Bioencapsulation Research Group

Bioencapsulation Innovations

February 2016

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EDITORIAL

PARTICIPATE TO THE BRG DEVELOPMENT

Twenty-five years ago, we decided to establish a new association, the Bioencapsulation Research Group. BRG has become today a major actor of the development of the microencapsulation. In 2017, we will celebrate the 25th International Conference on Bioencapsulation and the 20th Microencapsulation Industrial Convention. All together, we organized more than 70 meetings and training schools.

Already a quarter century, one generation ... and our group is more active than never. Last year, we decide to add in the banner of BRG web site the slogan "The largest participative network on microencapsulation". Our objective was to promote a new involvement of mmbers, especially young researchers, to make the association more dynamic et give us a stronger impact on the microencapsulation community.

> BRG wishes you an exceptional 2016 year and hope to welcome you to its events

In this issue, you will find several contributions from the speakers of the last Microencapsulation Industrial Convention, held last April in Eindhoven, the Netherlands. We are now preparing the next one (http://bioencapsulation.net/2016_Frankfurt/). To insure its success, on top of the internal BRG mailing, we have done agreement with several journals to publish a full page advertising and send invitations to more than 40 000 persons. We wish to extend this campaign to other journals and organizations, especially for the preparation of the 2017 Microencapsulation Industrial Convention to be held in New Jersey, USA, beginning of April 2017.

In this journal, you will find different useful information such as a conference calendar, 11 open positions, 3 PhD abstracts ... Our objective is to extend this service by posting this information on the BRG web site and/or on linkedin.

Regarding theses abstracts, several hundreds of students are registered to the BRG. They thus represent a potential of more than one hundred PhD abstracts per year likely to be published in our newsletter.

The newsletter is sent to more than 5000 persons. Maintaining the address-book is a heavy task as mainly 1/3 of the addresses have to be renewed or at least corrected every year. One difficulty is to identify new potential members. Many researchers use other keywords than "microencapsulation" making their identification more difficult. While it is easy to identify companies involved in encapsulation or using microcapsules, the identification of the person in charge of this question inside the company is not easy.

As you see, there is lot of place for your participation. We plan to develop in the near future some tools to help providing useful data.

In the meantime, if you wish to support us, please send a mail to : contact@bioencapsulation.net.

Best regards

Professor Denis Poncelet
BRG president

CALENDAR

PROGRAM 2016

February

9th International Conference on Advanced Technologies & Treatments for Diabetes (ATTD 2016)
February 3-6, 2016 -Milan, Italy
http://www.attd2016.com/

Mars

Advances in Nutraceuticals through Functional Ingredients and Targeted Delivery
March 2-3, 2016 - Darmstadt, Germany
http:// www.evonik.com/e-lab

Small Particle Formation - An Introductory Survey Surface Modification Chemistries for Particles and Interfaces
March 11-12 2016 - San Diego, Ca, USA
http://nanoparticles.org/courses/SanDiego-2016Courses.htm

April

Design and Manufacture of Functional Microcapsules and Engineered Particles
April 3-7, 2016 - Siracusa (Sicily), Italy
http://www.engconf.org/conferences/materials-science-including-nanotechnology/design-and-manufacture-of-functional-microcapsules-and-engineered-particles/

10th Workd Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology
April 4-7, 2016 - Glasgow, UK
http://www.worldmeeting.org/home/

19th Microencapsulation Industrial Convention
April 4-6, 2016 - Frankfurt, Germany
http://bioencapsulation.net/2016_Frankfurt

Granulating & Tableting
April 12-14, 2016
Weimar, Germany
http://www.ttc-binzen.de/cm/index.php?id=1070&L=1%2F

May - June

8th Training School on Microencapsulation
May 30 - June 2, 2016 - Cork, Ireland
http://bioencapsulation.net/2016_Cork

June

11th International Symposium on Polyelectrolyte
June 27-30, 2016 - Moscow, Russia
www.isp2016.org

July

CRS annual meeting and exposition
July 17-20, 2016 - Seattle, Washington, USA
http://www.controlledreleasesociety.org/meetings/annual/

September

22th Bratislava International Conference on Macromolecules: Polymers with Tailored Architecture and Properties - BIMac2016
September 6-9, 2016 -Bratislava Slovakia
http://polymer.sav.sk/bimac/

Pellets and Micropellets for oral solid dosage forms
September 2_22, 2016 - Binzen Germany
http://www.ttc-binzen.de/cm/index.php?id=1077

24th International Conference on Bioencapsulation
September 22-24, 2016 - Lisbon, Portugal
http://bioencapsulation.net/2016_Lisbon

Future

Send to contact@bioencapsulation.net any information about your future conference

CALENDAR

Bioencapsulation Research Group

24TH INTERNATIONAL CONFERENCE ON BIOENCAPSULATION

Lisbon, Portugal

September 22 - 24, 2016

125 to 150 participants

40 oral presentations

up to 80 posters

More information

http://bioencapsulation.net/2016_Lisbon/

Bioencapsulation Research Group

19TH MICROENCAPSULATION INDUSTRIAL SYMPOSIUM

Frankfurt, Germany

April 24-6, 2016

125 to 150 industrials

10 conferences by experts, Exhibition,

hundreds of BtoB meetings

More information

http://bioencapsulation.net/2016_Frankfurt/

Bioencapsulation Research Group

8TH TRAINING SCHOOL ON MICROENCAPSULATION

Cork, Ireland

May 30 - June 2, 2016

60 participants

12 Lectures by experts

8 pratical demonstrations

More information

http://bioencapsulation.net/2016_Cork

JOB OFFER

XEDEV Excellent in Development

(JUNIOR) SCIENTIST (M/F)

COMPANY

Xedev is a young and dynamic CRO specialized in feasibility studies for process and formulation development in particle engineering by agglomeration, drying, melt and coating. More information: www.xedev.com

JOB

- You are involved in the different projects both in process development and analysis of the final products
- You will carry out experimental work in a research environment together with data interpretation
- You are involved in the internal projects regarding process and product development

Contact/Link: *When you have interest in above vacant function, we ask you to send us your CV to fabienne@xedev.com. You will be invited for an interview when your profile matches.*

JOB OFFERS

2016 TRAINING FELLOWSHIP IN DRUG DELIVERY SYSTEMS

FELLOWSHIP

A training research position is immediately available in the DDS lab at CBIOS of Universidade Lusófona. Trainees in this CBIOS fellowship will have access to a variety of techniques. Several preparation methods of drug delivery systems have been developed and compared in our laboratory through cell culture models, animal and human models. Analytical tools according international guidelines are being currently explored. Group's research interests are centered in Drug Delivery Systems but this lab also offers complementary training in Non-Drug Delivery Systems (such as food supplements and cosmetics) and methods to assess its efficacy and safety. All candidates will be considered, although special consideration will be given to individuals who have 1) a solid academic background including, if possible, special interest in DDS, 2) good communication skills (written/spoken English), 3) interest and, if possible, previous research experience working in DDS, and 4) a keen desire to learn. Candidates eligible for CBIOS fellowship will benefit for a "zero" fees policy enjoying all benefits offered to the university student's. After the 1st semester evaluation, the candidate will eventually be able to apply to one of the scholarships available for PhD programs.

Contact/Link: *Luís Monteiro Rodrigues PhD, Director, monteiro.rodrigues@ulusofona.pt*

WEBSITE: *http://cbios.ulusofona.pt/opportunities/2016-training-fellowship-in-drug-delivery-systems*

5 MARIE CURIE PHD POSITIONS

SMARTMEM is a multidisciplinary project leveraging the emerging technology platforms around so-called smart membranes and evolving this platform to commercial use in consumer good products. P&G, together with academic partners, is seeking for:
5 PhD students with a Master's degree (or similar standard) in Chemistry, Chemical Engineering, Materials Science/ Engineering, Physics, Biochemistry or related science. It desirable that the candidate has experience with polymer science (synthesis, modification and/or material application, stimuli responsive polymers), membranes, particle/ capsules processes, surface coating or surface modification techniques and/or organic synthesis. To have knowledge in common characterization techniques of polymers/materials, membranes, particles and/or capsules is a plus.
Starting date : 1st October 2016.

Contact/Link: *Please, go to http://pgcareers.com and apply to job number RND00003097.*

FORMULATION DEVELOPMENT MANAGER

Apply and enforce hygiene and safety rules and regulations
Design and develop conventional formulations (solid, liquid) and innovative formulations integrating the requirements of animal nutrition, technical, industrial, commercial and regulatory fields
Develop dosage forms suitable for administration of the active ingredient, the scheduled dose, with the best possible guarantees of activity and stability
Technical and technological surveys and research both documentary and bibliographic
Define the resources and means necessary for the implementation of projects and works
Develop the analysis supporting the formulation
Develop and optimize processes so that these new formulas can be assessed in vitro and in vivo
Follow the manufacture of semi pilots and pilot batches
Manage and animate the pharmaceutical R & D formulation unit (2 to 4 people according to need)
At least 10 years' experience required in the food industry or ideally pharmacology field

Contact/Link: *Nabil ACHIK, contact@rh-adequation.fr*

3 MARIE CURIE RESEARCH FELLOW POSITIONS AVAILABLE WITH PHD IN CHEMISTRY OR CHEMICAL ENGINEERING

ISSFLOW aims at developing fundamental understanding of complex fluids to allow for the design of smart and functional gels and fluids via the development of novel rheology modifiers. P&G, together with 4 European partners is currently seeking :
1 Post-doc Research Fellow with a PhD degree in Chemistry or Chemical Engineering (Spain), knowledge on biopolymers and synthesis will be appreciated (job number RND00003091).
1 Post-doc Research Fellow with a PhD degree in Synthetic Organic Chemistry (Belgium) with experience in controlled release mechanisms from hydro and/or organogels is desired, especially related to pharma applications (job number RND00003089).
1 Post-doc Research Fellow with a PhD degree in Physical Chemistry, Chemistry or Chemical Engineering (Italy), spectroscopic skills, neutron and X-ray scattering and confocal microscopy, as well as knowledge in the area of colloidal chemistry and soft matter will be appreciated (job number RND00003090).
Starting date : 1st April 2016 onwards.

