

# Bioencapsulation Innovations

July 2015

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#BioMicroencapsulation

**EDITORIAL**
**INDUSTRIAL APPLICATIONS OF MICROCAPSULES**

Microencapsulation is a smart manner of improving the performance of products. By using this technology, an active of interest can be isolated and kept unmodified for extended periods of time and be released (or not) upon a change of the surrounding environmental conditions to target specific needs.

This simplistic idea has brought attention from different perspectives proven by the ever-increasing number of scientific and industrial research since the microencapsulation of ink for carbonless paper back in the middle of the last century.

Nowadays, microcapsules can not only be found in pharma products but in a huge variety of products and applications ranging from insulation technologies for houses to smart textiles and agricultural products as well as consumer products, like food, house and personal care products.

The generic microencapsulation definition can be misleading since this technology entails a multidisciplinary range of challenges which are at the same time similar in principle although different depending on the final use of the microcapsule. The multidisciplinary field of microencapsulation is involving a mixture of industries with a large spectrum of interests: start ups with novel processes to make capsules, big companies with a long track of chemical experience, fine chemical industries such

as perfume houses and biotechnological companies, consumer goods companies as well as research institutions bridging scientific knowledge with more practical industrial applications.

This combination of actors has been seen in the last **18th Microencapsulation Industrial Convention** held in Eindhoven, Netherlands on April 22-24, 2015.



Co-organized by TNO, the convention gathered more

than one hundred participants coming from 22 different countries. Fourteen experts from different domains presented an overview of microencapsulation technologies and applications. Convention diner took place in the DAF museum in a very friendly atmosphere. During the coffee-breaks and trade fair, sixteen exhibitors presented their materials and services, while more than 500 business-to-business meetings were organized, allowing participants to meet up to 18 potential partners.



The next coming **19th Microencapsulation Industrial Convention** to be held in Frankfurt, Germany on April 4-6, 2016, will be co-organized by Brace GmbH. Information will be available soon on [http://bioencapsulation.net/2016\\_Frankfurt](http://bioencapsulation.net/2016_Frankfurt).

**Note the dates on your calendar.**  
**Share information with colleagues !**


**Dr. Raúl Rodrigo Gómez**

Scientist at P&amp;G, Brussels, Belgium

R&amp;D Corporate Function

**CALENDAR**

PROGRAM 2015	
August	 <p><b>Surface Modification Chemistries for Particles and Interfaces</b>                      August, 21 2015                      Boston, USA  <a href="http://nanoparticles.org/courses/Boston2015Courses.htm">http://nanoparticles.org/courses/Boston2015Courses.htm</a></p>
August	 <p><b>23th annual «Advances in Tissue Engineering»</b>                      Rice University, Houston, Tx - August 12 -15, 2015.  <a href="http://www.tissue.rice.edu/">http://www.tissue.rice.edu/</a></p>
September	 <p><b>23th International Conference on Bioencapsulation</b>                      Delft, Netherlands                      September 2-4, 2015  <a href="http://bioencapsulation.net/2015_Delft/">http://bioencapsulation.net/2015_Delft/</a></p>
October	 <p><b>20th International Symposium on Microencapsulation</b>                      Boston, USA                      October 1-3, 2015  <a href="http://www.northeastern.edu/ims2015/">http://www.northeastern.edu/ims2015/</a></p>
	 <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>

PROGRAM 2016	
February	 <p><b>9th International Conference on Advanced Technologies &amp; Treatments for Diabetes (ATTD 2016)</b>                      February 3-6, 2016                      Milan, Italy  <a href="http://www.attd2016.com/">http://www.attd2016.com/</a></p>
April	<p><b>PBP</b>                      WORLDMEETING  <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>19th Microencapsulation Industrial Convention</b>                      April 4-6, 2016                      Frankfurt, Germany  <a href="http://bioencapsulation.net/2016_Frankfurt">http://bioencapsulation.net/2016_Frankfurt</a></p>

May - June	 <p><b>8th Training School on Microencapsulation</b>                      May 30 - June 2, 2016                      Cork, Ireland  <a href="http://bioencapsulation.net/2016_Cork">http://bioencapsulation.net/2016_Cork</a></p>
June	 <p><b>International Symposium on Polyelectrolytes 2016</b>                      June 27-30, 2016                      Moscow, Russia  <a href="http://www.isp2016.org">www.isp2016.org</a></p>
September	 <p><b>24th International Conference on Bioencapsulation</b>                      September 22-24, 2016                      Lisbon, Portugal  <a href="http://bioencapsulation.net/2016_Lisbon">http://bioencapsulation.net/2016_Lisbon</a></p>
Future	<p><b>Provide us information about your meeting(s), we will be happy to publish them</b>  <a href="mailto:contact@bioencapsulation.net">contact@bioencapsulation.net</a></p>



## 20TH INTERNATIONAL SYMPOSIUM ON MICROENCAPSULATION



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

## CALENDAR



## 23TH INTERNATIONAL CONFERENCE ON BIOENCAPSULATION



**Delft, Netherlands**  
**September 2-4, 2015**

125 to 150 participants  
40 oral presentations  
up to 80 posters

**More information**

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



## 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/](http://bioencapsulation.net/2016_Frankfurt/)



## 8TH TRAINING SCHOOL ON MICROENCAPSULATION



**Cork, Ireland**  
**May 30 - June 2, 2016**

60 participants  
12 Lectures by experts  
8 practical demonstrations

**More information**

[http://bioencapsulation.net/2016\\_Cork](http://bioencapsulation.net/2016_Cork)



## 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/](http://bioencapsulation.net/2016_Lisbon/)

# PRODUCTION OF EMULSIONS TO ENCAPSULATE LIPOPHILIC SUBSTANCES USING THE MJR TECHNOLOGY

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## INTRODUCTION

Many industries, including food, pharmaceutical and cosmetic industries require delivery vehicles that are able to encapsulate, protect or target release hydrophobic substances like bioactive lipids, flavors, antioxidants and drugs. Conventional oil-in-water emulsions represent one way and have been successfully used to encapsulate lipophilic bioactives (McClements, 2007). One drawback of emulsions is their break down due to physicochemical mechanisms like gravitational separation, flocculation, coalescence and Ostwald-ripening. In oil-in-water emulsions, the most common form of instability is gravitational separation in form of creaming, due to the lower density of the oil particles. According to Stoke's law, the creaming rate can be reduced by decreasing the droplet size or increasing the viscosity of the continuous phase. Furthermore, a sufficient high droplet concentration may prevent creaming by hindering the particle migration (Appelqvist, 2007; Matalanis, 2011; McClements, 2007). To form these emulsions, a variety of pro-

cesses are used, including high shear mixing, high pressure homogenization, microfluidization, colloid mills, ultrasonic homogenization or membrane emulsification (McClements, 2007). The MicroJet Reactor (MJR) technology represents a new technology to manufacture nanoparticles in suspensions or emulsions. Hence the present study deals with the application of this technology to produce emulsions for encapsulation of lipophilic substances. The influence of different parameters, including gas pressure, pump rate, number of cycles and nozzle size on the oil droplet size is investigated.



## MJR TECHNOLOGY

The MJR technology is based on two impinging jets that hit each other in a gas filled room (Penth, 2002). The working principle is shown in Figure

1. Two fluids are pumped into the MJR with a jet velocity of 100 m/s from both sides through nozzles with a diameter of 50-1000  $\mu\text{m}$ . As consequence of the rapid collision of these two linear streams, their kinetic energies are directly converted to the construction of a solvent-non solvent interface that forms turbulent like motion in the collision chamber. This results in the diffusion of the oil phase into the water phase and leads to an adsorption of the emulsifier to the surface of the oil droplets. A vertical applied gas flow then helps to carry the emulsion out of the reactor. Short mixing times of less than 0.1 ms result in the formation of nanoparticles, as it is lower than the nucleation induction time. Thus, the MJR provides the framework for the production of small particles with a narrow size distribution. The main advantages of the MJR technology are continuous process flow and simple scale-up by parallelization. Next to emulsions, nanoparticles of different reaction types can be produced by the MJR technology. Solvent-non solvent precipitation co-precipitation, pH-shift, precipitation through chemical reaction and complex formation are successfully applied reaction principles. Furthermore, it is possible to build reaction cascades by connecting MJRs in series.

## EXPERIMENTS

In this study, the MJR technology was used to produce emulsions to encapsulate a lipophilic substance in a biopolymer solution. The fluid streams were produced by two annular gear pumps (HNP, m<sub>z</sub> 7205 F) that were connected to the MJR. The maximum pump rate is 6000 rpm, which corresponds to 288 ml/min. Unless reported otherwise, a MJR with a nozzle size of 300  $\mu\text{m}$  was used and nitrogen was applied as carrier gas. In the following, the influence of different parameters of the MJR setup including gas pressure, pump rate, number of cycles and nozzle size on the droplet size of the emulsions were

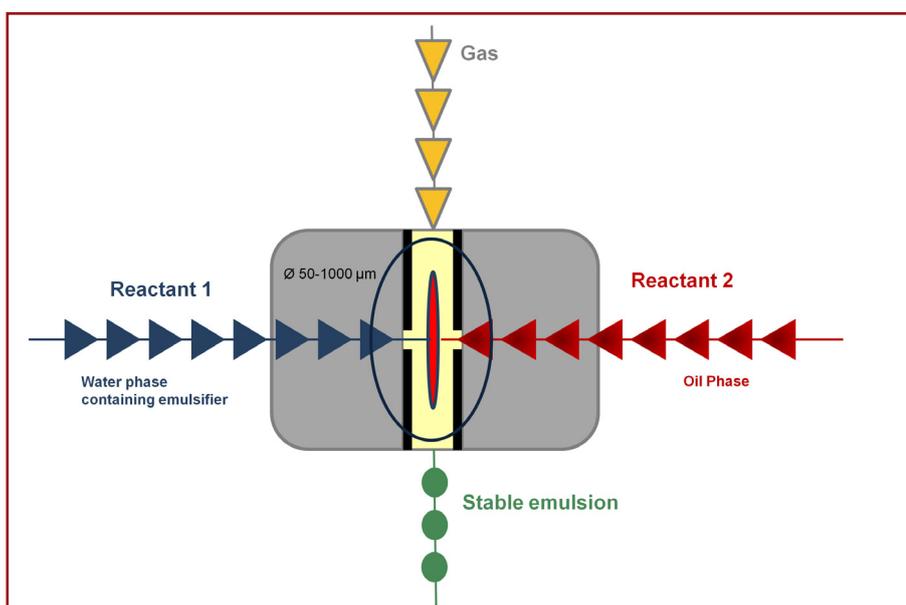


Figure 1: Working principle of the MJR technology.

