STUDY OF THE PARTICLE FORMATION AND MORPHOLOGY OF SINGLE MANNITOL-WATER DROPLETS DEPENDING ON THE DRYING CONDITIONS

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Key Words: acoustic levitation, bi-component droplet drying, particle morphology, drying kinetic, numerical simulation

In chemical, pharmaceutical and food processing industry, spray processes have a wide range of applications, especially in the production of tailor-made powder products of defined characteristics from solutions or suspensions. The effects of process parameters (e.g. temperature and relative humidity) on the drying kinetic of a droplet and the properties of the resulting particles are largely based on experience. Still there is a lack of information on the fundamentals of particle formation. To close this gap numerical simulations as well as single droplet experiments were carried out under various conditions. This study concerns the influences of relative humidity, drying temperature and mass fraction on the solid layer formation and on the particles of single droplets consisting of mannitol-water solutions. An acoustic levitator (Fig 1 a)) was used to carry out the single droplet experiments. By means of a camera and a light source shadowgraphy was used to analyze the droplet drying kinetic and the development of the droplet respectively. Raman spectroscopy was used to analyze the polymorphism[1] of oversaturated mannitol-water droplets (relative humidity above 10 %). Using a thin thermocouple (150 µm) the particle temperature was recorded. Typical drying curves showed a continuous decrease of the droplet surface area until the solid layer was formed. The progress of the droplet temperature during the evaporation depends on the increase of the mannitol concentration at the droplet surface and start crystallization. Numerically, the unsteady, one-dimensional mass and energy diffusion equations for spherically symmetric droplets were solved accounting for the occurrence of the solid layer formation. Moreover, the influence of the air humidity on the solid layer formation and the droplet temperature evolution was investigated experimentally and validated by simulations. It was shown that an increase in the humidity of the drying air leads to a delayed solid layer formation[2] and a decrease of the final particle porosity whereas a higher mannitol concentration and a higher temperature have a contrary effect. The validity of the numerical model concerning the time instance of the solid layer formation and the progress of the droplet temperature was confirmed. Using the numerical model the drying of a single droplet was successfully simulated. Additionally a morphology map for the obtained particles from the single droplet experiments was developed.

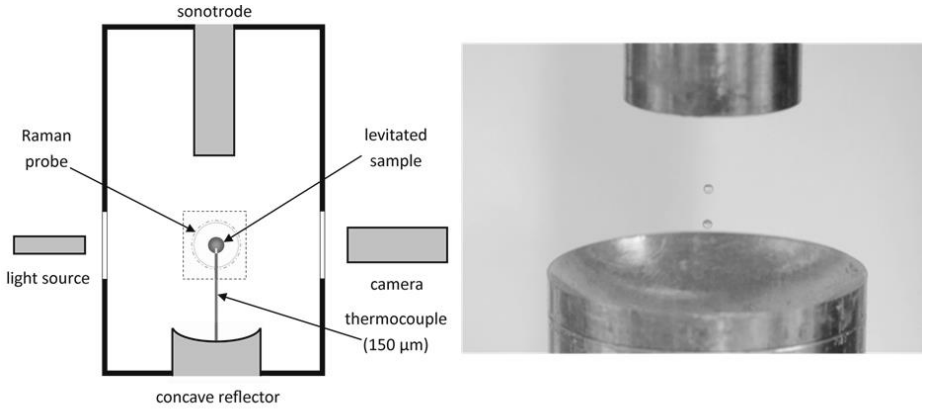

Figure 1 – a) Process chamber of the acoustic levitator with the Raman probe in the background outside the chamber, b) levitated mannitol-water droplets.