Contact/Link: *Please, go to http://pgcareers.com and apply to the selected job number.*

THESES ABSTRACTS

Protection of an enzyme by encapsulation during the incorporation in biodegradable plastics

AURÉLIE BIDORET

Supervisor Denis Poncelet
Date & Place 24-02-2016 – Nantes, France
Affiliation ONIRIS, Nantes

The development of biodegradable plastics by incorporating of enzymes is one of the potential solutions to the growing problems of domestic and industrial wastes. The objective of this thesis is to develop four encapsulation methods providing protection for the enzymes used in biodegradable plastics. The first method consists of forming polylactic-acid (PLA) microspheres by using encapsulation by solvent evaporation. To reduce costs and make an environmentally friendly process, an alternative was developed by using non-toxic solvents and by proceeding by solvent extraction. The second method is to form hydrogel beads by extruding an alginate/starch solution in the calcium bath. Analytical methods developed in this context showed that nearly 50% of enzymes are lost in the bath. To eliminate such losses, extrusion of hot carrageenan solution into cold air was tested and modeled. These three methods were not resulted in the production of small micro-particles and therefore could be used only for thick objects. A fourth method, consisted of pulverizing a polysaccharide solution in a spray dryer, produced small micro-particles (<50µm). These micro-particles were incorporated into PLA matrix at 40, 170 and 200°C maintaining the enzymes active at these temperatures.

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Crystallization and Encapsulation in Multi-component Mixtures

M.A. REUS

Supervisor A.E.D.M. van der Heijden & J.H. ter Horst
Date & Place 18-03-2016 – Delft, The Netherlands
Affiliation TUD, The Netherlands

Many products from chemical industries, such as consumer products, pharmaceuticals, food products and fine chemicals industries constitute particulate products. The functionality of these products depends among others on the properties of its constituents, their interactions and their distribution in the product. In this context, we investigated the crystallization in multicomponent mixtures as well as microencapsulation of various compounds.

Multicomponent particulate products are produced with different functionalities (improved stability, controlled release, protection from environment, etc.), and their performance is assessed. For each product, a suitable process was used, which takes into account all demands (e.g. purity, bioavailability, controlled release function) and limitations (e.g. temperature sensitivity, reactivity) of the specific system. Model compounds from various industrial fields (e.g. food, pharmaceutical and energetic material industries) are used to illustrate the wide applicability of the tested processes.

M.A.Reus@tudelft.nl

Once the PhD thesis has been issued, a pdf can be downloaded from http://repository.tudelft.nl

Oil encapsulation in alginate membrane by inverse gelation

EVANDRO MARTINS

Supervisor Denis Poncelet and Denis Renard
Date & Place 16-12-2015 – Nantes, France
Affiliation ONIRIS, Nantes

Encapsulation of oil by inverse gelation consists of dropwise addition of a calcium chloride/oil emulsion into an alginate bath. Calcium ions inside the emulsion migrate towards the bath cross-linking the alginate molecules (inverse gelation). Millimetric capsules (3-7 mm) with a core-shell structure are formed. However, the production of capsules with sizes lower than 1 mm by inverse gelation was never demonstrated. The interest of microcapsules is based on a vast range of applications for which the capsule does not have to or little interfere with the texture or the appearance of the end product. The objective of this thesis is therefore to develop an inverse gelation process that yields capsules at reduced sizes. In this frame, the comprehension of the inverse gelation mechanisms from oil-in-water (O/W) and water-in-oil (W/O) emulsions was also studied. In order to reduce the capsules size, a dispersion method was proposed. A dispersion method was therefore proposed to reduce the size of capsules, which consists in the formation of droplets by dispersion of the emulsion in a bath of alginate under stirring. After cross-linking of alginate to form the membrane, microcapsules of sizes between 370 and 600 µm were obtained. To control the wide size distribution of the microcapsules, the dispersion method was adapted for the millifluidic method. Monodispersed capsules with desired mean particle size were produced. The mean size of the particles (within 140 µm to 1.4 mm) was controlled by variation in the flow rates of the dispersed and continuous phases in the millifluidic circuit. 200°C maintaining the enzymes active at these temperatures.

evandrombi@yahoo.com.br

JOB REQUEST

Looking for R&D/FORMULATION SCIENTIST JOBS IN MICROENCAPSULATION

Jeronimo Jose Escudero Gonzalez, PhD in Pharmaceutical Technology

I am Pharmaceutical Technology PhD, I have experience in Controlled Release, Formulation (Cosmetics, Microencapsulation) QC, QA and my last 5 years I have been working in Microencapsulation via Spray Drying (Atomisation/droplet generation by Flow Focusing-Flow Blurring devices)

I am looking for new opportunities in Microencapsulation/ Spray drying field. I do not have preferences of where work and I am immediately available.

jjeg2011@gmail.com
Phone: +34 667781616

Linkedin: https://es.linkedin.com/in/jeronimoescudero1/en

ARTICLE

USING MICROFLUIDIC ENCAPSULATION FOR DEVELOPING SUSTAINED RELEASE MICROSPHERES

de Bruijn, R. – EmulTech b.v., The Netherlands

INTRODUCTION

Microfluidic emulsification, or droplet microfluidics, has been reported since 2001 as a tool for generating uniform droplets (Thorssen et al., 2001) in a carrier liquid, otherwise defined as an emulsion.

EmulTech
CONTROL YOUR DDS FORMULATION

Microspheres are complex formulations employing a carrier material, typically a biodegradable polymer, to molecularly or physically encapsulate an active, typically a drug substance. Sustained release is achieved by degradation of the polymer in vivo, providing prolonged exposure to drug substances that otherwise would have been cleared quickly. These formulations can deliver high added value in difficult and chronic treatments, by delivering therapeutic quantities for months of treatment in one injection. Especially ocular pathologies can effectively be treated with this type of product (Herrero-Vanrell et al., 2014).

Microfluidic emulsification is an excellent tool to prepare microspheres and microbeads, because of the direct production of droplets and eliminating errors and disruptions related to turbulent processes like homogenization. Moreover, the approach we developed adds exquisite control over droplet formation. Optimizing the operating conditions eliminates consistent size, absence of fouling and other process failures.

This presentation will give an overview of the benefits for sustained release drug products and the road to industrialization.

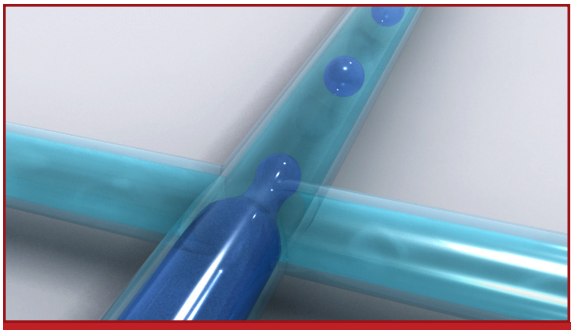

Figure 1: Schematic 3D picture of droplet formation

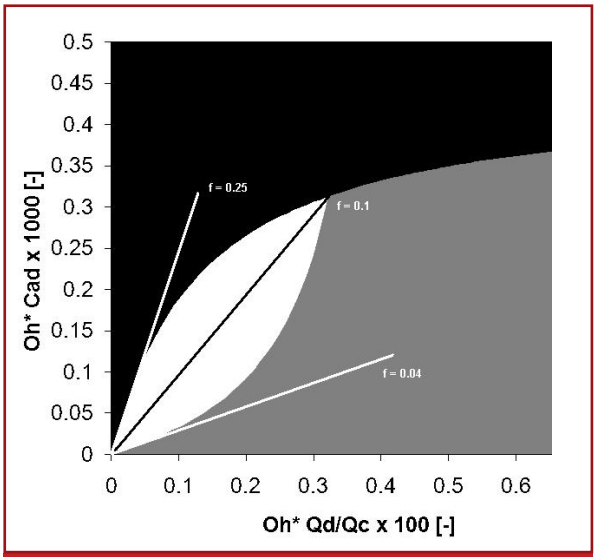

Figure 2: Flow map, depicting all combinations of liquid properties, microchannel size and flow rates. Combinations in the white area yield the desired process.

MATERIAL & METHODS

Preparing polymer microspheres with a hydrophobic small molecule starts with two solutions, the dispersed solvent phase (the liquid to form the droplet) containing the polymer and the small molecule and the aqueous continuous phase (the carrier liquid surrounding the droplet). These are pumped into a microchannel (size 5 – 1000 micron), the dispersed phase enters a cross junction where so called 'hydrodynamic flow focussing' of the continuous phase breaks the polymer solution in drops. These drops are the templates for microspheres, which reduce in size by eliminating the solvent.

To use the droplet formation in this set up in the most robust way, the correct flow rates should be calculated using our proprietary engineering relations and flow mapping (WO2010031709 A1), schematically given in the figure 2.

To operate within the window, the flow rates can readily be calculated using material specific properties, namely viscosity, interfacial tension and density, and the channel size. The equations to yield the (theoretical) optimum are:

$$Q_c = f \times A_\gamma / \mu_c \quad (1)$$

$$Q_d / Q_c = 0.00272 / (Oh_c \times Oh_d) \quad (2)$$

$$Oh_i = \mu_i / \sqrt{(\rho_i \gamma R)} \quad (3)$$

Q_c = Flow rate continuous phase

Q_d = Flow rate continuous phase

μ, γ, ρ = material properties

A, R = microchannel properties

Figure 3: High-speed microscopic image of the exit of a multi-microchannel prototype device (EmulTech designed). Drops are 50 micron

For the typical polymer microsphere process, the rates for a single channel device yield ~ 5 mg/hour of microspheres. To be able to achieve quantities that can be used for release experiments, scale up is done on chip up to 400 parallel channels.