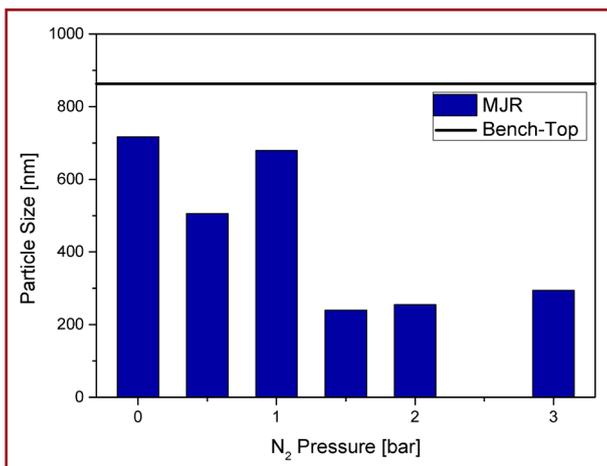


Figure 2: Influence of gas pressure on particle size

evaluated, whereas the concentration of biopolymer solution and the ratio of both fluids were kept constant. For the report of the particle size, the Z-average is used and was measured by a Malvern ZetaSizer Nano ZS90.

As reference a bench-top emulsion was produced using a high shear disperser (Heidolph SilentCrusher M, 26000 rpm). This emulsion had a particle size of 863 nm (depicted as line in Figures 2-5).

### Influence of gas pressure on particle size

The first parameter of the MJR that was investigated was the gas (N<sub>2</sub>) pressure. Both fluids were pumped into the MJR from both sides in the appropriate ratio using the maximum pump rate of 6000 rpm for the biopolymer solution. The N<sub>2</sub> gas pressure was varied from 0 to 4 bar. The results

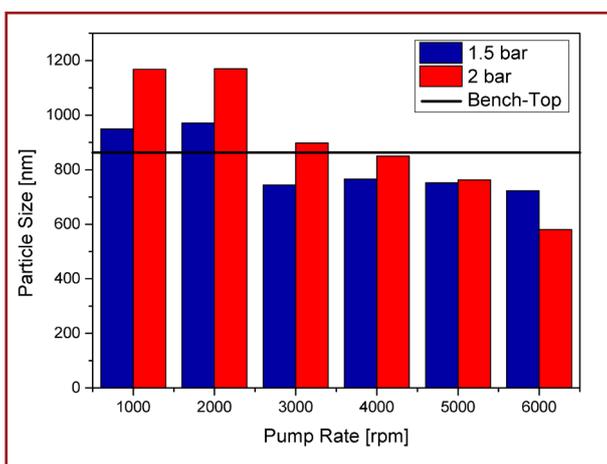


Figure 3: Influence of pump rate on particle size

are reported in Figure 2 and show that the particle size decreased from 717 nm to 240 nm with increasing gas pressure, always being smaller than the bench-top reference. The minimum particle size of 240 nm was observed at 1.5 bar N<sub>2</sub> pressure and again increased to 295 nm at 3 bar. When using a pressure of 4 bar N<sub>2</sub>, no emulsification took place and the two phases left the MJR separately. This indicated that the high gas pressure reduced

the mixing time in the chamber and the used system does not emulsify fast enough. Thus, an optimum N<sub>2</sub> pressure of 1.5 to 2 bar can be assumed.

### Influence of pump rate on particle size

To analyze the influence of the pump rate on the emulsion droplet size, the pump rate of the biopolymer solution was varied from 1000 to 6000 rpm. The N<sub>2</sub> pressures of 1.5 and 2 bar, which were identified as optimum before, were used.

As depicted in Figure 3, the particle size decreased from 1170 nm to 581 nm with increasing pump rate at 2 bar N<sub>2</sub> pressure. Using 1.5 bar N<sub>2</sub>, the particles were smaller for the lower pump rates of 1000 and 2000 rpm (950 nm and 971 nm), but then the droplet size remained around 750 nm for the pump rates between 3000 and 6000 rpm and no further decrease was observed.

To further investigate the influence of the pump rate on the particle size, a second experiment was conducted. Therefore, a coarse emulsion

was prepared by pre-dispersing the oil phase in the biopolymer solution by stirring with a magnetic stirrer. This coarse emulsion was then pumped into the MJR from both sides in a 1:1 ratio under agitation. The influence of different pump rates (1000 to 6000 rpm) and N<sub>2</sub> pressures (1, 1.5 and 2 bar) were evaluated. The results are shown in Figure 4. Using 1 and 1.5 bar N<sub>2</sub> pressure, the particle size in the emulsion decreased with increasing pump rate. Whereas the particle size difference is around 100 nm per 0.5 bar N<sub>2</sub> at 1000 rpm, there is no difference at 6000 rpm, where all emulsions show a droplet size of around 365 to 375 nm. At 2 bar N<sub>2</sub> pressure, the particle size varied only slightly and regarding the N<sub>2</sub> pressure, no trend was visible.

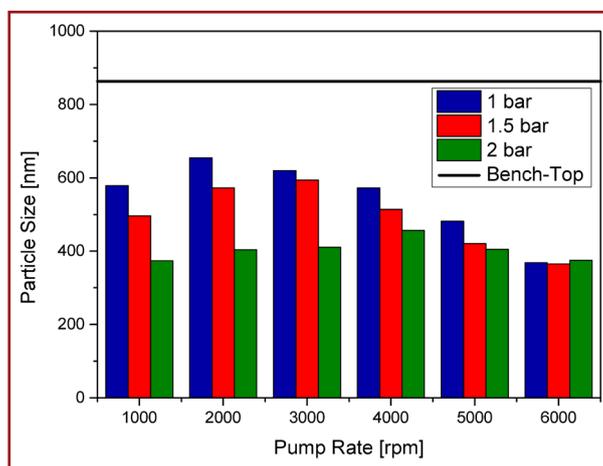


Figure 4: Influence of pump rate on particle size, using a coarse emulsion

As the use of the coarse emulsions was promising and this approach also is applied when using for example a high-pressure homogenizer, it was further followed in the next experiments.

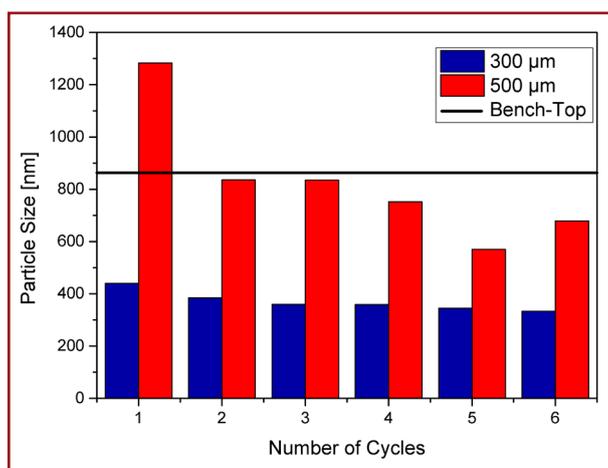
### Influence of number of cycles on particle size

It is known that the particle size decreases with the number of runs through a high pressure homogenizer (Yuan, 2008; Schulz, 2000). On account of this, it was investigated if corresponding results could be obtained by using the MJR technology. Therefore, the coarse emulsion was pumped into the MJR at a pump rate of 6000 and a N<sub>2</sub> pressure of 1.5 bar. The product

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was collected and again pumped into the MJR from both sides.

As expected, the particle size decreased from 440 nm to 333 nm (see Figure 5) with increasing number of cycles. From cycle 1 to cycle 2, the particle size decreased by 56 nm. This decrease got smaller with each further run. This corresponds to the results of studies using a high-pressure homogenizer: Yuan (2007) also reached the smallest particles after three passes and subsequent passed had no further effect.



**Figure 5: Influence of number of runs and nozzle size on particle size**

### Influence of nozzle size on particle size

The last studied parameter was the nozzle size of the MJR. As the use of the coarse emulsion the MJR produced the smallest particles, this approach was also used for the experiment with a MJR with a nozzle size of 500 µm. Figure 5 shows that the particle size decreased from 1283 nm (run 1) to 570 nm (run 5). As observed in the experiment with the 300 µm reactor, the decrease in particle size is not significant after 3 and more cycles.

By comparing the results of the 300 µm with the 500 µm nozzle size, the emulsions produced with the 500 µm nozzles were significantly larger than the ones produced with the 300 µm ones: 1280 nm vs. 440 nm after the first and 570 nm vs. 345 nm after the 5<sup>th</sup> cycle. This might be explained by

the different pressure of the reactants before entering the nozzle. Using the 300 µm nozzle size, a pressure of 25 bar can be observed in the capillaries right before the nozzle. In contrast to that, the pressure is only 5 bar when using the 500 µm nozzle. This indicates that a higher pressure in the system leads to smaller particles as it leads to higher energy input.

