Bioencapsulation Research Group

Bioencapsulation Innovations

June 2013

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We are waiting your contributions for the December 2013 on Enzyme encapsulation

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EDITORIAL

MICROFLUIDICS AND MICROENCAPSULATION

At the beginning of the 90s, Andreas Manz started to use microfabrication approaches for chemical applications and today is commonly known as microfluidics. Microfluidic chips are based on micro-scale channel wherein liquids flow, enabling a high control of their movement. Since the beginning, the field has been continuously growing as the microfluidics applications expand ranging from pressure regulators to organic synthesis and immunoassays. The growth of this field is demonstrated by the creation of specific peer-reviewed publications, such as Microfluidics and Nanofluidics and Lab-on-chip, and periodically conferences. Microencapsulation is included among the various uses of microfluidics. In fact, microfluidics have enabled the implementation and high control of a very complex process such as microencapsulation in just some millimeters of surface!

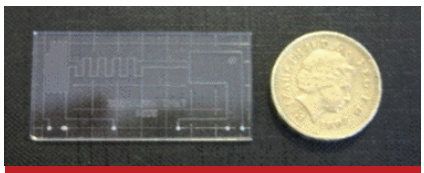
Andreas Manz

In order to manufacture particulate solids such as microcapsules, the process through microfluidics may have some advantages: the control of the particle size and its distribution, the capsules payload as well as the wall thickness. Beyond the capsule size control, microfluidics can also be used to produce controlled capsule shapes different from spherical, such as cylindric shapes. In summary, microfluidics are a highly advanced tool for tailoring the physical features of microcapsules.

Apart from the capsule geometry, another important feature for microcapsules is their wall since it is closely linked to the trigger mechanism. Within microfluidics, different processes have been used to form the capsule wall. Examples of these processes are coacervation, radical and interfacial polymerization and even colloidosomes. These processes could provide capsule walls with different types of triggers such as temperature, compression, pH, and so on. If the level of trigger applied to release the active is somehow related to the geometrical properties of the capsules, all the capsules obtained at the same conditions by microfluidics will release the active virtually at the same time and moment. This is one of the major advantages of using microfluidics for microencapsulation:

Microcapsule Uniformity.

From the industrial point of view, the main drawback of microfluidics is its production rate. Making capsules one-by-one entails a low production yield, and this fact makes this technology less cost effective. One of the main challenges for microencapsulation by microfluidics is the scaling up, in other words to increase microcapsule throughput with good property control of microcapsule. The first thought would be the parallel stacking of microchips in order to obtain a larger production rate, however, without any type of chip-pump system integration, the footprint and capital investment of the installation would become unaffordable. In any case, the coming years seem to be a very exciting time for the development of new microcapsules by using microfluidics and the scaling up of this technology to reach an actual industrial scale.



Microfluidic Chip

We hope that the current issue will get you informed as a first step in this exciting and expanding new field of encapsulation.

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CONFERENCES , WORKSHOPS ... CALENDAR

PROGRAM 2013

June

ESACT meeting
23-26 June 2013 – Lille, France
http://www.esact.org/index.aspx?p=NewsPage&NewsId=44

Bioencapsulation Research Group

16th Industrial Symp. and 6th Trade Fair on Microencapsulation
June 25-27, 2013 - Madison, USA
http://bioencapsulation.net/2013_Madison

ESACT meeting
23-26 June 2013 – Lille, France
http://www.esact.org/index.aspx?p=NewsPage&NewsId=44

17th Gums & Stabilisers for the Food Industry Conference
June 25th -28th 2013 - Glyndwr University, Wrexham, UK
http://www.gumsandstabilisers.org

JuLy

7th Annual PSSRC Symp.
«Advanced Characterization methods for Solid Pharmaceutical Dosage Forms»
July 5, 2013, Lille, France
http://www.apgi.org/pssrc_2013/

Powders & Grains 2013
July 8-12, 2013 - Sydney, Australia
http://www.pg2013.unsw.edu.au

August

ISOPOW XII conference –
August 19 – 23, 2013 - Fiskebäckskil, Sweden
http://www.isopow.org/

Bioencapsulation Research Group

21st International Conference on Bioencapsulation
August 28-30, 2013 - Berlin, Germany
http://bioencapsulation.net/2013_Berlin