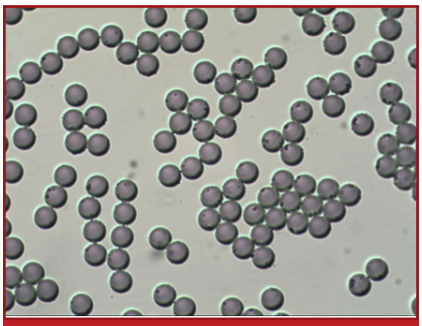

Figure 4: Hydrogel microbeads (hyaluronic acid), 40 micron. Image captured directly after exiting the process.

Intermezzo

Hydrogel beads can be formed in the same fashion as polymer microspheres, but employ a W/O approach. The hydrogel solution is dispersed in an inert oil, and by crosslinking or temperature switch the beads gel to semi-solid and stable suspenions.

RESULTS

Straightforward preparation of microspheres and microbeads of controlled size is confirmed by light microscopy directly after the process or electron microscopy after drying.

Drug release measured from uniform microspheres prepared using this highly controlled process show linear release over 90 days.

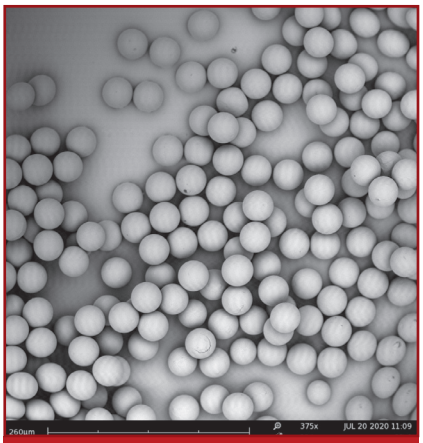

Figure 5: Polymer microspheres (poly-D,L-lactide-co-glycolide, PLGA), 40 micron

NEXT STEPS

Scale up to 400 parallel channels has shown to be straight forward, yielding reproducible results. The current manufacturing capacity is up to 1 kilogram dry weight of microspheres. A typical sustained release product requires 500 kilogram batches. The manufacturing plant, requiring a next hundreds-fold scale up, is planned to be designed in the same fashion as the first: parallelization. A 'microfluidic reactor' is being designed that will generate up to 20 million microspheres per second. The pilot plant project that has started has the goal to design, build and test the reactor.

The manufacturing plant will operate 10 reactors simultaneously.

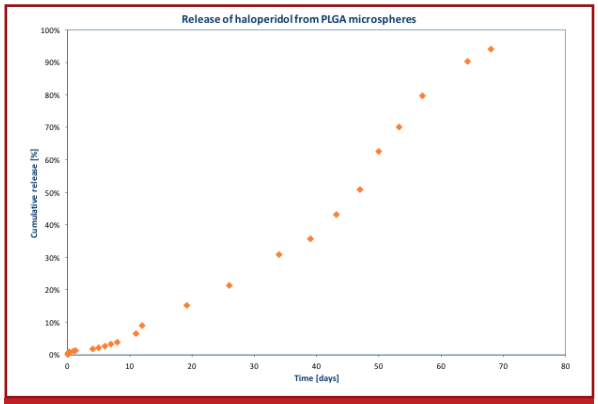

Figure 6: Drug release curve PLGA-HP

REFERENCES

- Thorssen, T., et al., Dynamic Pattern Formation in a Vesicle-Generating Microfluidic Device. Phys. Rev. Lett., Vol. 86, Iss. 18, 4163 – 4166 (2001)
- Herrero-Vanrell, R., et al., The potential of using biodegradable microspheres in retinal diseases and other intraocular pathologies. Progress in Retinal and Eye Research 42, 27-43 (2014)
- WO2010031709 A1

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Robin de Bruijn developed microencapsulation technology and founded EmulTech during his Process Engineering thesis at the TU/e. He has extensive expertise in using microfluidic emulsification for microparticle manufacturing. We have worked for Pharma, small to big, for 6 years now. EmulTech has engineered microparticles for over 20 customers, being evaluated in several animal models and clinical trials have been planned.

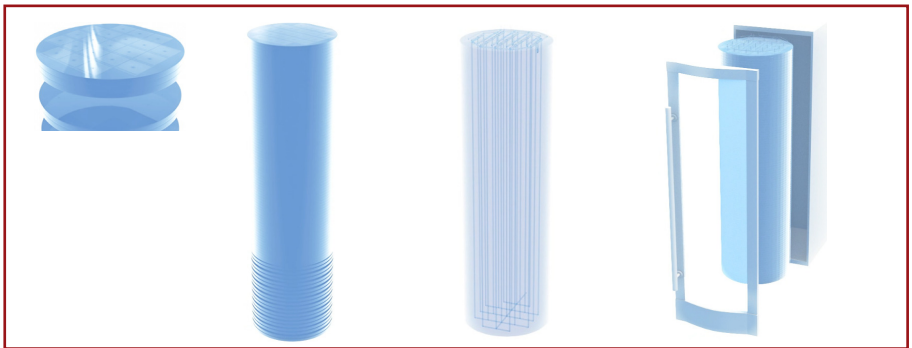

Figure 7: Build-up of a single 'microfluidic reactor' Wafer stack: 10, height: ~ 50 cm

ARTICLE

TESTING FRAGRANCE ENCAPSULATION *IN-VITRO* AND *IN-VIVO*

Ortiz, C., Holmgren, M., Klewsaat G. Colgate-Palmolive, 909 River Rd., Piscataway, NJ 08854 USA

INTRODUCTION

Today the use of encapsulates in the household and personal care products industry is widespread.(Park et al, 2003; Hawkins et al, 2006) Long lasting fragrance is especially important in underarm products where it signals to the consumer that the product is providing the desired odor and wetness protection. An example of these capsules being used in Antiperspirant Sticks is starch capsules[3] that are present in several commercial products. Therefore, encapsulation technologies that provide enhanced fragrance longevity are highly desirable in underarm products. In order to evaluate the stability and performance of these new technologies, a project was initiated to develop two methods. An in-vitro method to quantify the leakage of fragrance from capsules using GC Headspace and an *in-vivo* method to evaluate the performance of products with different fragrance encapsulates. These methods are currently being used to evaluate different fragrance capsules in underarm products.

COLGATE-PALMOLIVE

MATERIAL & METHODS

Samples of capsules were obtained from different suppliers and incorporated in the underarm product formulations to be evaluated. Stability experiments were carried out for 3 months in ovens set at room temperature and 40°C with measurements made at 4, 8 and 13 weeks. The underarm product samples were evaluated using a Perkin Elmer Clarus 500 GC with an FID detector using an automated sample headspace injector Perkin Elmer Turbo Matrix Headspace. The GC is equipped with a Zebron-Phase ZB-WAX column (L=30m x I.D. = 0.32mm x df=0.50um) with an oven starting temperature of 50°C and using a ramp of 5 degrees per minute up to 220°C. The underarm product sample (2g of sample as is, no preparation needed) is weighed in a GC vial (20 ml) and equilibrated in the headspace instrument for 1 hour at 50°C before injection of the headspace into the GC. All measurements are done in triplicate. Standard samples of the product are prepared at the same time as the samples with capsules with different amounts of fragrance (same fragrance used in the capsules). Three concentrations (1.00, 0.50 and 0.25%) of fragrance in the product were used. A set of 4 formulations is made for every capsule and divided in several containers to be placed in the stability ovens at RT and 40°C. The set of 4 formulations consists of the test formulation with 1% fragrance in the capsules (example: if capsule contains 50% fragrance then 2% of fragrance capsules is used). It is important to note that the standards are placed in the ovens together with the test sample and evaluated on the GC headspace at the same time in order to minimize any issues with stability of the fragrance in the product. Fragrance is normally composed of 20-100 ingredients and it is not possible to quantify each and every one of them. The main components (5-20) are quantified and taken as representation of the total fragrance quantification. The areas for the main peaks present in the fragrance are quantified for the set of 4 formulations. Using the standards with the different amounts of fragrance (1, 0.5 and 0.25%) a linear regression is calculated and used to quantify the amount of fragrance in the test formulation with the capsules at each time point. The software (Totalchrome) used to control the instrument (GC injections) has the capability of being programmed to do the calculations automatically so that you can obtain the % leakage of each peak directly from the software. We prefer to quantify each of of the GC peaks first then add them up and calculate the percent leakage.

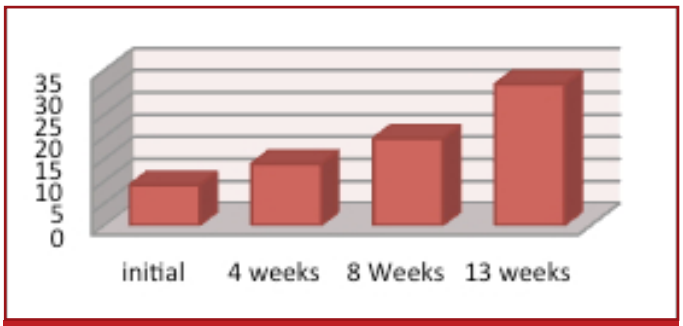

Figure 2. Leakage (%) at 40°C in AP Aerosol Base

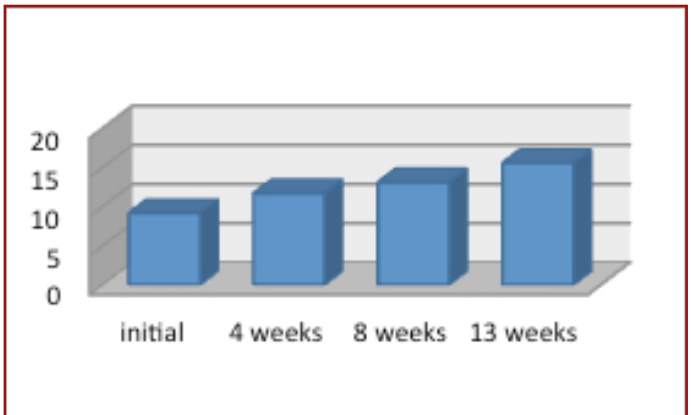

Figure 1. Leakage (%) at RT in AP Aerosol Base

The *in-vivo* self-assessment method was developed with the following characteristics: 36 subjects of the same gender evaluate the products by self-assessment in a paired comparison (product randomly assigned to left and right underarms). The pro-

duct is applied in the morning then they evaluate the fragrance intensity of each of the applied products at 0, 4, 8, 12 and 22 hr. on a scale of 0 to 7. The data obtained is analyzed using Repeated Measures Analysis (SAS)[4] with a 90% confidence level. All of the studies presented here were done with antiperspirant sticks, but the method has been used to evaluate aerosols and roll-ons as well.