## CONCLUSIONS

Using the MJR technology, emulsions with a particle size of around 350 nm can be produced. Compared to the bench-top experiment, the particle size could be reduced by a factor of 2.5. It was shown that the particle size is influenced by various MJR parameters including gas pressure, pump rate as well as the nozzle size. Smallest particles could be achieved with a N<sub>2</sub> pressure of 1.5-2 bar, the maximum pump rate of 6000 rpm and the nozzle size of 300 µm. This indicates that the overall pressure in the system is important to get small droplets in emulsions. Thus, further decrease of droplet size might be possible by increasing the pressure in the system. This could be achieved by increasing the pump rate of the reactants, by using pumps with a higher performance and/or a further decrease in the nozzle size of the MJR.

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Barbara Steiner works as a scientist for the nanoSaar AG since 2013. She graduated from Technical University of Munich in 2012 and holds a master's degree in Nutritional Science. Her major field of interest is the development of encapsulation systems for food and cosmetic applications. She has a special focus in the encapsulation of Omega-3 fatty acids what has already been the main topic of her master's thesis.

# DEVELOPMENT OF MICROCAPSULES AS ADDITIVES FOR ADVANCED COMPOSITES

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## INTRODUCTION

Over the last decades, polymeric microcapsules have attracted increasing interest in research, penetrating and changing markets relentlessly but also creating new opportunities. Devan Chemicals is a SME that develops speciality chemicals for the textile industry. This European sector suffered from globalization and the remaining companies are sustained by developing high added-value products. In this context Devan, with an open innovation mindset, is currently working on the development of microcapsules as additives not only for textile applications (core competence) but also for composite materials, ranging from everyday products to high-end niche applications.

## REACTIVE MICROENCAPSULATION PLATFORM

Microcapsules represent reservoirs of active ingredients which are stored and protected in the core from the surrounding matrices. Under certain conditions (trigger), the encapsulated active ingredients may be released giving the matrices a new (and desired) function. As a trivial example, textile

surfaces functionalized with microcapsules containing fragrance have the ability to store pleasant scents that are released upon the application of friction to the functional surface. In this example the textile surface is enhanced and provides an extra value which is olfactorily measurable. This opportunity has been extensively exploited in many industrial sectors to boost the customer's experience.

In Devan Chemicals, we also envisioned the development of smart materials containing encapsulated active products on textile surface as it is reflected by our extended product portfolio:

- **eSCENTial**® is our encapsulated fragrances product range,
- **THERMIC**® is our encapsulated Phase Change Materials for thermoregulation enhancement,
- **Insecta**™ product range is environmental friendly microencapsulated insect repellent actives,
- **Probiotex**® is composed of microencapsulated probiotic bacteria that have the ability to neutralise dust mites' allergens present in textiles.

In order to differentiate our product range, we developed expertise in the application and processing of microcapsule products but most importantly for our customers, we focused on the durability of the grafting of microcapsules to various textile surfaces. Understanding both textile surface chemistries and the functional groups displayed at the microcapsule walls is a vital point. On one hand, straightforward functionalization of microcapsules shells with reactive groups compatible with textile fibres (e.g. hydroxyl groups) and, on the other hand

a bi-functional coupler that can react selectively and stepwise with microcapsules and textile substrates, can be envisaged (Figure 1). As a result, the microcapsules are more durably bound to the textile surface, enhancing the added benefits of the treated textiles (Figure 2). These research and development efforts were rewarded by key patents that allow us to deliver on an industrial basis microcapsules with functional reactive groups for grafting to fibres (WO/2006/117702, WO/2014/044547).



## MICROENCAPSULATION OF HIGHLY REACTIVE INGREDIENTS

A notable application of microcapsules, having received great attention in the last decade, is their use in self-healing materials. Like in Nature, self-healing materials should have the built-in ability to fully or partially repair the damage occurring during their life time. To achieve this, microcapsules loaded with active ingredients may be embedded in the matrix and then, when a damage-induced crack occurs, the healing agent is released and can initiate a healing polymerization; in such cases, the "trigger" is simply the rupture of the capsules in the immediate vicinity of the crack (White et al, 2001).

Though there are few applications in the market today, it is foreseen that self-healing materials will provide added value in different industrial fields. Think for instance about scratches on car paint that can be repaired without intervention; or internal fatigue cracks

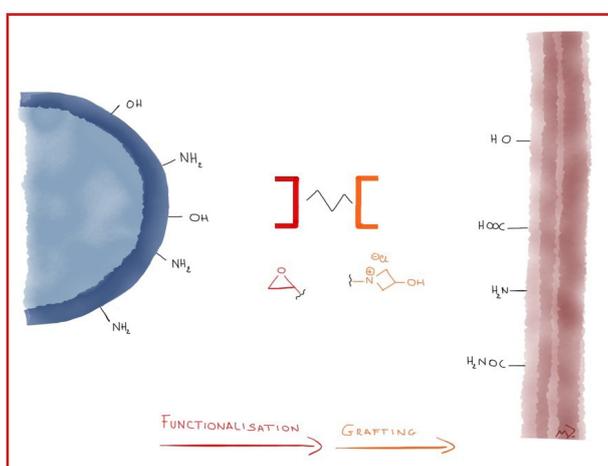
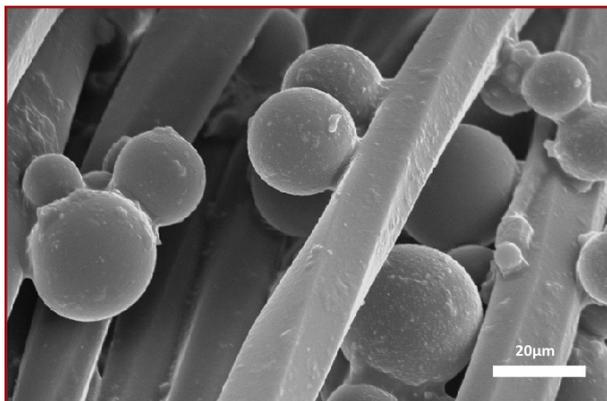


Figure 1: Concept of functionalization of microcapsules (step 1) followed by grafting on textile.

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hardly accessible in concrete bridges or tunnels which could benefit from self-repairing.

With its visionary attitude, Devan Che-



**Figure 2: Scanning Electron Micrograph of THERMIC® microcapsules with reactive groups grafted on polyester textile fabric.**

micals is involved in a research program towards the development of self-healing materials (SHE program under the umbrella of the Strategic Initiative Materials in Flanders). This strategic initiative aims at strengthening the scientific base and building technology platforms to industrial leadership and competitiveness in Flanders. In this context, we are developing microcapsule additives for coating resins that will intervene in the repair of micro-scratches (SHREC project). We also successfully integrated highly reactive components (crosslinking abilities) in microcapsules that are embedded in high fatigue polyurethane elastomers (PUrePAIR project). In both cases, the self-healing capacity is obtained by adding microcapsules loaded with an appropriate healing agent for the matrix.

Examples of such advanced microcapsules are the entrapment of a liquid isocyanate (hexamethylene diisocyanate isocyanurate trimer) in polyurea shell (Nguyen, 2015) with in-situ shell functionalization, and the encapsulation of multi-thiols by a polydimethylsiloxane (PDMS) type of shell (Teixeira, 2014), developed by the Du Prez group at Gent University (UGent). In the case of the encapsulation of isocyanates, particular attention must be given to the reactivity towards water or moisture. To prevent this and preserve the free isocyanate inside the microcapsules, different types of hydrophobic

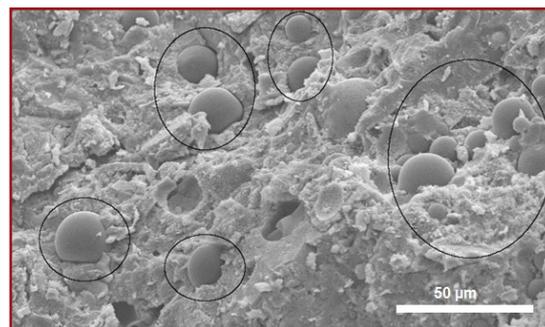
agents such as an alkylamine, fluorinated aromatic amine and/or perfluorinated amine and hexamethylenedisilazane were used to functionalize the microcapsule shells. The use of these functionalities not only helped in keeping the isocyanates stable for longer periods of time but also had a significant impact on the shell morphology of the microcapsules. For instance functionalization with hexamethylenedisilazane resulted in a smooth outer shell surface while functionalization with fluorinated aromatic amine resulted in a more rough shell surface. The microencapsulation of multi-thiols was performed by making use of two com-

mercially available functional PDMS polymers containing thiol and vinyl side groups. These shell components were mixed together with the core ingredient and tetrahydrofuran. The solution so obtained was added to water containing surfactant and, under agitation, core-shell particles were obtained by phase separation between the shell components (PDMS) and the core. Under the influence of photo-crosslinking (using 2,2-dimethoxy-2-phenylacetophenone) a thiol-ene radical addition was used to form a PDMS-thioether cross-linked shell.

The developed microcapsules need not only be able to protect the highly reactive cores, but also be compatible with the surrounding matrices. This compatibility may be achieved by selecting functional groups on the microcapsule surface shells that have a similar nature to the surrounding matrices. Moreover, control of the "engineering process" is also crucial. For example, the described polyurea microcapsules were incorporated in a polyurethane elastomer and foam before curing, and it was observed by our partners that good and homogeneous distribution of the microcapsules could only be achieved with the use of a SpeedMixer™, simply due to the fact that this equipment eliminates air bubbles generated during mixing.

At the European level (HEALCON project), we aim to self-heal concrete and enhance the durability of elements prone to bending cracks. To achieve this target, we have developed melamine formaldehyde shell microcapsules loaded with biogenic agents (WO2014131913 A1) that were dispersed in cement by the de Belie group (UGent). When a crack appears and propagates, it will cause the microcapsules to rupture, releasing the biogenic agents. In contact with a food source (pre-dispersed in the cement), the biogenic agents start to germinate and produce calcium carbonate, contributing to the healing of the concrete. Scanning electron microscope (SEM) micrographs of these microcapsules dispersed in cement (Figure 3), shows a good compatibility with the matrix.