September

19th International Symposium on Microencapsulation
September 09-11, 2013 Pamplona, Spain
http://www.symposiummicroencapsulation2013pamplona.com

3rd Conference on Innovation in Drug Delivery
Sept 22-25, 2013 - Pisa, Italy
http://www.apgi.org

PROGRAM 2013

Septembre

3rd Conference on Innovation in Drug Delivery
Sept 22-25, 2013 - Pisa, Italy
http://www.apgi.org

Continuous particle processing - TTC workshop 189
Set. 24-26 2013 – Weimar, Germany
http://www.ttc-binzen.de/cm/index.php?id=522

Powder handling, quality control, and applied powder technology
Sept 26-27 2013 - Copenhagen, Denmark
http://powderinfonews.com/wp-content/uploads/2012/10/Course-flyer-20131.pdf

5th Symposium on Delivery of Functionality in complex food systems
Sept 30-Oct 3 2013 - Haifa, Israel
http://DOF2013.org

October

Nano2013.pt
Oct 11, 2013 - Lisbon, Portugal
http://fcts.ulusofona.pt/index.php/eventos/simposios/details/64-Nano%202013

Pan Coating - TTC workshop 190
Oct 15-17, 2013 – Binzen, Germany
http://www.ttc-binzen.de/cm/index.php?id=511&L=0

Probio 2013
Oct 30-31 2013 – Montreal, P.Q., Canada
http://www.symposiumprobio.org

PROGRAM 2013

November

Pellets and Micropellets for oral multiparticulate dosage forms
Nov. 26-28, 2013 – Binzen, Germany
http://www.ttc-binzen.de/cm/index.php?id=533

Decembre

GTRV Annual Metting 2013
Dec. 2-4, 2013 – Orleans, France
http://www.gtrv.fr/?page_id=3267&lang=en

PROGRAM 2014

Janvier

International Symposium on Polyelectronites
Ein Gedi, Israel - Janauary 20-23, 2014
http://www.ortra.com/events/isp2014/

March

Bioencapsulation Research Group

VI Training School on Microencapsulation
March 4-8, 2014 - Nha Trang, Viet Nam
http://bioencapsulation.net/2013_Nha_Trang (to be open soon)

OPEN POSITION

UNIVERSITÉ LAVAL

Professor in Food Science and technology

Develop a research program in the field of Food Science and Technology in sectors relating to the eco-efficiency of milk and food processing.

Candidates should submit a letter of intent, their curriculum vitae and three letters of reference before August 18th 2013 to :

Prof. Gisèle LaPointe
Dpt sciences des aliments et de nutrition
Faculté des sciences de l'agriculture et de l'alimentation, Université Laval
Local 1312-A, Pavillon Paul-Comtois
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ARTICLE

FUNCTIONAL DROPLETS, MICROCAPSULES AND COLLOIDOSOMES MADE BY MICROFLUIDICS

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ENCAPSULATION THROUGH MICROFLUIDICS

The encapsulation and controlled release of reactive agents play a vital role in medicine, cosmetics, food and materials science. Some illustrative examples include the targeted release of pharmaceutical drugs, the protection of flavors and fragrances or the release of healing agents in self-healing materials.

Such varied applications require simultaneous control and tuning of numerous capsule parameters, including their size, permeability and mechanical properties, which can be difficult to achieve with traditional encapsulation techniques. Instead, double emulsion templates made using microfluidics can offer substantial advantages due to its inherent precision and control of a wide range of processing variables.

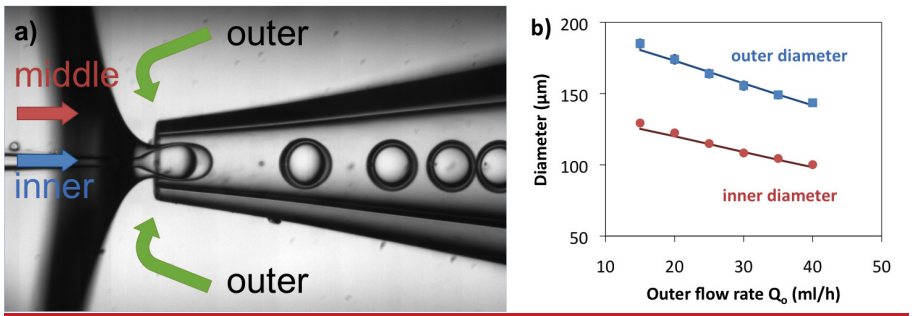

Fig. 1: a) Formation of w/o/w double emulsions within a microcapillary device. b) Control of emulsion sizes through tuning of flow rates. Reprinted with permission from (Chen, 2012). Copyright 2011 American Chemical Society.