Study 1 - Products with and without encapsulated fragrance. Samples: Antiperspirant sticks with 1% free, 2% free and 1% free + 1% encapsulated fragrance. The study was an incomplete block design with each panelist evaluating two products out of three tested.

Study 2 - Products with different encapsulates. Samples: Antiperspirant sticks with 3 different encapsulates (0.75% fragrance) were tested vs. a control also containing encapsulated fragrance. Since the sole purpose of the test was to determine differences in performance between the encapsulated fragrances, none of the products contained free fragrance. Every panelist evaluated all 3 pairs of products on different days (1 application per day).

Study 3 - Correlation to consumer test. Samples: 2 products with different formula bases (FB1 and FB2) and the same fragrance (1.2%). This study was done twice with application of different amounts of product on each underarm. Both products were used at 0.5g in the first test and 0.45g vs. 0.35g in the second test. The same samples were used in a normal consumer test with 26 questions. However, for correlation purposes only two questions related to fragrance longevity were taken.

RESULTS & DISCUSSION

This in-vitro method has been used to evaluate the stability of different fragrance capsules in several Personal Care products: Antiperspirant Sticks, Antiperspirant Aerosols and Antiperspirant Roll-ons. Here is one example of the application of this method in Antiperspirant Aerosols, but other examples will be illustrated in the final presentation. As can be seen in figures 1 and 2, the fragrance capsules, as expected, are more stable at Room Temperature (RT, 25°C) than at 40°C. The graphs also show that the capsules leak

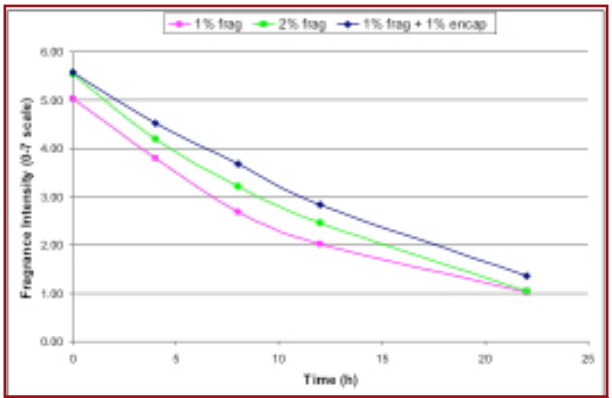

Figure 3. Products with and without encapsulated fragrance

more fragrance with time.

The final result is that after 3 months (13 weeks) there is 15% leakage of fragrance at RT and 30% leakage at 40°C. This result is acceptable since there is still 85 and 70% respectively

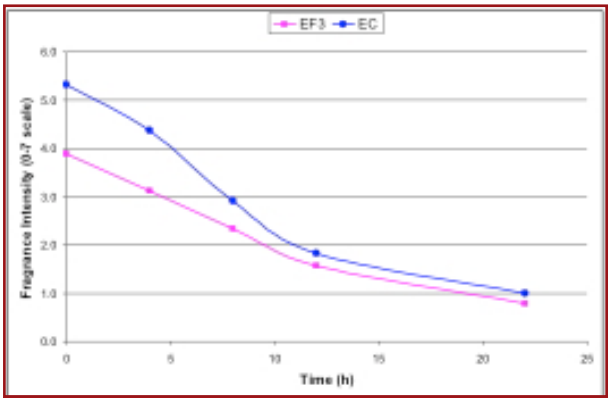

Figure 4. Encapsulated fragrance 3 (EF3) vs. control (EC)

encapsulated fragrance left in the product that can perform when used by the consumer.

The 3 study examples for the *in-vivo* method are described here.

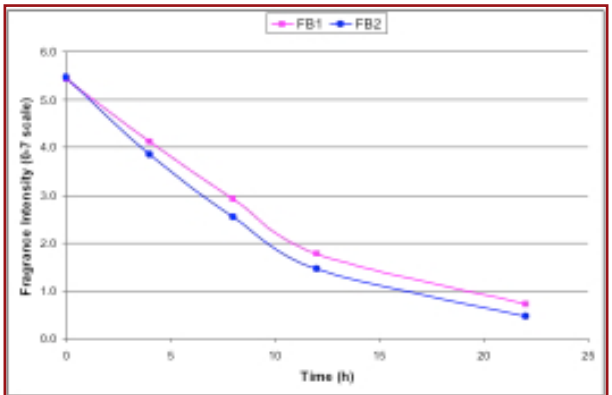

Figure 5. Products with different base (second test)

Study 1 - The results showed a significant difference in fragrance intensity scores between all 3 pairs of products (figure 3).

Study 2 - Only one encapsulate, EF3 (figure 4), showed a significant difference compared to the control with a p value of 0.009. The other two comparisons, EF1 & EF2 vs. EC, gave values of p>0.10 which indicates no significant difference between them.

Study 3 - The results of the first test showed no significant difference (p>0.10) when both products were applied to the underarms at 0.5g.

The consumer test showed a significant difference in the two fragrance longevity questions:

Length of time the fragrance lasted. Long lastingness of the fragrance.

This result did not correlate to the first test above, but we also noticed that the amount applied for each product (use-up rate) was significantly different for the 2 products: FB1 0.45g vs. FB2 0.35g p=0.0063. For this reason we performed a second test where the same amount of products were applied as the mean application amounts in the consumer test and the result was a significant difference with a p=0.068 (figure 5).

CONCLUSION

A very simple in-vitro method has been developed to quantify the leakage of fragrance from capsules in personal care products using GC Headspace.

The advantages of the method are:

We have shown that the in-vivo method developed can be very useful in evaluating differences in performance of pro-

ducts with encapsulated fragrance. The method has produced results that correlate well with consumer test results designed to detect differences in performance of fragrance in underarm products. Research is in progress to completely validate the method which will enhance our search for an encapsulated fragrance with even greater longevity than the ones we have evaluated to date.

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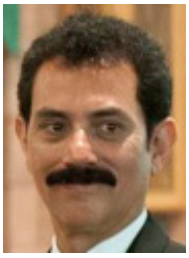

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PROTECTION AND DELIVERY OF THERAPEUTICS USING SILICA ENCAPSULATION

Barbé CJ, Khatri A, Finnie K S, Sommerville J A. Ceramisphere Pty Ltd, Australia

CERAMISPHERE™ ENCAPSULATION TECHNOLOGY

During the last 10 years, Ceramisphere has developed a number of patented processes that provides the ability to efficiently encapsulate most types of bioactives, irrespective of their chemical or physical nature, inside a protective silica matrix. These processes are carried out at ambient temperature, thus, making this technology ideal for the encapsulation of a wide range of temperature-sensitive bioactives such as nucleic acids (DNA, RNA and oligonucleotides) and proteins (enzymes, hormones and subunit vaccines). In addition, Ceramisphere technology allows efficient encapsulation of both water soluble and insoluble, small therapeutic drug molecules. The silica matrix is produced in the form of solid, homogeneous, spherical particles, with an average size that can be tailored from 10 nm to 100 µm. The release rate of the encapsulated species is controlled by the internal nanostructure of the spheres, which can be tailored by varying the sol gel chemical parameters (Figure 1 shows dissolution of microparticles) (Finnie et al., 2009). These emulsion-based processes are eminently scalable and cost effective.

SILICA AS A DRUG DELIVERY MATRIX

The silica particles are biodegradable, dissolving in biological fluids. Silica is also inert and there is minimal to no interaction with the encapsulated bioactive while still maintaining maximum protection of the payload. This coupled to the fact that silica is FDA approved for a wide range of formulations gives this technology a considerable edge over other drug delivery systems. The ability to tailor both particle sizes and release rates provides the flexibility to meet the complex requirements of preclinical and clinical applications. Ceramic matrices also provide longer shelf life and easier post-processing (tabletting, packaging) over their organic counterparts. In addition, relatively low cost and ease of scale-up will further facilitate the progression of products to the market.

DELIVERY OF THERAPEUTICS USING CERAMISPHERE™ TECHNOLOGY

Ceramisphere technology has shown promise as a delivery system for a

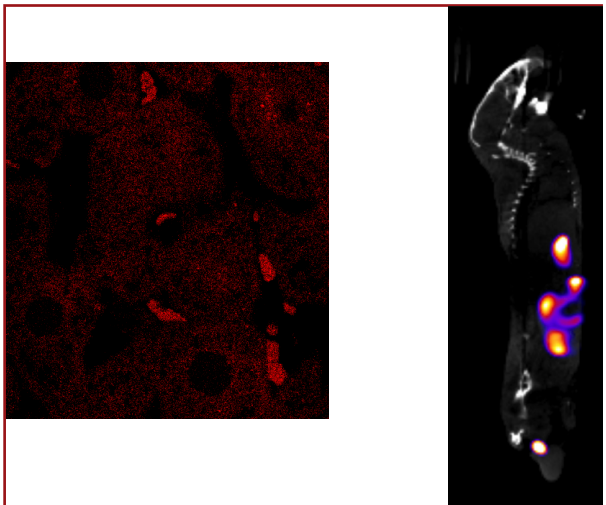

Figure 2: Uptake of silica particles in the target organs. Top Panel: SPECT/CT scan of Gastrointestinal tract of a rat given radiolabelled (111In) particles orally at 6H post dose. Bottom Panel: Confocal image of the mouse liver after intravenous administration of fluorescent silica particles.