## CONCLUSIONS AND



**Figure 3: Scanning Electron Micrograph of microcapsules dispersed in cement.**

## PERSPECTIVES

The use of microcapsules as additives has attracted much attention and it is expected to continue, especially for certain niche applications. In the textile market, microcapsules are associated with the introduction of comfort, sensorial aspects and health improvements. Self-healing materials are an emerging field, where microcapsules are being incorporated for more demanding technical challenges.

## ACKNOWLEDGMENTS

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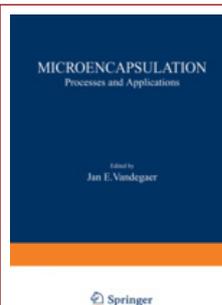
- WO/2006/117702 Microcapsules with functional reactive groups for binding to fibres and process of application and fixation.
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Roberto F. A. Teixeira obtained his Ph.D at Warwick University (UK) working on the fabrication of hybrid nanocomposite waterborne materials. In the fall of 2011, he started to work at the University of Ghent (Belgium) as a research fellow focusing on the microencapsulation of novel chemistries developed for self-healing applications. Since 2014, he joined Devan Chemicals as a project manager and is responsible for the microencapsulation related projects of the R&D team. His research interests include the design of assembled supracolloidal structures and the synthesis of their colloidal and macromolecular building blocks, microencapsulation of reactive chemicals, and self-healing.

## DIVERSIFIED NEWS

**MICROENCAPSULATION Processes and Applications**

Springer, February 16, 2012

**Jan E. Vandegaer** of McGill Univ, who talks about artificial cells prepared from semipermeable microcapsules. Also illustrative of this method is a contribution on microencapsulated pesticides by **C. B. Desavigny and E. E. Ivy** of Pennwalt Corp. Another method of polymerization in situ is micro encapsulation by vapor deposition, the subject of **W. M. Jayne** of Union Carbide Corp. The more mechanical methods of microencapsulation are represented by two techniques, one involving a fluidized bed the other involving mainly a centrifugal method. The fluidized bed method is covered in a paper by **H. Hall and T. M. Hinkes** of the Wisconsin Alumni Res. Foundation. The centrifugal and other related methods are treated by Mr. **J. E. Goodwin and Mr. Sommerville** of the SwRI. **Dr. G. Baxter** of Moore Business Forms, studied capsules made by mechanical methods as well as by chemical methods. **Mr. Russell G. Arnold** of the Bureau of Veterinary Medicine of the Food and Drug Administration draws our attention to the procedures to be used for securing approval of a new animal drug application for the marketing of microencapsulated products. And last but not least, we have a contribution by **Mr. G. O. Fanger** on «Micro encapsulation a Brief History and Introduction», whose title speaks for itself.

**More info on :**

<http://www.springer.com/us/book/9781468407419#aboutBook>

**Korea develops microencapsulation technology for displays**

Screen displays are important components of devices we use every day, like smartphones, laptops and TV's. Often we stare at two-dimensional images on these screens, but a team of experts at the Korea Advanced Institute of Science and Technology have developed technology that they say will help viewers see images three-dimensionally.

«We use molecular engineering to create rubber covered microcapsules that can move around in liquid and change shape and color, making displayed images look three dimensional.»

They say their technology, which microcapsules phototonic crystals, can be used for next generation reflective-type color displays that can bend or fold.

What's more, these microcapsules have characteristics that allows them to change colors based on varying temperatures, which would result in a more brilliant display panel. The team expects the technology will take off in the flexible display market, which is estimated to reach some 4-billion U.S. dollars in 2018. And it doesn't stop there.

«Not only can we make flexible displays using the microcapsule technology, but we can also use it for micro-lasers and special paints.»

The KAIST team's research on microcapsulating technology was published in the scientific journal *Advanced Materials*.

**More info on :**

[https://www.arirang.co.kr/News/News\\_View.asp?nseq=177270](https://www.arirang.co.kr/News/News_View.asp?nseq=177270)



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# IRON STABILIZATION IN FOOD - AN INDUSTRY PERSPECTIVE

Edwin Habeych, Violet van Kogelenberg, Martin Michel, Nicola Galaffu, Nestlé Research Center, Switzerland

## FOOD FORTIFICATION

Micronutrient malnutrition affects billions of people's lives around the world, causing many adverse effects on human health, not all of which are clinically evident. Worldwide, the two most common forms of micronutrient malnutrition are iron and vitamin A deficiency (Allen et al., 2006). Potential solutions include dietary diversification and food fortification, the latter being generally accepted as the most cost-effective solution (Hoddinott et al., 2012).



Fortifications of suitable food vehicles like condiments, dairy products, and beverages with relevant levels of micronutrients constitute a challenging process due to the difficulty to have compounds that can provide both stability (i.e., taste, color, and odor) and bioavailability. One approach to overcome this problem is through the use of encapsulated materials. However, classical micro-encapsulates obtained by powder technology are mainly applicable in dry food products and are not suitable for liquid

products. Moreover, the rather high cost of the encapsulated compounds poses important limitations for their applicability in food products. A good and more affordable alternative for food manufacturers is the use of delivery systems based on processes and ingredients already available during food production. Examples are different types of emulsions, proteins or lipid self-assembled structures (Sagalowicz and Leser, 2010). Even if these different technologies increase nutrient stability to a large extent for many products, those are not sufficient especially when trace elements, like iron, are present. Since iron is the micronutrient corresponding to the highest deficiency, fortified foods often need to contain this mineral. While protection of other nutrients is still required, it is also highly desirable to have iron delivery system that is nutritionally efficient while limiting degradation of food ingredients (e.g., lipid oxidation).

## CHALLENGES ON IRON FORTIFICATION

Food fortification with iron is challenging since the highest bioavailable forms of iron (i.e., dissolve instantaneously under gastric conditions) are chemically reactive and often create detrimental side effects in the food matrix (e.g., color change, metallic taste, and rancidity). By contrast, inert iron compounds are chemically stable in the food matrix but have low bioavailability in

humans due to their low solubility in the gastrointestinal tract during digestion (Figure 1).

As a result, the choice of iron fortificant during the development of fortified food products is often a compromise between reasonable cost, stability in the formulation, and adequate bioavailability of the selected fortificant.

Despite of the number of commercial iron fortificants, there are still products that are challenging to fortify with iron. For example, liquid food products containing ingredients with high levels of polyphenols such as fruits and vegetables, which in presence of iron develop undesirable color during processing and shelf-life.

## BATHOCHROMIC SHIFT

Products like condiments or fruit puree are examples of difficult to fortify matrices, which are also considered optimal carriers to deliver iron to their intended consumers. A common challenge encountered while fortifying these products with highly soluble and bioavailable iron compounds, such as ferrous sulfate, is the drastic change in color odor, and taste in the final product. This happens mainly due to two reasons: A) the pro-oxidant properties of iron in combination with air that can promote oxidation of sensitive compounds such as fatty acids, polyphenols and or pigments; B) the favorable metal chelation of ferrous or ferric ions by electron rich oxygen species such as polyphenols or conjugated carbonyl systems, responsible for bathochromic shifts and thus change in colors (i.e., from red to blue or yellow to dark blue). The following reaction describes the mechanism of color formation of iron in presence of polyphenols:



where n can be 2 (ferrous iron) or 3

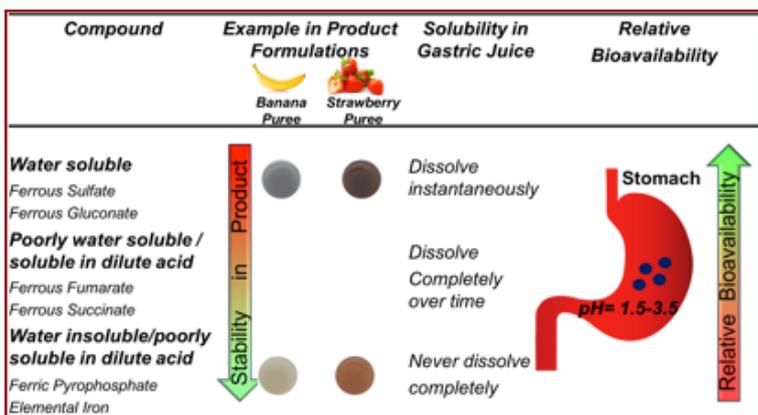


Figure 1. General classification of iron compounds in term of stability and bioavailability.

## ARTICLE

(ferric iron), *PP* is a generic polyphenolic compounds, and *FePP* is the iron-polyphenol complex.  $K_s$  is known as the complexation or stability constant. It is a measure of the strength of the interaction between the ligand and the specific metal ion. Catecholate complexes of  $Fe^{3+}$  exhibit extremely high stability constants ( $K_s \approx 40-49$ ) making this reaction very challenging to repress [Perron et al., 2009].

The stoichiometry of this reaction can vary depending on the type of phenolic compound, pH, coordination number and stability constant with iron.

## STRATEGIES TO LIMIT BATHOCHROMIC SHIFT

A strategy often used to overcome the bathochromic shift in liquid food products containing polyphenols and fortified with iron is through the inclusion of a competitive ligand that can shift the equilibrium towards a colorless reaction. The following conditions represent two strategies to put in place to avoid color changes with iron:

$$K_{Fe-L} > K_{Fe-PP}, [L] < [PP]^*$$

$$K_{Fe-L} \leq K_{Fe-PP}, [L] > [PP]^*$$

where L represents a competitive ligand (e.g., EDTA, citric acid, lactic acid). According to the expression above, the interaction between iron and polyphenols can be reduced by either using a ligand with higher binding capacity than the polyphenol or at higher concentration. To assess this hypothesis, it was proposed to use citric acid in a fortified banana puree with iron sulfate at 0.8 mg Fe/100 g product ( $\approx 15\%$

Recommended daily intake for Toddles) and measure the color change using a reflectance spectrometer (X-Rite ColorEye 7000A) set to a D65 illuminant and a  $10^\circ$  observer.