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INFLUENCE OF OPERATING PARAMETERS OF A SPRAY TOWER ON SPRAY POLYMERIZATION PRODUCT PROPERTIES

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Key Words: Spray polymerization, tower reactor, polymer particles, particle morphology, particle formation

Spray drying is a process mainly used in the pharmaceutical, chemical and in the food industry to produce particles with definite properties for various applications [1]. The spray polymerization is a technical development of spray drying. Spray polymerization is a fusion of polymerization and spray drying. Due to the phenomenon of the wet-bulb temperature of a droplet, the polymerization enthalpy is removed by evaporation of the dispersion medium. Thus, the droplet temperature can be assumed as isothermal. After shell formation the droplet temperature drastically increases and the ongoing polymerization leads to the final particle. Due to the process intensification the spray polymerization is interesting for industrial use. The constant and controllable particle morphology plays an important role for industrial applications. Just like the product morphology during spray drying [2], properties and morphology in the spray polymerization can be controlled by operating parameters such as gas flow rate, gas stream composition and temperature. These parameters affect the spray characteristics and, in particular, the later product properties, like stickiness, porosity, surface texture or morphology, flowability, storage stability. E.g. Krueger investigated the product morphology during co-current flow of the tower reactor [3]. Results for countercurrent operation are not published yet. This study shows that the process temperature has an influence on both, particle size distribution and inner as well as upper surface morphology in a countercurrent operation mode of the spray reactor. Further, we are able to show a dependence of the morphology on the gas flow rate, gas composition and countercurrent flow rate. The above mentioned process parameters are also analyzed regarding their influence on product characteristics such as molecular weight, residual monomer content and residual moisture. Figure 1 shows the technical drawing of the tower reactor used in this study and an example of a powdery product.

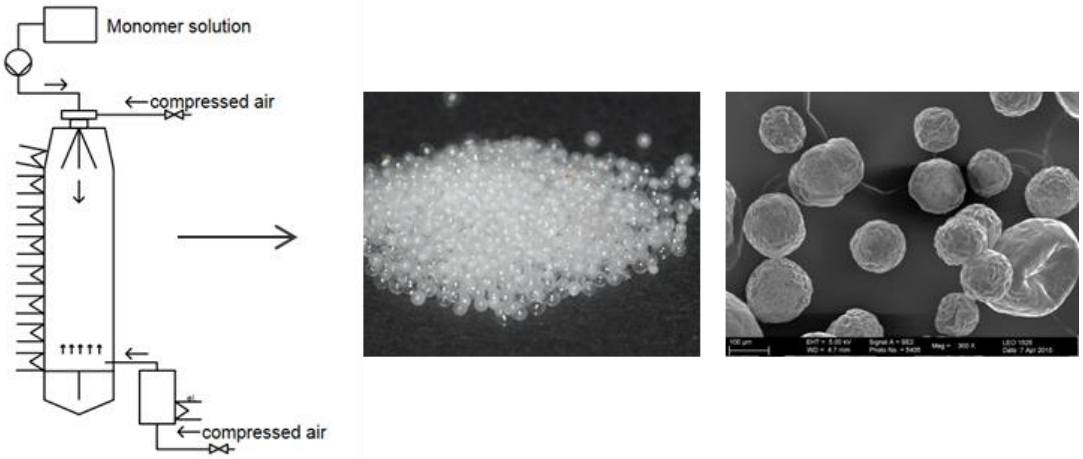

Figure 1 - Technical drawing of the tower reactor (left) and the dry powdery polymer product (middle) and a SEM picture of the polymerized particles (right).

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SALT-HYDROGEL MARBLES AND HOLLOW-SHELL MICROCAPSULES FOR REDUCED SALT INTAKE

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Key Words: salt, hydrogel, liquid marbles, microcapsules, hollow-shell capsules

We designed a new method for preparation of liquid marbles by using hydrophilic particles [1] (Fig.1). Salt-hydrogel marbles were prepared by atomising droplets of hydrogel solution in a cold air column followed by rolling of the collected hydrogel microbeads in a bed of micrometre size salt particles. Evaporation of the water from the resulting salt marbles with a hydrogel core yielded hollow-shell salt microcapsules. The method is not limited to hydrophilic particles and could potentially be also applied to other materials, such as graphite, carbon, silica and others. The structure and morphology of the salt-hydrogel marbles were analysed with SEM and their particle size distributions were measured. We also tested the dissolution times of the dried salt marbles compared them to these for table salt samples at the same conditions. The high accessible surface area of the shell of salt microcrystals allows a faster initial release of salt from the hollow-shell salt capsules upon their dissolution in water than from the same amount of table salt. The results suggest that such hollow-shell particles could find applications as a table salt substitute in dry food products and salt seasoning formulations with reduced salt content without the loss of saltiness.