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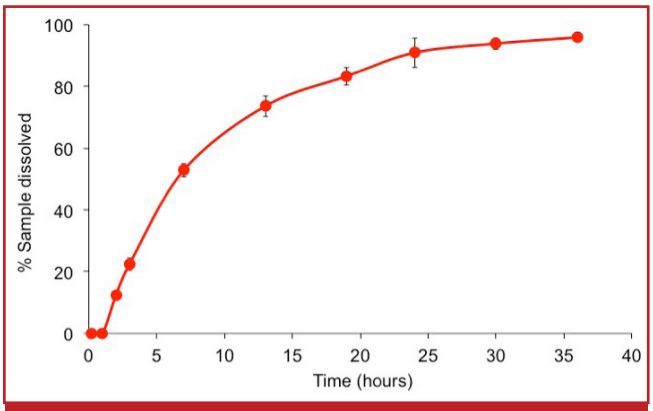

Figure 1: Dissolution of silica microparticles in vitro (USP 4- Open system model).

variety of applications including siRNA delivery, vaccination, delivery of proteins and small molecules through intravenous, subcutaneous or transmucosal (intranasal & oral) routes.

In vitro evaluations have demonstrated that silica matrix can effectively protect the encapsulated molecules against the harsh outside environment. For example, encapsulated proteins are protected against high temperature (e.g. 550C), degradation at a low pH (in the stomach) or from enzymatic digestion in the gastrointestinal tract. Similarly, the encapsulated RNA is protected from RNAse degradation.

The silica particles have been shown to be non-toxic in vivo. Intravenously administered particles were non-toxic with the maximum tolerated single dose being 200 mg/kg and a cumulative dose of up to 400mg/kg was well tolerated with no liver or kidney toxicity. Similarly, when administered through other routes e.g. oral, intranasal subcutaneous or topical, the particles were non-toxic at the tested doses. The particles are able to reach the target organ and deliver the payload. Both in vitro and in vivo studies have indicated efficient uptake and intracellular release of intravenously given siRNA or siDNA particles and their cargo. Intravenously given fluorescent and gold-labelled particles show uptake in up to 90% of target organ with release of the payload in the cytoplasm of at least 20% of the target cells (Figure 2). When given orally, fluorescent, gold-labelled or radioactive particles displayed up to 10% of injected dose in the GIT of the animals (Figure 2).

Several in vivo trials using particles with protein cargo have successfully shown their ability to effectively deliver and generate the required biological response. The efficacy of ceramisphere vaccines in generating systemic (oral or subcutaneous administration) or transmucosal immune response has been shown unequivocally (Figure 3). The vaccine particles generated antigen-specific systemic and mucosal immune response in 50-80% of orally treated mice and in 100% of intranasally treated mice. Similarly, silica particles used to deliver insulin orally, showed superior efficacy when compared to the unencapsulated protein. Finally, silica particles are able to release their therapeutic cargo sustainably when given topically to mice with minor burn injury; the wound healing engendered by one dose of therapeutic particles containing Epithelial Growth Factor (EGF) was significantly improved over that obtained by multiple applications of un-encapsulated EGF.

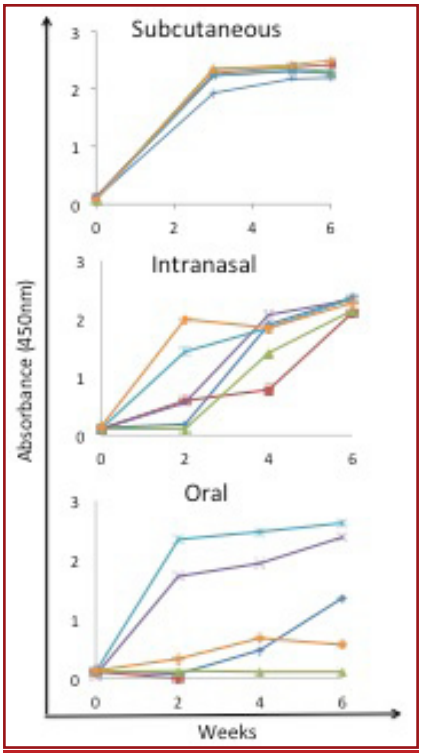

Figure 3: Efficacy of vaccine antigens delivered using Ceramisphere technology through different routes: The Graphs show the IgG levels in mouse sera given the silica encapsulated vaccine antigen through subcutaneous and mucosal routes (Intranasal and Oral).

CONCLUSION

Ceramisphere technology provides a unique and versatile delivery platform that combines highly potent features such as, low toxicity, biodegradability, excellent protection of the payload along with tailorable size and release rates. Indeed, silica particles effectively protect and deliver fragile bioactives through various administration routes including intravenous, subcutaneous, oral, dermal and intranasal. Ceramisphere technology can potentially help where other more classic drug delivery technologies have failed.

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Chris is the CEO of Ceramisphere Pty Ltd, an Australian biotech company based on sol-gel technology. Chris received his BSc from the Université Pierre et Marie Curie, Paris (France) and a PhD in Materials Science from the Swiss Federal Institute of Technology (EPFL). He has over 20 Years experience in Materials Science at the Australian Nuclear Science and Technology (ANSTO), the Swiss Federal Institute of Technology (EPFL) and Dupont Central Research in the USA, working on topics as varied as oxide superconductors, biosensors and dye sensitized solar cells. He currently leads Ceramisphere, expanding and commercializing its proprietary encapsulation and controlled release technology.

More info : www.ceramisphere.com

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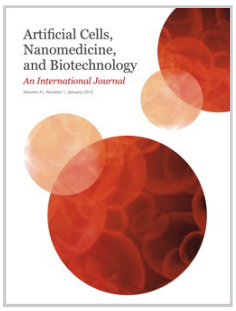

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DIVERSIFIED NEWS

SwRI expands microencapsulation capabilities with customized fluid bed coater

Southwest Research Institute® (SwRI) has expanded its microencapsulation research and development capabilities with a Glatt GPGC-2 Fluid Bed Coater. This customized device increases SwRI's capacity to create special processes and coatings for ingredients used in pharmaceuticals, consumer products, and other applications.

"This custom fluid bed coater will expand our coatings capacity sixfold from our current 2 liter drying chamber to a 12 liter drying chamber," said James Oxley, Ph.D., a principal scientist in the SwRI Chemistry and Chemical Engineering Division. "It allows us to handle volatile solvents and to use 'melts,' which are waxes and fats used to coat pharmaceuticals, processed food, and animal feed."

More info *: http://www.swri.org/9what/releases/2015/swri-microencapsulation-capabilities.htm#.VhbRR2fovIV*

SwRI expands microencapsulation capabilities with customized fluid bed coater

DIOSNA is geared as a company to supply the international bakery and food industries as well as the pharmaceutical and chemical industries with highly developed production and laboratory plants and equipment.

DIOSNA offers different equipment for coating and drying, air fluidized-bed processors, granulating.

More info : *http://www.diosna.com/uk/food-industry/products/fluid-bed-processor.html*

Bionov is the world's largest producer of Natural and Bioactive SuperOxide Dismutase (SOD) from Cantaloup French melon (Cucumis melo L.)

Bionov is an active ingredient supplier for the nutraceutical, food, dermo-pharmaceutical, cosmetic, feed and pet care industries.

Bionov is the only industrial producer of 100% natural and bioactive SuperOxide Dismutase (SOD), from a proprietary variety of melon (Cucumis melo L.).

SOD Dimpless® is a microencapsulated formulation of this enzyme with antioxidant properties. Its efficacy has been confirmed in several published clinical studies.

More info : *http://www.bionov.fr*

Enteric coating function for the release of active substances out of nutraceuticals in the guts

Anita Bénech from NOREVO GmbH publishes an article in the journal Innovation in Food Technology, Number 69 November 2015 p. 30 about «How the aqueous shellac solution NORELAC B20 facilitates a targeted absorption of active principles by the human intestine.

More info : *http://www.bionov.fr*

Creathes plays with microencapsulation

Creathes launches a unique video game to illustrate the microencapsulation in our daily lives: «Mic et Caps Super Runners».

More info *: http://alpha.allucyne.com/creathes/*

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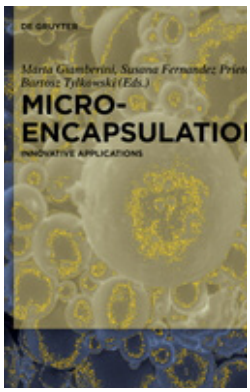

MICRO-ENCAPSULATION Innovative Applications

Ed. by **Giamberini, Marta / Fernandez Prieto, Susana / Tylkowski, Bartosz**

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Aims and Scope

Microencapsulation has become a promising technology for new applications in fields like drug delivery, biosensing, biomaterials, catalysis, intelligent microstructures and microsystems, as well as in the field of consumer goods. This book is written by authors from academia and industry and aims to present industrial adoption of microcapsules as an innovative solution for problems concerning environmentally-friendly production methods, health protection, and increase of citizen daily life standard and decrease of its costs.

More info : *http://www.degruyter.com/view/product/210674?rskey=NACYXe&result=1*

THEY SUPPORTED BRG IN BEING EXHIBITORS

ARTICLE

MICRO-SPHERES/CAPSULES: BY POLY-(ADDITION / CONDENSATION) IN NON-AQUEOUS MEDIUM

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INTRODUCTION

Polymer microspheres and microcapsules show great potential in many applications of chemical and life sciences. These applications include consumer products, ion exchange, chromatography, controlled release systems, biomedical diagnostics, coatings, paints etc. Polymer microspheres are prepared either by in situ polymerization of respective monomer(s) or by physicochemical or mechanical processes from preformed polymers. Preparation of polymers in particulate form by the former process has been well studied using techniques such as suspension, emulsion and dispersion polymerization. Although particle-forming methods especially for free radical polymerization in non-aqueous medium are well documented those for poly- addition/ condensation processes are less developed. The key parameter for preparation of polymer particles or capsules in non-aqueous medium is use of suitable polymeric surfactant.