In our work, we utilize established glass capillary microfluidic devices (Utada, 2005) to create deliberately tailored double emulsions that can be used directly as functional nanoliter carriers or can be further processed to obtain functional microcapsules or colloidosomes. Here, we describe a few examples of encapsulation systems that can be produced through microfluidic emulsification. We focus on water/oil/water (w/o/w) double emulsions that are obtained by first dripping an aqueous liquid into an immiscible oil to generate droplets, which are then dripped into an outer aqueous phase (Fig. 1a). By proper selection of the liquid phases we can create a variety of encapsulation systems, from responsive double emulsions to functional capsules with inorganic or polymeric shells.

The size of the double emulsions and thus the capsules can be easily varied through the flow rates and the capillary dimensions. To understand the dependencies of the outer droplet size do on these parameters, we developed an analytical model based on a balance between the shear forces promoting droplet break-up and the interfacial tension opposing it (Erb, 2011). The model shows close agreement with experimental and literature data (Fig. 1b), allowing us to predict capsule sizes based on the flow rates, fluid parameters and device dimensions.

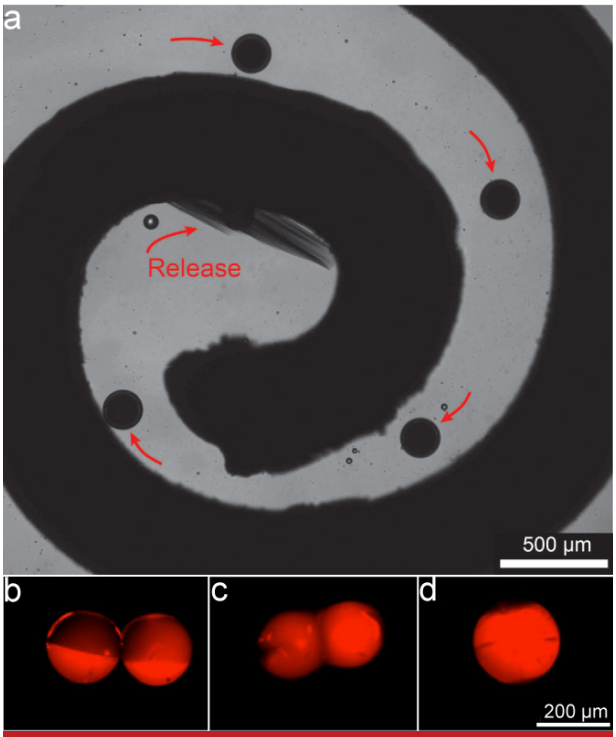

Fig. 2: a) Overlay of images showing magnetically guided transport and rupture of a double emulsion droplet with magnetic particles in the innermost phase. b-d) Magnetically induced fusion and mixing of the middle phase of two double emulsion droplets. Reprinted with permission from (Sander, 2012). Copyright 2012 Wiley & Sons.

MAGNETICALLY RESPONSIVE NANOLITER DROPLETS

By incorporating superparamagnetic iron oxide nanoparticles (SPIONs) in either the middle oil or innermost aqueous phase of double emulsion droplets, we can create soft microcarriers that are responsive to magnetic fields (Sander, 2012). In this case, the stability of the double emulsion is adjusted so that at low magnetic fields the droplets can be manipulated or chained, whereas at high magnetic fields the middle oil phase is disrupted to eventually release the innermost water phase. Since the SPIONs can be selectively added either to the innermost aqueous or the middle oil phase, undesired interactions between SPIONS and the cargo are minimized. The stability of the emulsion droplet is not only governed by the attractive magnetic force acting between them but also by the repulsive force arising from surfactant molecules on the liquid surface. For magnetized single emulsion droplets stabilized by a charged surfactant, we find that the magnetic force needed to fuse them can be reduced significantly upon addition of ions that screen the repulsive