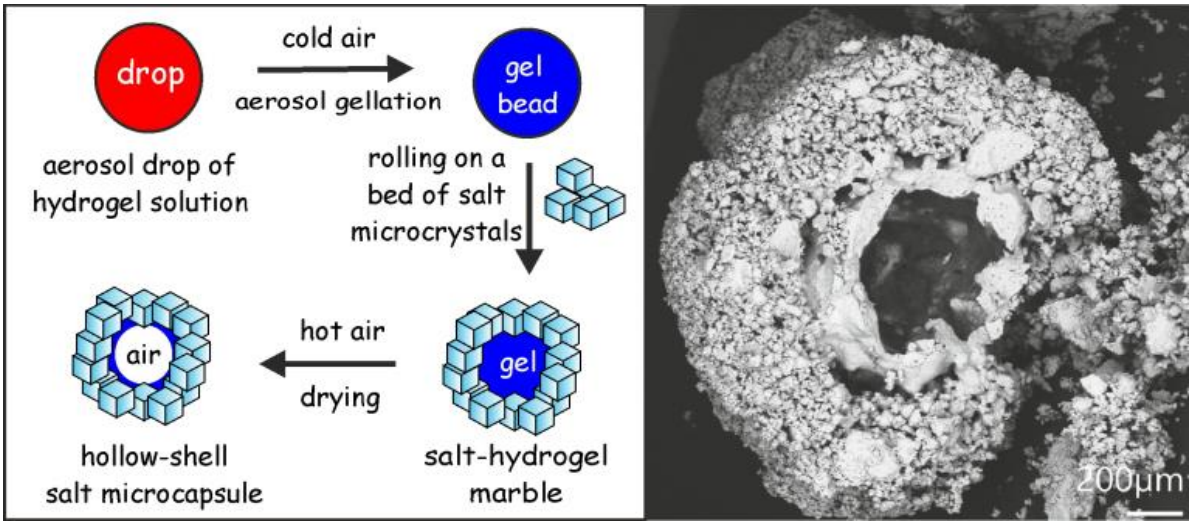

Fig. 1. Possible outcomes in the fabrication of salt marbles: Top mechanism shows production of the salt granules, where the liquid drop wets the hydrophilic salt particles to form salt granules. The bottom mechanism shows the preparation of the salt-hydrogel marbles, where a gel bead is formed before rolling onto the bed of salt microcrystals. Here, the salt crystals cannot penetrate into the hydrogel core and form a shell around it. Hollow-shell salt microcapsules are produced upon drying of the salt-hydrogel marbles.

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CONSTRUCTION OF BIONANOPARTICLES WITH THE USE OF RECOMBINANT DNA VECTOR-ENZYMATIC SYSTEM CONTAINING ARTIFICIAL POLIEPITOPIC PROTEINS FOR DELIVERY OF NEW GENERATION VACCINES.