Council of Scientific and Industrial Research
National Chemical Laboratory

ROLE OF POLYMERIC SURFACTANT

Stable dispersion of particles in a aqueous or non-aqueous medium results when potential energy of repulsion (VR) arising from the approach of charged (or covered with polymer layer) particles is greater than the inherent attractive energy (VA) between the particles over a certain distance of separation.

Aqueous colloidal dispersions can be prepared without much difficulty with conventional ionic surfactants as these will be stable as a result of simple coulombic repulsion. But such dispersion fails in non-polar organic liquids. This failure can be attributed to polarity of dispersion medium. Coulombic repulsive potential between two charged particles VR is directly proportional to dielectric constant (ε) of dispersion medium. Thus, the essential differences in the power of electrostatic stabilization in water and typical organic liquid lies in the difference between the values of their dielectric constants. In the case of non-polar liquids ε → 0, as a result VR → 0 and, thus, dispersion of particles in non-polar liquids (e.g. aliphatic hydrocarbons) fails due to non-availability of sufficient amount of repulsive potential. In such cases stabilization can be accomplished by the use of repulsive forces generated by the interaction of opposing dissolved polymers chains attached to the dispersed particles, that is, by steric stabilization with the help of polymeric surfactants.

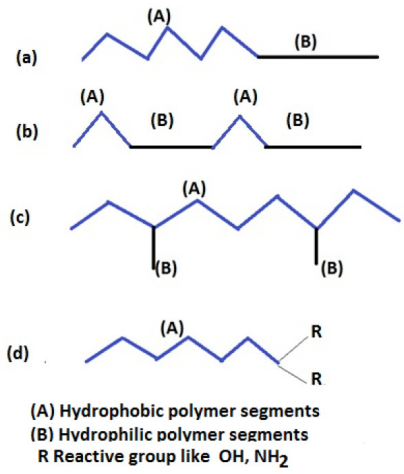

Figure 1. Polymeric surfactants: (a) and (b) Block copolymer (c) Graft copolymer (d) Polymerizable surfactant

Polymeric surfactants are mainly divided into three categories namely 1) block and graft copolymers (Fig 1a-c) 2) polymerizable surfactants which have reactive groups (Fig 1 d) and 3) homopolymers The former two types are of interest to many researchers and industries. Block copolymers can be $(A)_n(B)_m$ or ABAB type.

If the surfactant has the configuration, ABAB or double comb graft, it is likely to be adsorbed at the particle surface. The surfactant of this type will be more effectively anchored than assembly of separate amphiphathic molecule $(A)_n$ - $(B)_m$ because the probability of detaching all the anchor groups simultaneously is much less in the former type than the chance that a proportion of the latter type will be desorbed.

Important advantage of polymeric surfactant is that they can be tailored to the desired requirement of properties by 1) changing the molecular weight of soluble and insoluble anchoring polymer components 2) by changing the nature and composition of soluble and insoluble components.

PARTICLE/ CAPSULE FORMING POLYMERIZATION PATHS

There can be two major types of paths PI and PII for particle formation and CI and CII for capsule formation (Fig 2) in non-aqueous continuous medium (S2) which is usually aliphatic or cycloaliphatic liquid containing suitable polymeric surfactant. S1 is another liquid

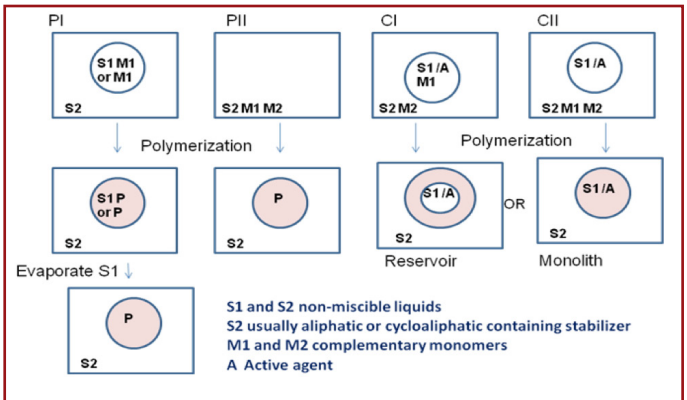

Figure 2: Formation of polymer particles and polymer capsules in non-aqueous continuous medium by different paths

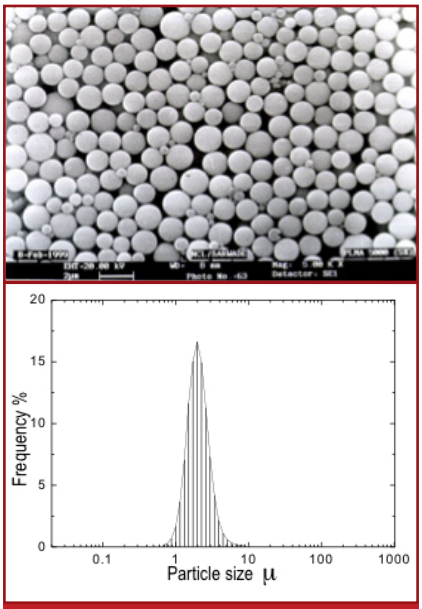

Figure 3: SEM and particle size distribution of polyurethane microspheres

(or active agent A in capsule formation) which is non-miscible with S2. M1 and M2 are complementary monomers such as diisocyanate and diol. In path P1, M1 is selectively soluble in S1. S1 containing M1 is emulsified in S2 followed by addition of M2 which is also soluble in S1. M2 diffuses into S1 and when polymerization takes place there is polymer particle formation. Example of this system is formation of polyester particles where S1 is acetonitrile, S2 is cyclohexane, M1 is diol and M2 is dichloride. In path PII both monomers M1 and M2 are initially soluble in S2 and polymerization leads to polymer particle formation. In path CI initially solution of M1 and S1 or M1 in active agent A is emulsified in S2 contianing monomer M2. When polymerization is initiated M1 and M2 react at the interface forming polymer capsules containing S1 or A. In path CII, S1 or A are emulsified in solution S2 containing monomer M1 and M2. Polymerization results in formation of polymer capsules containing S1 or A. In both cases (CI and CII) depending on solubility of initial oligomer molecules in S1 or A, reservoir or monolith type of capsules are obtained.

WORK AT CSIR-NCL

We have prepared polymer nano/microspheres and microcapsules in non-aqueous medium. The work was mostly concentrated on polyurethane particles and microcapsules. Different types of block and graft copolymers and polymerizable surfactants were synthesized and were explored to prepare free flowing polyurethane particles, with uniform particle size, in the range of 0.1 to 100 μ. (Fig 3) Microcapsules containing water sensitive / soluble active agents like monocrotophos (MCR), Ibuprofen-Na (IBP-Na) and polyamine were successfully prepared. In the case of polyurethane, diols like ethylene glycol (EG), propane diol (PD), butane diol (BD), 2-Ethyl-1,3-hexylene glycol (EHG) and diisocyanate like toluene diisocyanate (TDI), isophorone diisocyanate (IPDI) were explored. Microcapsules containing polyamine involve polyurea wall formation where part of core material reacts with isocyanate. Microcapsules containing water-soluble pesticide MCR were prepared by path CI and CII. Fig 4 shows pristine MCR microcapsules (by path CI) and those from which MCR is extracted out and this broken caspule shows reservoir type of capsule form.

It has been observed that size and size distribution of microspheres depend on composition of polymeric surfactant, molecular weight of hydrophobic and hydrophilic polymer segments of surfactant, solubility parameter of continuous non-aqueous medium.

Morphology of microcapsule (reservoir and monolith type) depends on the type of microencapsulation path (CI and CII). Desired release profile of active agent from microcapsules can be achieved by capsule wall polymer architecture. For example in case of polyurethane it was shown that release rate decreases with increasing hydrophobicity of diol. Microcapsules with EG release IBP-Na at faster rate than those with BD. The another approach is by changing the crosslink density. As the incorporation of crosslinker –trimethylol propane (TMP) in polyurethane is increased, release rate decreases.

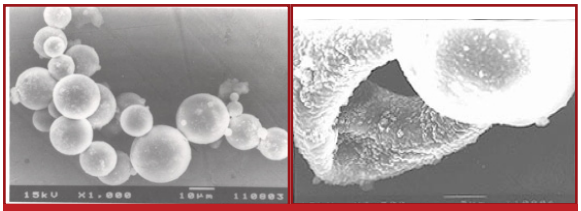

Figure 4: SEM of polyurethane microcapsules containing MCR (a) Pristine (b) broken showing reservoir type of microcapsule

Polyurethane microcapsules prepared in non-aqueous medium show good control over release profile as compared to those prepared in aqueous medium with same monomers and active agent. In aqueous medium along with urethane linkages there is formation of urea linkages as isocyanate reacts with water resulting in formation of CO_2 which leads to porous capsule wall.

Polyurethane (PU) microspheres were shown to be useful in enzyme immobilization on PU-gold core shell particles.

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Parshuram obtained his Ph.D. in 1992 from University of Pune, India. He has more than 32 years of research experience in Polymers and Controlled Release (CR) Technology which includes development of CR formulations of active agents like perfume, pesticide, pharmaceuticals, enzymes, based on natural and synthetic polymers, different microencapsulation techniques and transport phenomenon in CR system. His research also includes synthesis of polymer nano and microspheres.

ARTICLE

ENCAPSULATION OF INDUSTRIAL ENZYMES: CASE STUDIES UTILIZING FLUID BED COATING

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INTRODUCTION

Industrial enzymes have been in produced and marketed for decades and serve many different applications. In general, the markets served can be regarded as anything that is not considered a pharmaceutical application, such as detergents, food, animal nutrition, textiles, fuel ethanol and biofuels to name a few. The diversity of these applications introduces a range of environmental and use conditions where the enzymes must be protected in order to maintain shelf life and deliver their activity when required to provide the expected benefit. Stabilization, controlled release and delivery through encapsulation techniques are a key way of achieving these goals. There have been many successful encapsulation techniques utilized to meet the requirements such as fluid bed coating, wet granulation such as extrusion or high shear granulation, and spray drying / agglomeration. In this manuscript the utilization of fluid bed coating will be explored in two applications, specifically detergents (laundry and dish) and animal nutrition.