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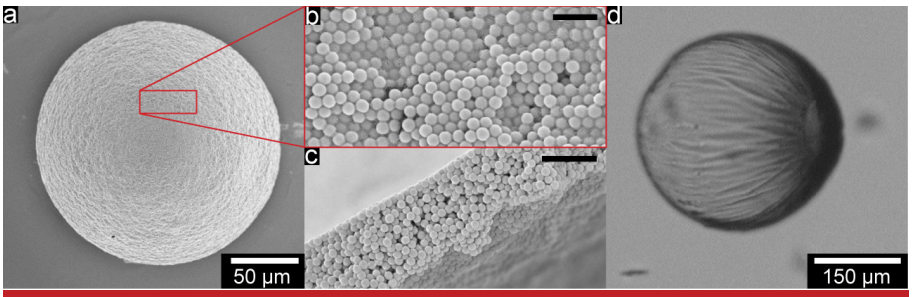

Fig 3: a)-c) Scanning electron microscopy images of a colloidosome made from densely packed silica particles. Scale bars: 200 nm (in b) and 1 µm (in c). d) Microscopy image of a magnetic Fe3O4-SiO2 Janus colloidosome. Reprinted with permission from (Sander 2011). Copyright 2011 American Chemical Society.

force. The deliberate control over the stability of double emulsion droplets and our ability to transport them using magnetic fields enables us to selectively release reactive particles from the innermost aqueous phase in order to initiate local reactions or to mix nanoliter amounts of reagent by fusion of the middle oil phase (Fig. 2).

FUNCTIONAL COLLOIDOSOMES

Double emulsions made by microfluidics can generate solid microcapsules upon consolidation of the middle oil phase after emulsification. In one possible approach, colloidal particles can be added to the middle phase to generate hollow capsules with a shell made of nanoparticles upon removal of the oil. Such microcapsules, known as colloidosomes, exhibit a rigid shell that is selectively permeable to molecules that are small enough to diffuse through the particle interstitials. This controllable permeability makes colloidosomes very interesting for encapsulation and release applications as well as for microreactors. Assembly of colloidosomes from double emulsion templates allows for the formation of thick multiwalled colloidosomes (Lee, 2008). In a typical assembly process, the nanoparticles that will later constitute the shell are surface hydrophobized to enable efficient dispersion in the middle oil phase during the microfluidic double emulsification. Because of the shorter timescales of microfluidic emulsification as compared to conventional mixing processes, stabilization of the double emulsion templates is crucial for the successful preparation of colloidosomes. This is especially important for particle-stabilized systems due to the slow kinetics for particle adsorption at the oil-water interface. Partially hydrolyzed poly(vinyl alcohol) added to the aqueous phase was shown to efficiently stabilize the double emulsion templates by rapidly forming a strong viscoelastic interfacial film together with the nanoparticles initially present in the oil phase (Sander, 2012). Since the toluene used as middle oil phase displays a certain solubility in water, it can be slowly dissolved in the continuous phase while the nanoparticles are jammed together to form the capsule shell. By adjusting the surface chemistry of initially hydrophilic particles we are able to make colloidosomes from many different materials, leading to functional shells that are for instance photocatalytically active, bioresorbable or magnetic (Fig. 3) (Sander, 2011).

POLYMER MICRO-CAPSULES WITH TUNABLE MECHANICS

Solid capsules can also be formed by using a monomer solution as the middle oil fluid and polymerizing the double emulsions via UV light. UV polymerization of the middle phase can be carried out *in situ* and takes only a few minutes or less. To facilitate droplet formation through dripping at the capillary tip (Fig. 1), we use hydrophobic, low-viscosity acrylate monomers as the middle oil phase. By choosing different monomer compositions and various additives such as plasticizers, cross-linkers and reinforcing particles, we can easily tune the permeability and mechanical properties of the resulting capsule shell (Chen, 2012). For example, high glass transition temperature (T_g) monomers such as isobornyl acrylate (IBOA) will lead to brittle shells, while monomers with low T_g such as 2-phenoxyethyl acrylate (PEA) result in elastomeric capsules (Fig. 4). Thereby, capsule mechanics can be adapted to specific situations. For instance, brittle capsules that are stiffer but fracture at low strains are suitable for self-healing applications, where release at low external strains is desirable. In contrast, elastomeric capsules are useful in applications that demand effective protection of the encapsulant. In this case, the extensive and partially reversible deformation of the shell can absorb large amounts of strain energy, thereby preventing release of the encapsulant.

