to devise equipment with multiple injection points for both precursors,

such that multiple ALD cycles can be carried out. Currently, we are able to produce coated nanoparticles via ALD at a production rate of about 1 g/min (van Ommen et al., 2015).

However, the experience with pneumatic transport from other fields opens up promising scale-up prospects for continuous particle ALD.

## CONCLUDING REMARKS

ALD is an attractive technique to efficiently encapsulate particles via a gas-phase process. Since the obtained coating has a very high quality, excellent encapsulation results can be obtained with films of just a few nm. With ALD, many different inorganic coatings can be deposited, such as oxides, nitrides and pure metals. Its organic counterpart MLD, which received less research attention up to now, can also be very relevant for encapsulation. We have demonstrated that ALD of alumina can be carried out at atmospheric pressure and room temperature, opening the door for coating sensitive substrates, and for carrying out the coating at large scale. The coating can be carried out either on batches of particles in a fluidized bed, or on continuously transported particles with a pneumatic transport reactor.

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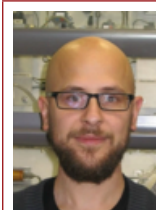
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Aristeidis Goulas holds a Dipl. Eng. degree in chemical engineering (Thessaloniki, 2008) and an MSc in sustainable energy technology (Delft, 2011). Since 2011 he has been a researcher at Delft University of Technology) focusing in gas-phase nanostructuring of particles. In 2015 he joined the spin-off company Delft IMP (Intensified Materials Production) as a project manager. He is responsible for the planning and execution of ALD coating solutions for several industrial clients.



## JOB REQUESTS



**Looking for a research engineer position in the field of encapsulation**

**Elodie Souron, PhD**

I am currently working as a research engineer for the CNRS (National Center for Scientific Research) in Strasbourg, France. I synthesize, modify and graft reloadable microcapsules onto natural or synthetic fibers to develop smart textiles (e.g. deodorant, anti-mosquito or fire retardant properties). I obtained my PhD, working on the immobilization of ionic liquids in "layer by layer" microcapsules and biopolymer beads for applications in catalysis.

I have recently helped with the organization of the 7th Training School on Microencapsulation (Strasbourg, 2015).

I have experience on various techniques of encapsulation such as interfacial polycondensation, radical polymerization, gelation and freeze-drying (alginate and chitosan), layer by layer and the characterization techniques associated. I have also skills in communication, internship supervision and collaboration management (industrial and academic).

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**Looking for an industrial R&D position in the food, cosmetic, chemistry or pharmaceutical fields.**

**Marta Muñoz Ibañez, PhD**

Specialist in interface science and particle technology, Marie Curie Fellow, I hold a PhD in Food Process Engineering from AgroParisTech (France) and a MSc in Chemical Engineering from Imperial College London (UK).

During the PhD I worked at DSM Food Specialities (The Netherlands) and collaborated with two European institutions. The research was focused on the encapsulation of food ingredients (oil-based and enzymes) at pilot and industrial scale.

The areas of interest include:

1. Emulsion/dry-emulsion science: rheology and particle characterization.
2. Emulsion processing: homogenization and atomization.
3. Powder technology (spray drying): glass transition, stickiness, desorption kinetics.

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**Looking for a job in R&D in the field of food, pharmaceutical or cosmetic industries**

**Pérignon Carole, PhD**

Master 1 in Chemistry and Graduated in Food Sciences at Ecole Nationale Supérieure d'Agronomie et des Industries Agroalimentaires (ENSAIA) in Nancy, I did my PhD in chemical reactions in microencapsulation under the direction of Dr. Poncelet at Oniris in Nantes. This multidisciplinary formation gave me broad knowledge over various fields such as food formulation, polymer physico-chemistry and encapsulation technologies.

My last experience within the company Capsugel allowed me to apply my technical skills in encapsulation in the pharmaceutical field. I have developed and optimized innovative encapsulation processes for the formation of solid lipid microparticulates.

I am experienced in project management and in team work. Perseverance, organization and flexibility are my qualities when leading a project.

I am looking for an opportunity as a project manager in R&D in food, pharmaceutical or cosmetic fields.

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**Igor Lacik**

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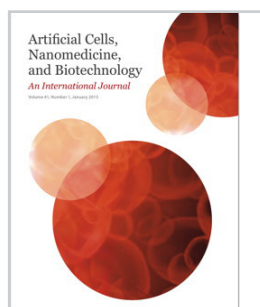
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