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DNA/RNA amplification technologies, such as the *Polymerase Chain Reaction* have revolutionized modern biology, medical diagnostics and forensic analyses, among others. A number of alternative nucleic acids amplification methods have been developed, tailored to specific applications. Here we present a refined version of a DNA fragment amplification technology, which enables the construction of ordered concatemers in a head-to-tail-orientation. A very high number of DNA segments, at least 500 copies, can be consecutively linked. Other key features include: (i) the application of a dedicated vector-enzymatic system, including selected subtype IIS restriction endonucleases, which has been designed to automatically generate long Open Reading Frames and (ii) an amplification-expression vector with a built-in strong transcription promoter along with optimal translation initiation signals, which allow for a high level of expression of the constructed artificial poliepitopic protein. This highly advanced technology makes it possible to obtain ordered polymers of monomeric, synthetic or natural, DNA far beyond the capabilities of current chemical synthesis methods. The constructed poliepitopic proteins are further used for construction of several types of nanoparticles, including inclusion bodies and bacteriophages, containing multiple genetic fusion with poliepitopic proteins.The technology offers significant advances in a number of scientific, industrial and medical applications, including new vaccines and tissue pro-regenerative methods. The technology is protected by an international patent application and is available for licensing.

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MICROBIOLOGICAL CHARACTERIZATION OF PSYCHRO-MEZO-THERMOPHILIC ENDOSPORE-PRODUCING BACILLUS SPECIES ISOLATED FROM INDUSTRIAL PROBIOTICS PARTICLES.

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Probiotics are either bacteria which naturally and steadily reside in the human gastrointestinal tract (GIT), such as certain Lactobacillus sp., or are bimodal, i.e. capable of proliferation both in GIT, as well as in the external environment, these include certain Bacillus sp. In this report we characterize a mixture of Bacillus species present in widely used commercial preparations, present in lyophilized particles. Four endospore-producing species were detected through MALDI TOF mass spectrometry and microbiological analyses: Bacillus mojavensis, Bacillus vallismortis, Bacillus pumilus and Bacillus subtilis. They exhibit an exceptionally wide range of growth temperature: from 20°C to 58oC, thus they are environmentally multi-modal and cover areas occupied both by psychrophiles, mesophiles and thermophiles. Thus, they are exceedingly adaptive to different environments and able to proliferate in highly diverse niches, including the human GIT. Considering that all of the four characterized species have similar characteristics, including endospore production and growth in a wide range of pH, which allows them to survive in transiently low pH during GIT passage, as well as their widespread occurrence in the environment, it is very likely that they have evolved along with mammals as their natural, transient or permanent, GIT inhabitants, though they are not limited to this niche.

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STIMULI SENSITIVE MICROCAPSULES WITH MACROPOROUS POLYMER SHELLS

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Key Words: microfluidics, capsules, porous materials, stimuli responsive materials.

Porous microcapsules are of great interest in diverse applications, ranging from encapsulation for controlled release, to catalyst support to filtration and purification systems in analytical science.
Here, we demonstrate a novel method to obtain porous microcapsules with polymer shells whose macroporosity and mechanical properties can be tuned within a wide range. Microcapsules are produced by microfluidics, using a co-flow flow-focusing glass capillary device to make water-oil-water (W/O/W) double emulsion templates. A mixture of acrylate monomers (glycidyl methacrylate and ethylene glycol dimethacrylate) and porogens (phthalate-based, alkanes or linear alcohols) is used as oil phase. Heterogeneous polymerization of the acrylate monomers leads to a biphasic structure in the capsule shell, in which a network of polymer beads is permeated by the liquid porogen. In the presence of hydrophobic porogens, the formation of a thin and tight polymer skin is observed on the inner and outer surfaces of the shell. This leads to sealed pores within the shell of the microcapsules, which can be used for the storage of chemicals in addition to the main encapsulant in the capsule core. As a proof of concept of such co-encapsulation of reactive compounds, we produced capsules loaded with separately stored monomers commonly used for two-components epoxy resins. Such capsules provide a rich platform for the design of solid adhesive and self-healing materials. Furthermore, the utilization of porogens with low boiling point, such as a short alkanes, leads to thermosensitive capsules that explosively release their content within seconds. Combining these capsules with magnetic particles heated by magnetic hyperthermia, we achieved a magnetic release of the capsules content within seconds and without over-heating the surrounding matrix. Incorporation of glycidyl methacrylate monomers results in polymer capsules with epoxy-functionalized surfaces, which can be further reacted with amine-based functional compounds. Exploiting such epoxy groups as anchors for grafting of sensitive polymers and for covalently attaching nanoparticles, we prepared multi-functional capsules with tailored shell structure and surface chemistries.