FLUID BED COATING

Fluid bed coating has been utilized in many applications, such as pharmaceuticals, food, confectionary and industrial applications as an efficient way to apply functional layers to particles. There are several producers of fluid bed equipment including Glatt Air Techniques, Freund-Vector, Fluid Air and GEA. This equipment can be arranged in a variety of configurations, including "Top Spray" counter current application, Wurster and Continuous modes. One of the reasons for the broad utilization of this technology is the ability to layer different materials to create unique properties and release profiles. Figure 1 illustrates several ways in which particles can be manipulated to deliver a variety of properties or structures.

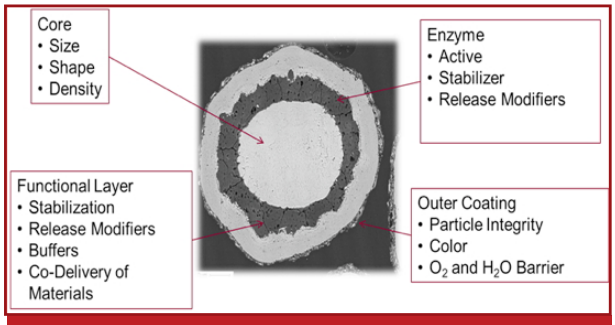

Figure 1: SEM cross section image of a fluid bed coated particle illustrating how various layers could be utilized to deliver desired properties.

CASE STUDY 1: DETERGENTS

One of the major applications of industrial enzymes is detergent applications, both laundry and auto-dish. Enzymes utilized include protease, amylase, lipase, cellulase, and mannanase, Each of these serve to catalytically break down a stain or soil so that it can be more readily removed by the detergent.

However, the detergent composition is a very harsh environment for enzymes. The presence of surfactants, chelators, bleaching agents and high alkalinity can dramatically reduce an enzyme's activity and thus its performance in the wash. One of these mechanisms is oxidation of amino acid side chains. Figure 2 illustrates how a peptide from a tryptic digest of a protease molecule becomes oxidized with time when stored in bleach containing laundry detergents. The top panel shows the native enzyme tryptic peptide pattern as viewed on an HPLC plot, highlighting the 10T peptide with contains a methionine residue. As time progresses during storage in detergent, the presence of an oxidized peptide, $10T_{ox}$, occurs with the simultaneous reduction of the 10T peak (middle panel). Longer storage results in the complete disappearance

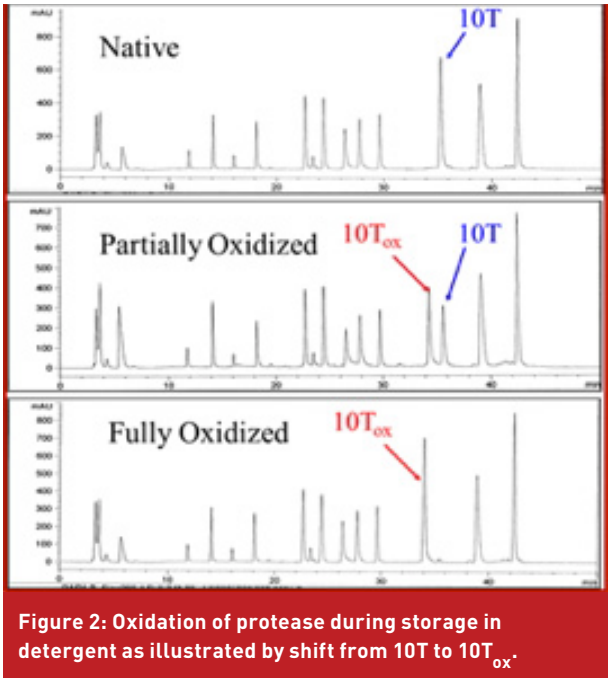

Figure 2: Oxidation of protease during storage in detergent as illustrated by shift from 10T to $10T_{ox}$.

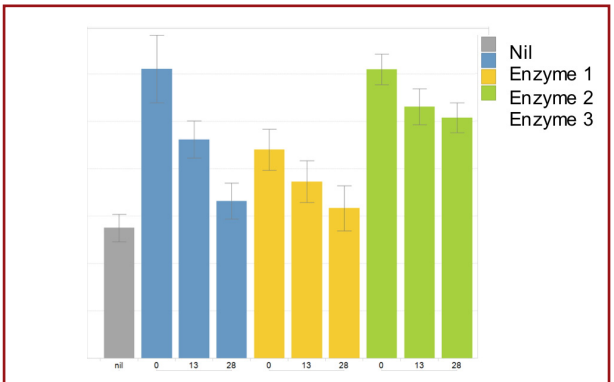

Figure 3: Storage stability of enzyme in detergents as shown by cleaning performance over time.

of 10T, with only $10T_{ox}$ present (bottom panel). This is also reflected in the loss of cleaning performance with time when stored in detergent as indicated in Figure 3.

Prevention of this oxidation event can be addressed via multiple routes utilizing fluid be coating. For example, stabilizers could be added directly to the enzyme layer and/or stabilizers or barrier materials could be incorporated into subsequent layers that would either react with the oxidant before it encounters the enzyme, or completely preventing the oxidant from penetrating the granule, thus protecting the enzyme. The flexibility of fluid bed coating to allow multiple routes to prevention of such an event, results in a robust product offering that will maintain cleaning performance with time.

CASE STUDY 2: ANIMAL NUTRITION

The use of enzymes in animal nutrition applications is also very prevalent. Enzymes utilized include phytase, xyalanase, amylase and protease for example. Unlike the detergent application where the chemical environment is the major source of enzyme inactivation, the physical environmental conditions that the enzymes are exposed to during the production of pelleted animal feed can result in the destruction of activity. The pelleting process is outlined in Figure 4. During this process the enzyme can be exposed shear, moisture and heat at various points in the process. Shear is introduced during mixing, transport and in the pellet mill where the feed is pressed through the die. Moisture and temperature (up to and above 100C) is introduced in the pelleting conditioner and carried through the pellet mill until the resulting pellets are cooled and dried.

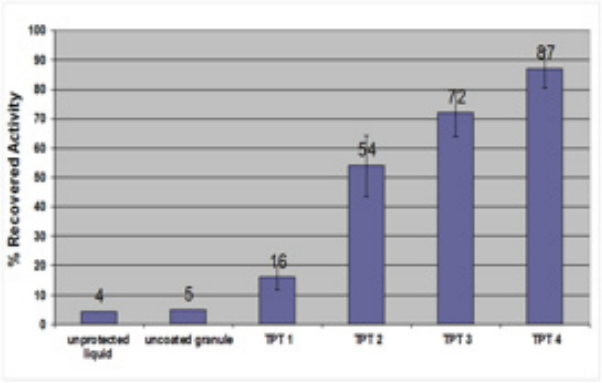

Figure 5: Illustration of evolution of coating formulations resulting in increased pelleting stabilty.

The impact of these environmental conditions is clearly illustrated in Figure 5, where either a liquid or unprotected granulated enzyme (columns 1 & 2) lose nearly all of their activity after passing through the pelleting process. The remaining columns (TPT 1 – 4), show that incorporating either enzyme stabilizers or increasing barrier materials improve the survivability of the enzyme through the process by either protecting the enzyme from denaturing or blocking steam from entering the granule. The resulting protected product allows the animal feed producer to confidently incorporate enzymes into their production process knowing that the desired activity and effect will be present when fed to the animal.

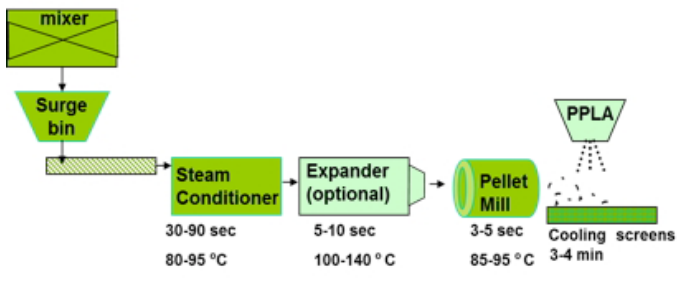

Figure 4: Schematic of animal feed pelleting process and association conditions.

CONCLUSIONS

Industrial enzymes are utilized across a wide variety of applications that can introduce a range of chemicals or environments that can damage or modify the enzyme structure, which can lead to reduced performance. Fluid bed coating is one of many technologies that can be applied to protect the enzyme or other active to insure that it will execute its reaction when required in the application. The flexibility to apply multiple layers with different functionalities provides a means to deliver a protective solution that meets the requirements of a given application.

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ARTICLE

PHYSICO-CHEMICAL CHALLENGES OF DESIGNING DELIVERY SYSTEMS FOR CONSUMER AND INDUSTRIAL APPLICATIONS

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ABSTRACT SUMMARY

There is an increasing use of delivery systems for active ingredients in consumer and industrial applications. The most common systems include microcapsules, polymeric absorbents and associative complexes. Primary advantages offered by these systems include extended release, prolonged protection and reduction in the use of active ingredients and, occasionally, enhanced formulation compatibility. However, significant physico-chemical challenges arise during the design of a commercially viable delivery system. This presentation offers examples of technical approaches developed at The Dow Chemical Company to overcome some of these physico-chemical challenges.