Figure 2 shows the outcome of this work where  $\Delta E$  refers to a measure of the overall color change in the sample; differences of color with  $\Delta E > 3.0$  are considered to be noticeable by the human eye. According to Figure 2, citrate was successful to reduce the off-color develop in presence of iron at concentrations above 0.1%. On the other hand, citrate concentrations above 1.2% did not further improve the color of the samples.

A second strategy that can be used to reduce the interaction between iron and polyphenols is the addition of divalent cations such as  $Zn^{2+}$ ,  $Ca^{2+}$ , and  $Mg^{2+}$  that can block the binding sites of polyphenols.

In this study, this approach was assessed in a system containing Gallic acid (as model for polyphenols) in acetate buffer (pH 4.4) with 0.1 mg/mL of iron sulfate.  $Zn^{2+}$ ,  $Ca^{2+}$ , and  $Mg^{2+}$  were used at different concentrations with a maximum equivalent to 15% of recommended daily intake for adults.

Figure 3 shows a reduction in batho-

chromic shift at high concentrations of  $Ca^{2+}$  and  $Mg^{2+}$  independent of the application of heat. On the other hand,  $Zn^{2+}$  did not reduce the interaction with iron, which may be explained by the low concentration used of this cation in this work. Overall, the affinity constants of polyphenols with zinc, calcium, and magnesium are considerably lower than with iron, thus the color development of Gallic acid in presence of iron was reduced only when high concentration of these cations were used. These results suggest that  $Ca^{2+}$  and  $Mg^{2+}$  are able to compete for the binding sites of polyphenols, making them less available to interact with  $Fe^{2+}$ .

## CONCLUSION

Micronutrient fortification is the most cost-effective approach to reduce micronutrient malnutrition. However, its implementation is not always straightforward since aspects like stability, cost, and bioavailability are highly critical and rarely available in a single solution. Classical micro-encapsulation of micronutrients is suitable for dry food products and limited liquid products; especially those fortified with iron and containing fruits. Approaches for iron stabilization include complexation with stable ligands and saturation with dietary minerals.

In the future, effort should be put on better understanding the reaction mechanisms involved in the degradation of fortified food products. Based on this knowledge, it would be possible to develop more stable formulations

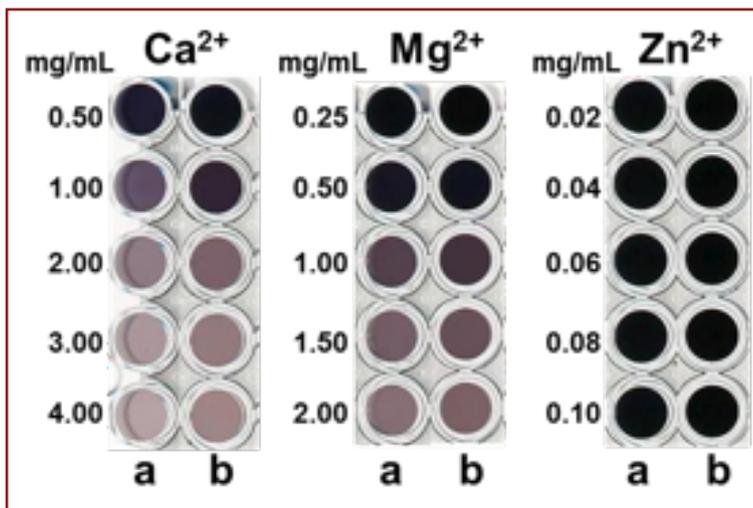


Figure 3. Effect of pretreatment of Gallic acid with divalent cations prior addition of iron. a) unheated, b) heated at 95 °C for 45 min.

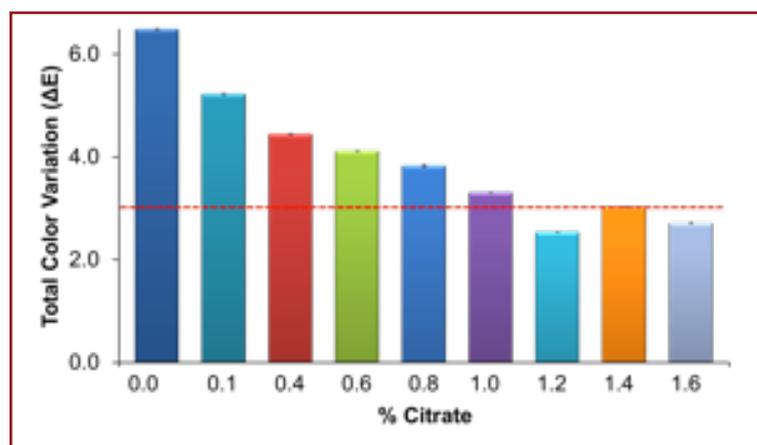


Figure 2. Effect of citrate on color change of iron fortified banana purée.

through the use of appropriate process conditions and ingredients that allow matching product quality and stability. Moreover, the protection of sensitive/reactive compounds can also be envisaged to be integrated during the manufacturing of the products.

## ACKNOWLEDGEMENT

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### Watson Inc. Publishes Webinar on Microencapsulation Technology

used in Value Added Nutrient Premix Applications for the Food and Supplement Industry

Watson Inc. published a 15 minute on-demand webinar designed to explain the applications and benefits of different microencapsulation technologies, such as: hot melt, solvent based, aqueous, and spray drying.

#### More info on:

<http://www.prweb.com/releases/2015/05/prweb12700428.htm>



THE NATURAL SOLUTION

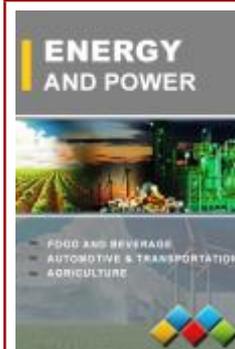
### Edenresearch

Working closely with major universities and commercial research organisations in the USA, Europe and parts of the Southern hemisphere, Eden is now concentrating on developing commercial products for agricultural use in the treatment of plant diseases in a wide variety of crops, as well as pest control issues. Foliar products have been developed to control mildews and moulds, with scope for much wider use. We are also making rapid progress towards developing an effective nematode-control product. More recent agricultural research has revealed the ability of our encapsulated products to control spider mites in glasshouses and to combat foliar and soil borne bacterial diseases.

Eden has therefore reached an advanced stage in the development of a series of competitive antimicrobial and invertebrate-control agents suitable for use in vineyards and greenhouses and on a variety of high-value agricultural/horticultural field crops. The potential for finding further applications of terpene formulations in both the agricultural and healthcare sectors is vast and clearly exciting.

#### More info on:

<http://www.edenresearch.com/html/technology/EDS.asp>



### Food Encapsulation Market by Technology, Shell Materials & Core Phase - Global Trends & Forecasts to 2018

'Food Encapsulation Market by Technology (Microencapsulation, Macroencapsulation, Nanoencapsulation, Hybrid) by Shell Materials (Hydrocolloids, Lipids, Polymers, Melts) by Core Phase (Vitamins, Minerals, Probiotics, Colors, Flavors & Essence) - Global Trends & Forecasts to 2018'

The primary factor driving the growth of the food encapsulation market is the rise in demand for functional foods which offer intended health benefits. This report estimates the market size of the food encapsulation market in terms of value. Bakery & confectionery, dairy & frozen desserts, convenience foods, functional foods, beverages, and meat, poultry & seafood are the key applications for encapsulation. In terms of geography, the report is segmented into Asia-Pacific, Europe, North America, and Rest of the World (ROW). The food encapsulation market is broadly divided on the basis of shell materials, core phase, and technology. With the increasing penchant for product aesthetics and taste, the market is likely to witness substantial growth in the coming years.

#### More info on:

<http://www.researchandmarkets.com/research/p3q2ch/food> and  
<http://www.prnewswire.com/news-releases/food-encapsulation-market-by-technology-shell-materials--core-phase---global-trends--forecasts-to-2018-245448041.html>



Information collected by Victor Roulier,  
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# DESIGNING FRAGRANCE RELEASE SYSTEMS FOR SUPERIOR PERFORMANCE

Pluyter, J. G. L., International Flavors and Fragrances, USA

Microcapsules have become a key technology to enable efficient delivery of fragrances during the product use in home care (fabric conditioners and detergents) and personal care (hair and skin care, antiperspirants/ deodorants).



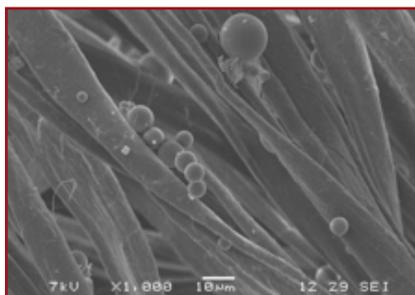
Reasons for using a fragrance in a delivery system can be: (1) to protect ingredients in application media, (2) provide efficient transfer and deposition of fragrance ingredients onto substrates, (3) keeping the fragrance composition together until release and (4) providing fragrance release at the right consumer-relevant moments. The latter is based on when the consumer wants to smell the fragrance. As such, the type of trigger (friction, temperature, humidity, ionic strength, pH, light) is essential as well as the dynamics of the release. Furthermore, the release can be diffusive or continuous in nature. Of course, when the consumer product is used there are various stages at which the consumer wants to smell a particular level or type of fragrance. The objective of the technical work is to be able to dial in the delivery system technology such that these performance characteristics can be employed effectively. This work has to be done alongside the perfumers as the fragrance characteristics are crucial here as well. This presentation will provide an overview of the capsules, capsule types and what characteristics are being pursued.