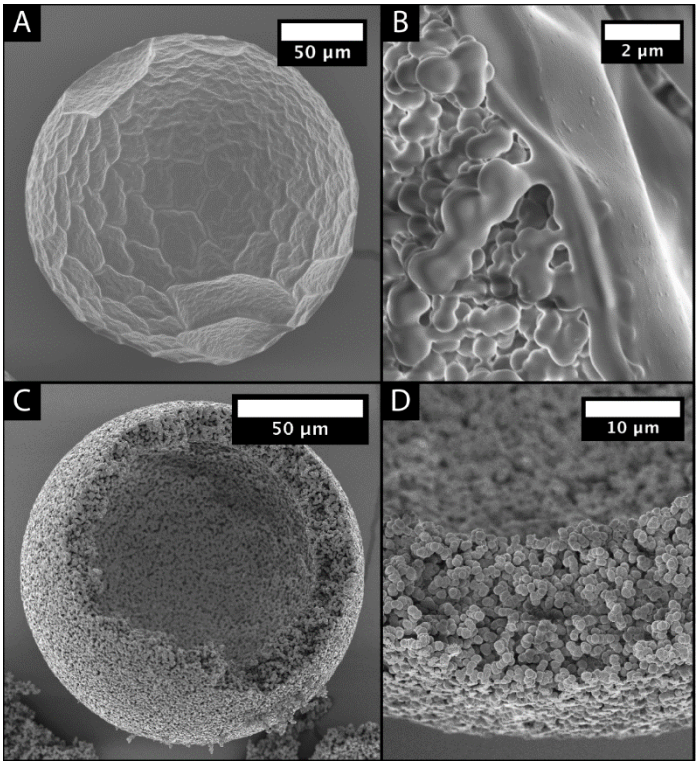

Figure 2 – A and B: Skin formation on capsules produced with 35 wt % of diisodecylphthalate. C and D: Open porous structure on capsules produced with 30 wt % undecanol.

PROBING NANOPARTICLE INTERACTIONS WITH BIOLOGICAL SYSTEM FOR DRUG DELIVERY APPLICATIONS

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Before any drug administered to the gastro-intestinal tract reaches the epithelium, it must traverse a layer of mucus. The main polymeric component of mucus is the glycoproteins collectively called mucins. These are complex gel-forming polymers which exhibit electrostatic, hydrophobic and H-bonding interactions and are responsible for the viscous and elastic gel-like properties of the mucus layer.

The efficacy of nanoparticles (NPs) to penetrate this layer, and deliver macromolecular drugs in therapeutic concentrations to the epithelium will depend on the surface chemistry (decoration) of the NPs. Quantifying the interactions between these NPs and the mucin gel is essential for designing successful drug delivery systems. In this project various decorations were fabricated, including zeta potential changing, slippery, and proteolytic enzymes. Figure 1 illustrates slippery and proteolytic enzyme decorated NPs penetrating a mucus layer that would stop conventional NPs.

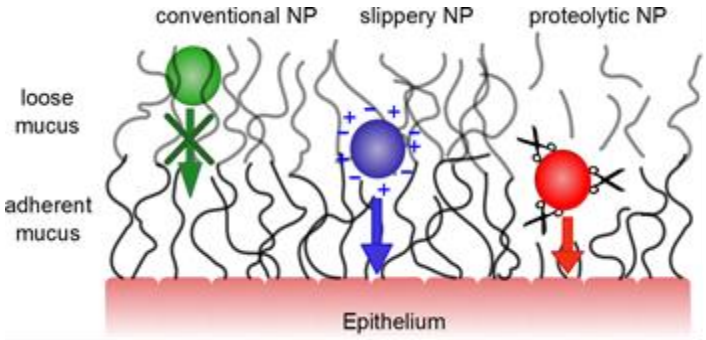

Figure 1: Possible scenarios of mucus interactions with particles of different surface chemistries

The effect of these NPs on the mobility of intestinal mucin gel was assessed by pulse-gradient-spin-echo NMR (PGSE-NMR); whereas the potential of the NPs to interact with the mucus and alter its tridimensional structure was investigated using two scattering techniques, small angle neutron scattering (SANS) and spin-echo SANS (SESANS).