MICRO-ENCAPSULATION OF ANTIMICROBIAL AGENT

A key antimicrobial agent used in solvent-based marine anti-fouling paints (MAF) is 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one (DCOIT). This active ingredient is extremely effective in preventing algal fouling on the surface of ships. It has broad spectrum activity as well as excellent eco-toxicological profile due to its short half-life in sea water (<24 hr) (Jacobson, et al,, 2004). If the concentration of DCOIT is high enough, it is proven that DCOIT can also be effective for controlling "hard" fouling. However, DCOIT is also a known film plasticizer, which limits its use level from a leach rate and coating performance perspective. Controlling DCOIT release via micro-encapsulation technology could overcome these problems, thus allowing the customer to reduce initial loading levels (for low end paints) or increase paint lifetime (for higher end, 5 year paints). Micro-capsules of DCOIT were prepared through interfacial polymerization process based on aminoplast chemistry. By varying the shell chemistry, micro-capsules with various release profiles were obtained. A well-balanced capsule should have excellent in-can stability in the formulation and desirable release profile in the end use application. As shown in Figure 1, varying capsule chemistry can offer a range of sea water-triggered release profiles.

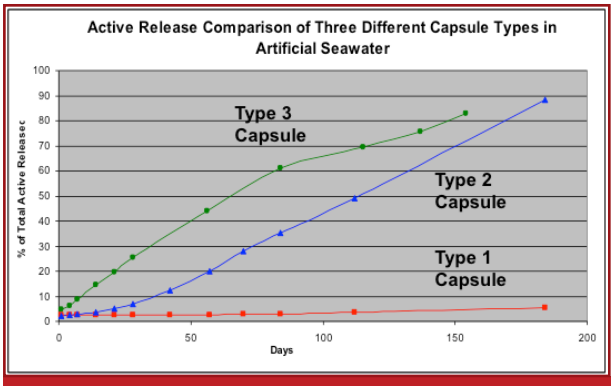

Figure 1. Effective active release profiles for microcapsule type 1, 2, 3 respectively.

Interestingly, all capsules maintain excellent in-can stability in various solvent combinations as shown in Figure 2 under accelerated testing conditions at 50 °C.

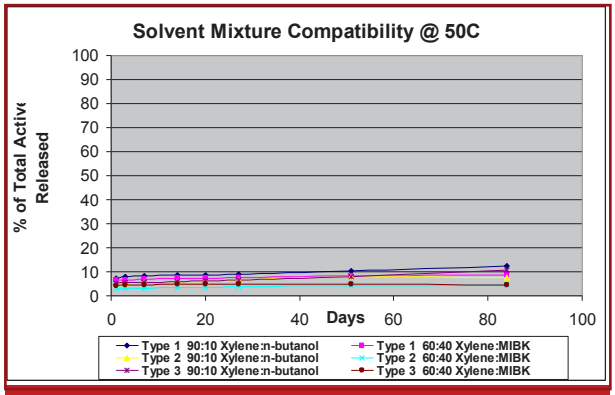

Figure 2. Accelerated in-can stability for microcapsule type 1, 2, 3 respectively.

As shown in Figure 3, raft panel (right) coated with type 3 DCOIT microcapsule-containing paints has less fouling than the panel with a conventional copper-based coating (left) in a ten month sea water raft panel test. Key challenges overcome in this problem included prevention of leaching of the active by the solvent in the formulation, enabling leaching by sea water at a rate necessary for the desired efficacy and loading adequate active in the capsules to minimize capsule concentration in the final coating.

Figure 3. Ten month raft panel test results of copper-based: 45% Cu_2O + 3% copper pyrithione (left), and copper-free coating: 5% Type 3 DCOIT microcapsule (right).

Imbibing of the Active into a Latex Particle

DCOIT is also an effective active ingredient for wood preservation. If used alone, DCOIT can migrate rapidly and bloom to the surface of pressure treated lumber resulting in unnecessarily high surface concentrations. At the same time, prevention of fungal

growth requires a minimum concentration of biocide to be present on the surface at all times. To balance these competing drivers, a new delivery system was developed by a two-step process (Fig. 4): 1) firstly, DCOIT was imbibed into latex particles in the presence of surfactant; 2) then the wood was treated with the resulting DCOIT-rich latex. Due to the strong affinity of DCOIT to the polymer matrix, the latex particle functions as both a carrier and a control release agent. This new system provides deep penetration of active ingredient inside the wood, markedly reduces the migration of active to the surface, resulting in better longevity of wood preservation and satisfactory regulatory profile.

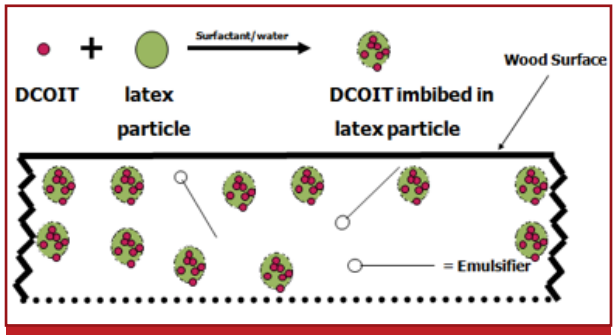

Figure 4. Imbibing of the active into the latex particle for wood preservation

Controlled Release of Antimicrobial Agent via Metal ion-Polymer Complexation

Hygiene is a universal need that is highly desired and sought after by consumers. One approach to achieve this objective is to modify surfaces with antimicrobial materials to inhibit the growth of detrimental microbes. Various classes of antimicrobial materials have been reported in the literature, including small molecule biocides, heavy metals, polymeric materials, regenerated halogen-containing molecules. Among them, silver-based materials have received significant attention recently from both industrial and academic institutions (Sambhy et al., 2006). There has been a long history of use of silver as a broad spectrum antimicrobial agent. However, the active ingredient, silver ion (Ag^+), is highly light and heat sensitive and has very limited compatibility in various formulations.

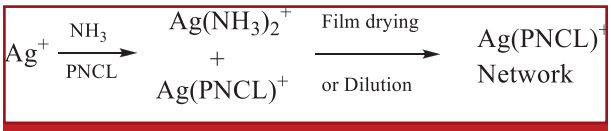

Figure 5. Competitive complex formation between a fugitive ammonia ligand and a permanent PNCL with Ag^+

The stabilization and controlled release of silver ion was achieved via a metal-ion-polymer complexation mechanism.

As illustrated in Figure 5, this novel delivery system makes use of the competitive complex formation between a fugitive ammonia ligand and a proprietary polymeric nitrogen-containing ligand (PNCL) with Ag^+. When the material is supplied, it exists as an easily pourable and low viscosity liquid. Once applied to the end use application, the fugitive ammonia ligand evaporates, resulting in the formation of a polymeric network containing Ag^+ complexed with the PNCL. The silver ion is only released in the presence of water and serves to kill the bacteria therein. Further ion release occurs only when the ionic concentration in the liquid drops and shifts the equilibrium. Textiles and non-wovens treated with this material demonstrate long-lasting anti-microbial protection and wash durability. Key to the success of this solution was the balance between strength of the complex and need to have an adequate ionic concentration to achieve the biocidal efficacy.

Delivery System with Dissolvable Film Technology

The use of dissolvable film technology has attracted considerable attention in medical and nutraceutical applications. Various water-soluble polymers, esp. those based on plant derived celluloses are used as film formers. Film strips containing various personal care actives were prepared through a solvent casting process. Plasticizers were added to the formulation in order to achieve desirable balance between mechanical properties and disintegration time. In comparison to conventional approaches, a delivery system based on dissolvable film technology offers several advantages including high purity with high payload, ease of use, portability, precision of delivery location, and enhanced formulation stability.

CONCLUSION

Several delivery systems including micro-encapsulation, imbibing of actives into latex particles, metal ion-polymer complexes, and dissolvable film technology for consumer and industrial applications are presented. The physico-chemical challenges, presented by the delivery objectives, require innovation in polymer chemistry and system design.

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ARTICLE

ENCAPSULATING PARTICLES WITH NANOSCALE PRECISION USING ATOMIC LAYER DEPOSITION

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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 µm-range. Following Moore's law, there is a 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 alternatingly. 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 (Miikkulainen 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).

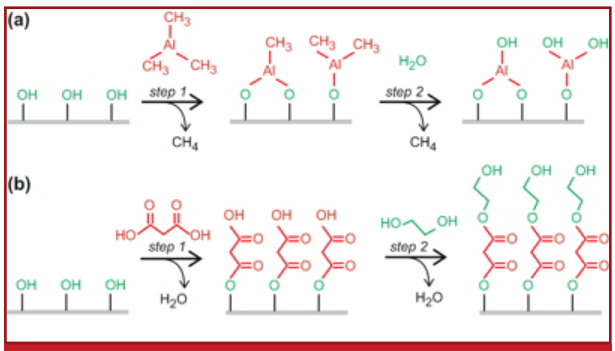

Fig. 1. Schematics of the subsequent steps of (a) Atomic Layer Deposition and (b) Molecular Layer Deposition.

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 µm 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 µm), 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°C and 300°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 confor-

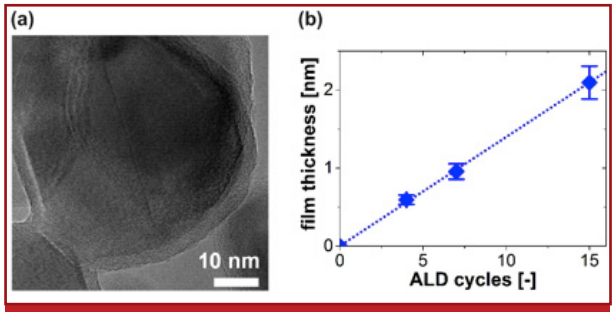

Fig. 2. Alumina coating of titania nanoparticles: (a) TEM picture of a particle coated with 15 ALD cycles; (b) film thickness as a function of the number of cycles.

mal, homogenous coatings (see Fig. 2.a). Moreover, the coating thickness linearly increases with the number of cycles applied (see Fig. 2.b), demonstrating he 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 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 µm 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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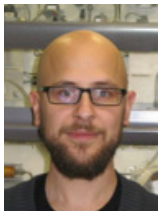

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