The ultimate objective is to provide a superior fragrance experience. For instance, for laundry applications it is essential to obtain performance benefits such as a longer lasting release of the fragrance, a higher quality of a longer lasting fragrance (lasting freshness), and a sufficient fragrance release during handling of wet and dry fabrics. Furthermore, it is also important to release the fragrance sufficiently during enhanced physi-

cal activity of the wearer, as well as enhanced bloom during application. In order to obtain sufficient performance from rinse-off applications (detergent, shampoo, conditioner, body wash) a key aspect of the microcapsule performance is that the level of deposition onto the substrate of interest is as high as possible. This provides for an efficient use of the fragrance in comparison to using neat fragrance oil where most of the fragrance is rinsed down the drain during rinse-off applications. Maximizing capsule deposition is a difficult task since most rinse-off applications such as detergents, shampoo and body washes were designed to remove particulates from the substrate (fabric, cotton, skin). Therefore, the deposition technology to be employed must work according to a mechanism that counteracts the surfactant cleaning action.

Fragrance performance from detergents can be greatly enhanced with fragrance microcapsules using a tailored deposition technology. Figure 1 shows an example of fragrance microcapsules deposited onto cotton from a detergent.

Another key aspect of the microcapsules is the extent of fragrance diffusion out of the capsules into the consumer product upon aging, which is really related to the shelf life and product stability during transportation in hot climates. A further aspect of the microcapsules is the release trigger during the use/application of the product and wear of the microcapsules on the substrate. Such triggers can be based on friction, moisture, tempera-



**Figure 1. Fragrance microcapsules deposited onto cotton from a detergent treatment.**

ture, pH, salt and light.

A further key aspect to consider for optimum sensory experience is the olfactory character and intensity of the encapsulated fragrances and the additional fragrance oil that is added. Since the fragrance is to be more effectively delivered it is even more important that the customer likes the fragrance or fragrance combination.

In order to maximize the sensory performance of microencapsulated fragrances all these aspects have to be dialed-in to match the desired sensory experience.

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# CHALLENGES FOR MICROENCAPSULATED FORMULATIONS IN AGRICULTURE

Steinbrenner, U., Bratz, M. – BASF SE, Germany

## INTRODUCTION

In agricultural chemistry the micro-encapsulation of active ingredients is a tool which allows modification of the properties of a given active compound without changing the chemical identity of the latter.

However, agriculture poses a different challenge to the properties and the behavior of these microcapsules compared to many other applications, mainly due to the fact that the conditions in storage as well as during and after application, the “environmental conditions”, are quite diverse and variable.

## MATERIAL & METHODS

As examples four different commercial products or technologies – all containing microcapsules – from four different manufacturers have been selected to elucidate why encapsulation has been chosen as formulation technology:

- Stomp® Aqua of BASF
- Centium® 360 CS from FMC
- Karate with Zeon Technology® from Syngenta
- Micro-Tech® from Monsanto

Furthermore, the commercial rice fungicide Seltima® of BASF has been selected to illustrate options for triggered re-release from microcapsules in agricultural chemistry.

## RESULTS & DISCUSSION

In agricultural chemistry it is necessary to evenly distribute small quantities of active ingredients across large areas, which is only possible with micro-capsules below ca. 10 microns. Macro-capsules on the other hand – like e.g. granules – would either lead to un-realistic volumes or inferior coverage.

But why is encapsulation of agroche-

micals done at all? To answer this question we will now present four market products containing micro-capsules:

### Examples of market products containing microcapsules

In the case of Stomp® aqua micro-encapsulation mainly has been undertaken, because the herbicide pendimethalin is a powerful yellow dye, which permanently stains all surfaces it is in contact with and thus makes the handling of the free active somewhat cumbersome. Furthermore, the encapsulation allows the production of an essentially solvent-free product, improves storage stability – especially against very cold or hot temperatures – and shows agronomic advantages in no till situations, since the capsules are less prone to bind to the mulch coverage than the free herbicide. Rather, they are washed down reaching the soil surface where they can suppress the emergence of undesired, competing weeds.



In the case of Centium® 360 CS micro-encapsulation is the method of choice to reduce off-site movement of the active component clomazone. This herbicide is a powerful bleacher, but it has a non-negligible vapor pressure, too, and significant buffer strips to non-target areas are necessary if free clomazone is applied to a field. Encapsulation of clomazone greatly reduces the vapor pressure and consequently the necessity of broad buffer strips.

In the case of the cypermethrin insecticides microencapsulation has been chosen in the product line Karate with Zeon technology® of Syngenta,

since the acute toxicity of the active is significantly reduced by the capsules. Additionally, the amount of solvent in the product can be reduced and the chemical stability of the active is improved.

Finally, Monsanto uses their Micro-Tech® technology to microencapsulate chloroacetamide herbicides and gains both a reduced volatility and a longer lasting action against weeds.

In all four cases encapsulation has been performed to mitigate undesired short-term effects – effects in the range between minutes and days – mainly related to the physics, chemistry, toxicity or ecotoxicity of the active ingredient. But the mid to long term performance of the latter has to stay at least on the same level as the non-encapsulated product.

Today's microencapsulation technology in agricultural chemistry

The usual encapsulation technology in the market is the formation of a polyurea shell polymer at the interface of an emulsion template, borne from multivalent isocyanate monomers in the oil and amine monomers in the water phase.

It is believed that the preference for this technology arises from three main facts:

- the reaction is “selfhealing”, which means that the polymer formation is fastest at the thinnest part of the growing shell
- the reaction between isocyanate and amine is fairly robust, easy and tolerant
- a very stable and highly cross-linked, thus insoluble and inert polymer results

### Release from microcapsules

Release methods after application range from capsule wall cross-diffusion via breaking under environ-

mentally induced micro-stress up to mechanical destruction by chewing or trampling in the case of insect control.

BASF's rice fungicide product Seltima®, which has been designed especially for Asian rice fields, is an example where microencapsulation allows combining both good crop protection performance and high environmental safety.

The capsules open as a result of the significant environmental difference between capsules on a surface and in water.

After spray application, microcapsules "landing" in the water will sink to the ground where the fungicide is bound to the sediment and degraded over time. On the other side, microcapsules "landing" on rice leaves will break due to environmental stress, upon drying in the sun, changes in humidity and temperature during the day, thereby releasing the fungicide which will subsequently enter the leaf and protect the rice plant against fungal diseases, especially rice blast, *pyricularia oryzae*, which is claimed to be the most important disease concerning the rice crop in the world.

Diffusive release on the other side leads to a constant stream of active ingredient being supplied to the target over time, and it allows releasing different active ingredients at different rates from the same capsule.

Like the triggered release the diffusive release can also be tweaked to the application needs:

Firstly, the total release current can be easily adjusted, because for a given weight percentage of polymer per capsule, the diffusive release current approximately scales with the capsule diameter to the power of minus two.

Secondly, the choice of monomers and thus the polymer network wall density also allows adjusting the release current, additionally it creates the nice possibility to release different active materials at different speeds, and here orders of magnitude in the variation of speeds are possible.

Thirdly, the capsule size distribution can be used to fine-tune release rates. Monodisperse microcapsules clearly lead to a constant release current, whilst broad distributions rather exhibit an exponential release similar to a

first order kinetics.

During and after diffusive release those capsules resemble "deflated volley-balls" under the electron microscope, with no broken capsule shells visible.

## Boundary conditions and challenges

Finally, we have to face that in agricultural chemistry microencapsulation is challenging because the final product has to be robust and stable on one side but has to work reliably under not-so-controlled conditions. And not only the farmer expects robustness, the authorities explicitly ask for proof of robustness before granting registration and approval.

The products usually must have up to two years shelflife if stored in barns where they sometimes are subjected to cold or hot temperatures. They are mixed with water of different quality and temperature, often mixed with other agricultural products, too, and then applied by a vast number of different equipment, form a small backpack to huge boom sprayers.

On the other side the farmer expects a reliable performance irrespective of the weather, of different soils, different weeds or different crop varieties.

## CONCLUSION & PERSPECTIVES

We see that microencapsulation is a versatile tool to modify the properties of the active ingredients in a way that they are safer to the people and the environment, perform better or longer, show better crop tolerance, improve the handling properties, and reduce the necessary work for the farmer.

But it has to be pointed out that both good and also robust microcapsules for agriculture are challenging to produce.

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Dr. Ulrich Steinbrenner studied chemistry at the University of Stuttgart, Germany, as well as the University of Cincinnati, USA. He worked from 1994 to 1997 at the MPI of Solid State Research in Stuttgart, before he entered BASF, where he worked in solid catalysis, in the technical marketing of surfactants, in product stewardship and chemlaw. Currently he is responsible for formulating herbicides.

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Dr. Matthias Bratz studied chemistry at the University of Göttingen, Germany and the University of California, Irvine. He is with BASF since 1990 and his research interests are in the development of biologically active molecules and their delivery to the target. Currently he has global responsibility for formulation development in Agro for BASF

# MICROENCAPSULATION: GUIDE TO INDUSTRIAL APPLICATIONS

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## INTRODUCTION

The use of microencapsulation continues to grow within and throughout multiple industries. As unique controlled release solutions propagate between industries, new uses and applications emerge in the form of new or improved products. Many recently published books and patents capture these innovations, but are concentrated within a specific industry. With a few exceptions, a comprehensive collection of microencapsulation applications and products is elusive. (Arshady et. al. 2003). Continued examination of the current applications is required to continue the proliferation of microencapsulation technologies.

## INFORMATION SOURCES

Information on applications and developments in the microencapsulation industry are spread across press releases, academic journals, patents, and books. Internet-based search engines such as Google Scholar, Scopus®, or SciFinder ® indicate a current publication rate approaching 15 articles per day with references to micro- or nanoencapsulation spread across hundreds of journals. The global patent award rate is approximately 3.5 patents per day. Additionally, over a dozen books focused on microencapsulation applications have been published in the past decade, however their focus is on a specific industry. The growing wealth of information provides insight into microencapsulation trends and developments, but does not capture the knowledge and science protected as corporate trade secrets.