The proteolytic strategy showed promising results, *i.e*. insertion of 0.5wt% of enzyme functionalized NPs to 5wt% intestinal mucin solution led to *c.a*. 2 fold increase in the mobility of the mucin molecules as measured by PGSE-NMR, this is indicative of a significant change in the structure of the mucin.
Scattering measurements also revealed a change in the mucus structure upon addition of functionalized NPs, occurring mostly at a lengthscale larger than 0.5µm.

CONTROLLING COMPETITIVE AND SYNERGISTIC INTERACTIONS IN FORMULATIONS

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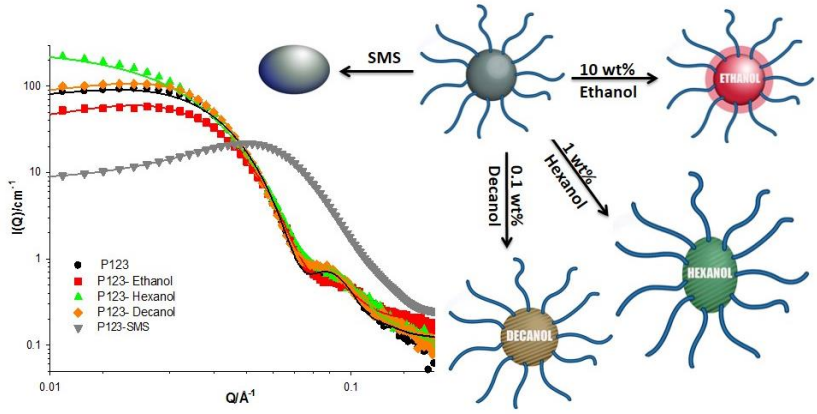
Amphiphilic block copolymers of the poly (ethylene oxide)–poly (propylene oxide) (PEO–PPO) group (commercially available as Pluronic or Poloxamers) are widely used in numerous applications, especially the pharmaceutical, consumer, technological and formulation areas. Whilst mixtures of small molecule surfactants and Pluronics have previously been examined, as has the effect of alcohols on Pluronic behavior, there are far fewer studies of the quaternary systems; Pluronic/small molecule surfactants/alcohol/water.

Against this background, we have employed a range of techniques including surface tension, pulsed gradient spin-echo nuclear magnetic resonance (PGSE-NMR) and small- angle neutron scattering (SANS) to quantify the interaction between these small molecule surfactants (sodium dodecyl sulphate, dodecyltrimethylammonium bromide and polyoxyethylene (23) lauryl ether) and short, medium and long chain alcohols (ethanol, hexanol and decanol respectively) on the critical micelle concentration (CMC) and subsequently the micellar structure. SANS data for aqueous Pluronic solutions with added alcohols fitted to a charged spherical core/shell model for the micelle. The addition of the surfactants led to significantly smaller, oblate elliptical mixed micelles in the absence of alcohols. Addition of ethanol to the system led to a decrease in the micelle size, whereas larger micelles were observed upon addition of longer chain alcohols. NMR studies provided a complementary estimate of the micelle composition using average diffusion coefficients. These observations extend our understanding of the synergistic interactions between the Pluronic and small molecule surfactants when the partitioning of the added alcohol perturbs the interaction between the two types of surfactants.



MICROENCAPSULATION OF MAGNESIUM AND BORON POWDERS FOR THE SYNTHESIS OF MAGNESIUM DIBORIDE

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Key Words: Microencapsulation, Magnesium, Boron, Magnesium diboride, Superconductor

Magnesium powders are highly reactive at room temperature and very volatile at elevated temperatures near melting point. This causes some difficulty in synthesizing superconducting magnesium diboride *via in-situ* reaction of magnesium with boron. It is thus desirable to coat the surface of magnesium with a protective layer of polymer for controlled synthesizing reaction. In the present work, both magnesium and boron particles were coated with cellulose-based polymers. The microencapsulation was carried out by mixing of magnesium/boron powders with cellulose-based polymers dissolved in the organic solvent such as dimethylformamide. Ethanol was then added to the mixture to precipitate polymers on the surface of magnesium and boron. The resulting encapsulated powders exhibited a quite good thermal and chemical stability up to ~300oC. The microencapsulated powders were mixed to give a stoichiometric composition of magnesium diboride, followed by a die compaction. The pellets were then *in-situ* reacted at different temperatures to form superconducting phase. The encapsulated powders as the starting material resulted in improved superconducting properties due to the controlled reaction of active materials.

FACILE SYNTHESIS OF SELF-HEALING MICROCAPSULES

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Key Words: Hydrogel, microcapsules, particle-stabilized, self-healing

In nature biological materials self-heal and adapt repeatedly to stresses caused by the environment. So far, major efforts have been made to create engineered microcapsules that can, upon rupturing, release a healing agent. To mimic the dynamic biological function, we create functional microcapsules that release self-healing agents, but may also themselves be healed, allowing for multiple release events. Currently there are many limitations in synthesizing microcapsules with self-healing hydrogel shells. We address these challenges with a facile strategy for synthesizing monodisperse hydrogel microcapsules by the deprotection and aqueous solubilization of an initially water-insoluble polymer shell. We use a microfluidic approach to produce w/o/w emulsions as a template for microcapsules [1], where the monomer is in the oil phase. Using such a technique one can prepare poly(acrylic acid) shell microcapsules by the deprotection of a poly(tert-butyl acrylate) shell microcapsule through hydrolysis [2]. Hydrophobic comonomers and water insoluble interpenetrating polymers may be included with the tert-butyl acrylate monomer in order to form microcapsules with self-healing shell materials such as semi-interpenetrating hydrogels or hydrophobic association hydrogels [3,4]. To stabilize self-healing microcapsules we used particle armoring as self-healing hydrogels posses sticky surfaces and tend to aggregate [5]. With this work we demonstrate an easy approach to produce microcapsules with self-healing shells. These capsules will open up the possibility of repeated release from microcapsules, taking a step closer to reproducing self-healing processes seen in nature.

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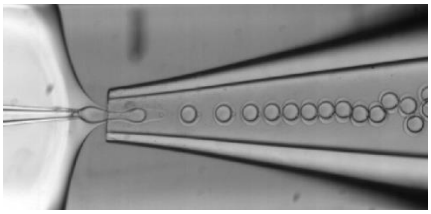

Figure 1. Synthesis of poly(tert-butyl acrylate) microcapsules using a combination of alumina nanoparticles and surfactant as stabilizers.

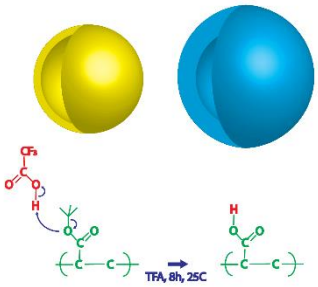

Figure 2. Hydrolysis of poly(tert-butyl acrylate) microcapsule to form poly(acrylic acid) hydrogel microcapsule.

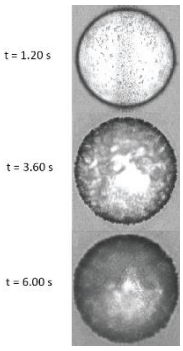

Figure 3. Oil droplets in water, stabilized by alumina nanoparticles at increasing residence time in a microfluidic channel.