## APPLICATIONS

Microencapsulation has facilitated the development of new products and improvement of existing products by solving unique challenges such as converting liquids to solids, separating reactive components, protecting ingredients from the environment, controlling release, or masking ingredients. The resulting applications use

encapsulated solids, liquids, or gases prepared from the dozens of processes and thousands of formulation combinations that have evolved with the encapsulation field.

### Pharmaceuticals

The pharmaceutical industry currently leads encapsulation research and development in both academia and industrial applications. The global impact of encapsulation is evident in the dominance of products that use encapsulation to mask taste, control release, improve bioavailability, target certain parts of the body, or enable drug stabilization for pro-longed shelf-life. Examples of products include taste-masked diphenhydramine orally dissolving tablets for children's allergy treat, or liposomes of doxorubicin for chemotherapy.

### Nutraceuticals

With the rise of functional foods and popularity of nutritional supplements, many of the encapsulation advancements in the pharmaceutical industry have been adopted by the nutraceutical industry. Similar challenges, such as taste masking, stabilization, and bioavailability benefit from encapsulation and are required for the success of many products on the market. The use of encapsulation goes beyond standard dosage forms, such as tablet and gencaps, to water-dispersible powders from a sachet or single serving liquid shots. Some of the most common encapsulated nutrients include omega-3 oil and beta-carotene for protection against oxidation.



Figure 1. Encapsulated fish oil (omega-3).

### Food & Beverages

Many of the fundamental formulations and processes in microencapsulation, such as spray drying, emerged from the food industry. Initially used for converting liquids to solids, such as powdered eggs or flavours, the application of encapsulation has grown to address multiple problems and create new products. Encapsulation is now used to stabilize ingredients, prolong shelf-life, control taste, aid in processing, and reduce cost while increasing value. Many examples of products on the market, such as fortification with omega-3, utilize the same technologies employed in the nutraceutical industry. Another example includes the controlled release of leavening agents in frozen dough for storage stability and controlled release when cooked by the consumer.

### Flavours & Fragrances

Flavours and fragrances generally present the same encapsulation challenges, and span multiple industries. Initially investigated for converting liquid flavours and fragrances to powders, encapsulation is now used to control release and stabilize in multiple products. A few common applications of encapsulated flavors include powdered drink mixes, chewing gum, and frozen pre-baked items. Fragrance applications range from scratch-n-sniff to fabric softeners. The common factor linking flavours and fragrances is their complexity. Flavour and fragrances are often complex mixtures of chemicals with varying solubility, reactivity, and volatility. Often, flavour or fragrance mixtures are designed around an encapsulation process to account for processing conditions and component loss, resulting in a capsule that contains the final proper balance of flavour or fragrance components.

### Cosmetics

Microcapsules and nanocapsules, such as liposomes, are often used in cosmetic products to add controlled release to the ingredient, increase

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bioavailability, stabilize a product, improve product appearance, or as a marketing tool. Factors such as particle size, cost, and innovation drive encapsulation research in the cosmetic industry. Particle size is often the critical parameter, requiring the development of microcapsules that do not impact skin feel of a product. Similar to other industries, cost drives the extent of development and sets the limits on what processes and materials can be used for encapsulation.



Figure 2. Encapsulated pesticides.

## Consumer Products

Microencapsulation in consumer products spans a wide range of applications, including facial tissues, razor blades, deodorant, toothpaste, and more specialized products such as displays in some consumer electronics. The applications in this area continue to grow, and also present some of the most significant encapsulation challenges. The wide range of product matrices and manufacturing processes place numerous restrictions on the potential materials that can be used for encapsulation, while the size and morphology requirements further restrict the possible encapsulation processes. Many potential applications are not fully realized due to the cost of encapsulation, which is related to availability and scalability of the required encapsulation process.

## Agriculture

The use of microencapsulation in agriculture started with controlled release of pesticides and fertilizers, and has expanded to include animal health. As the widespread use of antibiotics is discontinued on commercial farms, specialized nutrition is required to maintain good animal health. Similar to its applications in food, encapsulation is used to improve the stability

and availability of feed ingredients. For vegetation, the encapsulation of pesticides and fertilizers continues to be used to enhance controlled release, minimize quantities for effective use, and reduce frequency of treatments.

## Textiles

Examples of applications in textiles include cosmetotextiles, insect repellents, flame retardants, fabric care, color changing fabrics, and phase change materials. The field of cosmetotextiles bridges textiles and cosmetics, often using the same encapsulation formulation and technologies to introduce functional ingredients, such as fragrance or skin cares. Emerging applications include self-healing textiles and smart fabrics.

## Paints & Coatings

The modern encapsulation era began in the paints and coatings industry with the development of carbonless copy paper. Since then, the list of applications continues to grow and now includes bruisable paints, thermal indication, antifouling, self-healing, pressure indication, and other functional inclusions. Due to the relative thinness of most paint and coating applications, the capsules typically used are small and prepared using standard emulsion-based encapsulation processes. It is the limitations on emulsion-based processes that currently limit the applications of microcapsules in paints and coatings.

## Other Applications

Many other applications benefit from the use of encapsulation, including energy, construction, environmental, automotive, and petrochemical. These industries often present some of the harshest challenges, including capsules with thermal stability over 500 °C for solar thermal energy storage or high pressures in petrochemical drilling applications. The variety of applications will continue to increase as new advancements in encapsulation formulations and processes reach an affordable manufacturing scale.

## CONCLUSIONS

Since the emergence of spray drying

at the end of the 19th century and invention of carbonless copy paper in the middle of the 20th century, microencapsulation has expanded into most commercial products. In addition to providing enhanced value and utility for some products, it has also enabled the manufacture of new products. As new and emerging applications enter their respective markets, a general understanding of when and how encapsulation is applied must be followed to continue the successful growth of the field. A balance of intellectual property, trade secret, and academic advancements needs to be maintained to protect industrial innovators while permitting the transcendence of unique developments to non-competing applications.

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# SUPERCRITICAL CO<sub>2</sub> ENCAPSULATION

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## INTRODUCTION

For more than 40 years, supercritical carbon dioxide has been used as a renewable solvent for the extraction of ingredients such as caffeine from coffee beans and oils from flowers, herbs and spices. These extraction processes take advantage of the novel chemical and physical properties of CO<sub>2</sub> in the supercritical state, which occurs above 74bar and 31°C respectively. Under these conditions, the phase boundary between liquid and gas no longer exists and CO<sub>2</sub> exhibits properties that are somewhere between these two states, namely liquid-like densities but gas-like diffusivities and no surface tension. Combining these features with its non-polar nature, CO<sub>2</sub> can be used as a solvent for other non-polar compounds such as fats, oils and other hydrophobic compounds.

Aside from extraction, supercritical CO<sub>2</sub> can also be considered for other chemical processes. In particular, the mild processing conditions (low temperatures and inert atmosphere) in combination with high solvent power and no surface tension make supercritical CO<sub>2</sub> an interesting medium for encapsulation. In contrast to hot air spray drying, the mild processing conditions are especially beneficial for the encapsulation of sensitive ingredients that are susceptible to heat and oxidation. Furthermore, the ability to tune the processing conditions by adjusting the temperature and pressure, in combination with the possibility to process a wide range of ingredients and formulations, allow for the production of encapsulates with novel product functionalities. For many years, CO<sub>2</sub> encapsulation processes were only implemented on the lab scale, yet more recently, the process has also been demonstrated on a pilot scale, thus paving the way for eventual commercial implementation. Some of the CO<sub>2</sub> process is presented below, along with examples of encapsulates that benefit from CO<sub>2</sub> processing environment.

## MATERIALS&METHODS

Supercritical CO<sub>2</sub> can facilitate encapsulation in a number of ways, namely by acting as 1) a drying medium, 2) an anti-solvent and 3) a solute. In all cases, the encapsulation typically takes place by spraying a solution, emulsion or a melt consisting of the ingredients to be encapsulated along with the coating materials. The main variables that influence the ability to form the encapsulates are the CO<sub>2</sub> density, which influences the solvent capacity of CO<sub>2</sub> and the atomization process, as well as the choice of nozzle and the flow rates, which affect the droplet size and particle formation. One advantage of using CO<sub>2</sub> as a means for encapsulation is that it is applicable to both polar and non-polar coatings and ingredients. A brief description of the different encapsulation processes are as follows.

### CO<sub>2</sub> as a drying medium

In a process that is analogous to hot air spraying, CO<sub>2</sub> can be used to spray dry droplets to form microencapsulates. The CO<sub>2</sub> acts as both an atomizing agent and a drying medium. When water based solutions, emulsions or dispersions are sprayed into the vessel, the drying takes place via mass transfer of the water from the sprayed droplets to the CO<sub>2</sub>, to form particles where the active ingredient is entrapped in the coating material. The efficiency of the encapsulation process is dependent on the water uptake by the CO<sub>2</sub> relative to the amount of solution that is sprayed over time. The particle size and morphology can be influenced by the choice of nozzle, pressure, temperature and flow ratios. After depressurizing the system to remove the CO<sub>2</sub>, the resultant product typically is a solvent-free powder.

### CO<sub>2</sub> as an anti-solvent

In a similar manner to the process above, an organic solution is sprayed into a vessel of pressurized CO<sub>2</sub>. When the CO<sub>2</sub> enters into the droplets,

it reduces the solubility of the solute (coating material) thus inducing precipitation to form the encapsulated product. The anti-solvent process is predominantly dependent on the ratio of CO<sub>2</sub> to solute, and thus can be controlled by adjusting the density of the CO<sub>2</sub> in combination with the flow rates. Subsequent depressurization of the system results again in a dry, solvent-free product.



### CO<sub>2</sub> as a solute

The previous two methods involve spraying a solution into CO<sub>2</sub>, yet it is also possible to use CO<sub>2</sub> as a solute, where it is mixed with a solution or melt consisting of the active ingredient and coating material. The combined mixture is then expanded over a nozzle by spraying into a vessel that is at a lower pressure. The atomization of the mixture, plus the pressure difference upon expansion, results in rapid cooling of the droplets, which induces the precipitation/solidification of the solvent-free encapsulated particles. The main variables for this process are the choice of nozzle, temperature, pressure, ratio of CO<sub>2</sub> to the solution/melt, spraying rate and the conditions (temperature and pressure) in the collection vessel.

## PRODUCT EXAMPLES

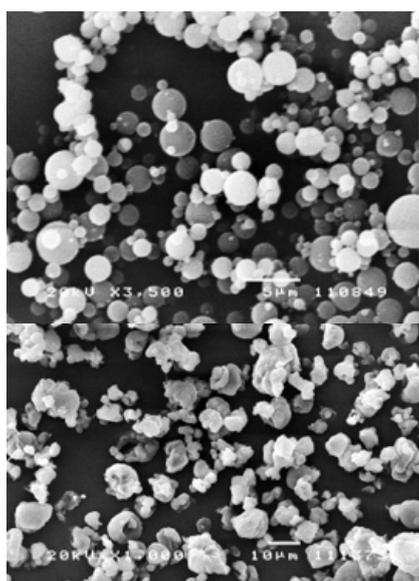
### Water-dispersible nutraceuticals

When fortifying foods with nutraceutical actives, the active ingredient should not affect the colour, taste or mouth-feel of the food yet remain bioavailable. Consequently, the active is often encapsulated in order to address these issues. In the scenario presented here, an unpleasant tasting active that is sensitive to oxygen was intended to be added to water-based beverages. The challenge, therefore,

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was to coat the active so that it could withstand the aqueous environment yet be released upon digestion. In order to achieve this, a double encapsulation approach was chosen. This involved preparing a pH sensitive inner core particle, which allows for the active to be released in the stomach, that was subsequently coated with a hydrophobic shell that would stabilize the encapsulated material when dispersed in the beverage. In this case, the advantage of using supercritical CO<sub>2</sub> encapsulation over hot air spray drying is two-fold: the inert atmosphere used in the CO<sub>2</sub> process avoids oxidation of the active and the ability to spray organic solutions means that a greater range of materials can be considered when selecting the material to form the hydrophobic shell.

The core was prepared by dissolving both the nutraceutical and core coating material in water and spraying the solution into a vessel containing supercritical CO<sub>2</sub>. By adjusting the temperature, pressure and flow rates of the solution and CO<sub>2</sub>, small, spherical particles of the order of 1-5µm were obtained (Fig 1). These core particles were then dispersed into an organic solution consisting of the shell material. The suspension was then sprayed in a similar manner to the core particles, with the processing conditions adjusted accordingly. The resultant particles were irregular with a particle size of 10-20µm (see Fig 1).



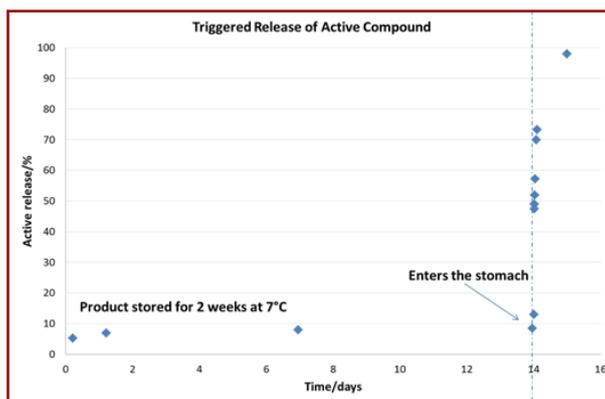
**Figure 1. SEM images of the core particles (top) that are subsequently coated with the shell material (bottom) for encapsulation of nutraceuticals.**

To evaluate the efficacy of the core-shell coating, the encapsulates were placed in a model beverage and the release of the active monitored over time using ICP-OES analysis. During 2 weeks, the beverage was kept at pH7 and minimal release of the active was observed (<10%). To simulate the conditions in the stomach, acid was added and immediately, the capsules broke to release the active ingredient. During the following 2 hours, more than 70% of the active was released (Fig 2). From this, it can be concluded that such core-shell encapsulates can be used to achieve shelf-life stability while retaining bioavailability.

### Encapsulation of oils

Natural oils, particularly those from fish and seeds, are a valuable source of ω-3 and ω-6 fatty acids that are essential for the human body. However, these oils are sensitive to oxygen and heat, leading to rancidity and a loss in nutritional quality. Consequently, encapsulating these oils can stabilize them against degradation. With traditional hot air spray drying methods, the exposure to both oxygen and heat can affect the quality of the product obtained. In this respect, the use of supercritical CO<sub>2</sub> processes for encapsulation offer a low temperature and oxygen-free processing medium that preserves the functionality, composition and nutritional value of the oil in the resultant product.

The method for encapsulating oils typically involves preparing a water-based solution consisting of the coating material and emulsifiers, to which the oil is added. After mixing and homogenization, a stable emulsion of the oil droplets dispersed in the water is obtained. This emulsion is then sprayed into a pressurized vessel containing CO<sub>2</sub>, where the water is removed from the droplets to form the oil encapsulates. By adjusting the processing conditions, the resultant product is a solid, closed particle that protects the oil from oxygen. Depending on the choice of coating material, the oil can later be released in res-



**Figure 2. Release of the active ingredient during a storage period of 2 weeks followed by triggered release at low pH.**

ponse to a trigger, such as humidity or pH. With this method, very high encapsulation efficiencies can be achieved (>99%) and shelf-life stabilities of more than a yields are attainable.

### PERSPECTIVES

CO<sub>2</sub> has been shown to be a suitable medium for encapsulating sensitive ingredients. The flexibility of the technology in combination with the mild processing conditions makes it an attractive alternative to hot air spray drying. Recent developments in up-scaling are paving the way for industrial implementation of the encapsulation with CO<sub>2</sub>.



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# 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 ecotoxicological profile due to its short half-life in sea water (<24 hr).<sup>1</sup> 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

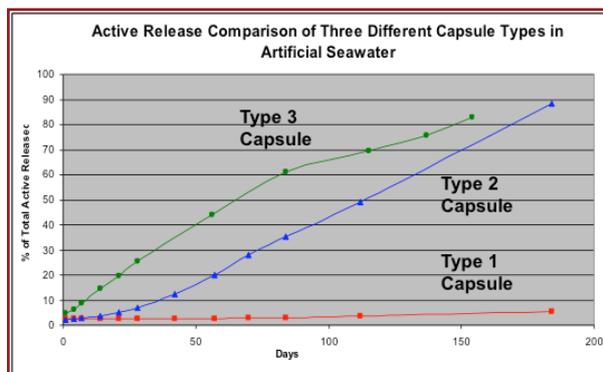


Figure 1. Effective active release profiles for microcapsule type 1, 2, 3 respectively.

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.

Interestingly, all capsules maintain excellent in-can stability in various solvent combina-

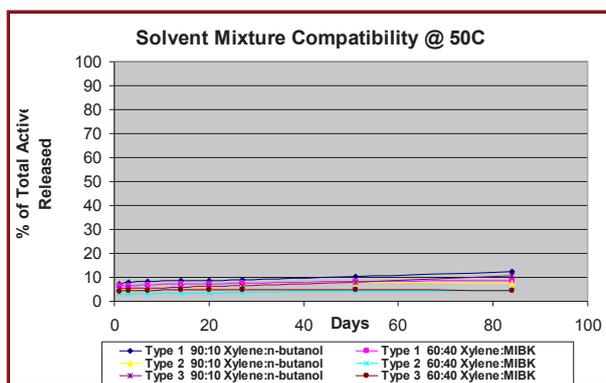


Figure 2. Accelerated in-can stability for microcapsule type 1, 2, 3 respectively.

tions as shown in Figure 2 under accelerated testing conditions at 50 °C.

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 formula-



Figure 3. Ten month raft panel test results of copper-based: 45% Cu<sub>2</sub>O + 3% copper pyrithione (left), and copper-free coating: 5% Type 3 DCOIT microcapsule (right).

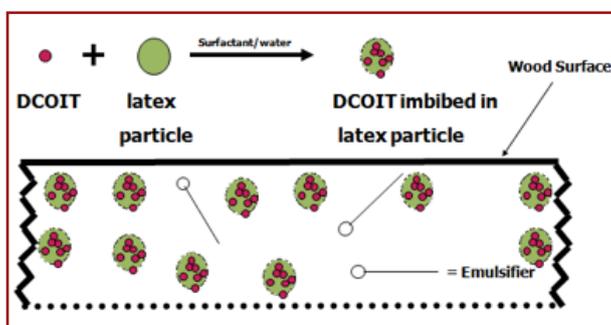
tion, enabling leaching by sea water at a rate necessary for the desired efficacy and loading adequate active in the capsules to minimize capsule concentration in the final coating.

## 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

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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.

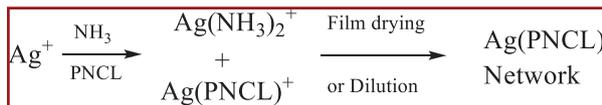


**Figure 4. Imbibing of the active into the latex particle for wood preservation**

### 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.<sup>2</sup> There has been a long history of use of silver as a broad spectrum antimicrobial agent. However, the active ingredient, silver ion ( $\text{Ag}^+$ ), is highly light and heat sensitive and has very limited compatibility in various formulations.

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



**Figure 5. Competitive complex formation between a fugitive ammonia ligand and a permanent PNCL with  $\text{Ag}^+$**

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  $\text{Ag}^+$ . 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  $\text{Ag}^+$  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 antimicrobial 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 tech-

nology 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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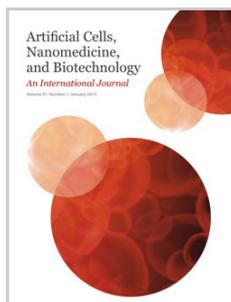
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