CONCLUSION

Double emulsions made using microfluidics are versatile templates for a multitude of encapsulation, delivery and storage systems. The high degree of control and compatibility with different materials provided by microfluidics enables the production of highly monodisperse soft carriers or functional capsules with tailored size, chemistry, permeability and mechanical strength.

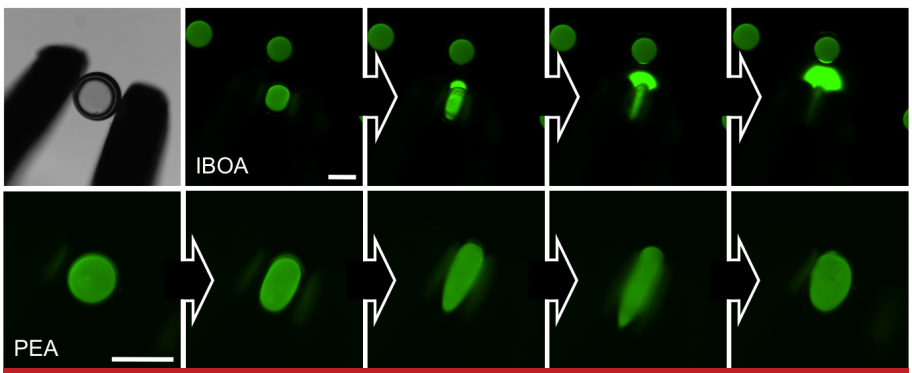

Fig. 4: Manual deformation of microcapsules filled with a fluorescent dye. Brittle capsules (top row, Ø 140 µm) fail after low amounts of strain, while ductile capsules (bottom row, Ø 140 µm) can be deformed extensively and reversibly without failure. Reprinted with permission from (Chen, 2012). Copyright 2011 American Chemical Society.

ARTICLE

REFERENCES

1. Utada, A.; Lorenceau, E.; Link, D.; Kaplan, P.; Stone, H.; Weitz, D., Monodisperse Double Emulsions Generated from a Microcapillary Device. Science 2005, 308, (5721), 537-541.
2. Erb, R. M.; Obrist, D.; Chen, P. W.; Studer, J.; Studart, A. R., Predicting sizes of droplets made by microfluidic flow-induced dripping. Soft Matter 2011, 7, (19), 8757-8761.
3. Sander, J. S.; Erb, R. M.; Denier, C.; Studart, A. R., Magnetic Transport, Mixing and Release of Cargo with Tailored Nanoliter Droplets. Advanced Materials 2012, 24, (19), 2582-2587.
4. Lee, D.; Weitz, D., Double Emulsion-Templated Nanoparticle Colloidosomes with Selective Permeability. Advanced Materials 2008, 20, (18), 3498-3503.
5. Sander, J. S.; Isa, L.; Ruhs, P. A.; Fischer, P.; Studart, A. R., Stabilization mechanism of double emulsions made by microfluidics. Soft Matter 2012, 8, (45), 11471-11477.
6. Sander, J. S.; Studart, A. R., Monodisperse Functional Colloidosomes with Tailored Nanoparticle Shells. Langmuir 2011, 27, (7), 3301-3307.
7. Chen, P. W.; Erb, R. M.; Studart, A. R., Designer Polymer-Based Microcapsules Made Using Microfluidics. Langmuir 2012, 28, (1), 144-152.

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André R. Studart has published 78 scientific papers in international peer-reviewed journals, holds seven patents and is co-author of an undergraduate textbook on ceramic processing. His main research interests are on bioinspired complex materials with potential applications as medical implants, energy conversion systems and smart structures. In addition to his current activities on complex materials, he has also carried out research on novel methods for processing of refractory castables and near-net-shape advanced ceramics (PhD thesis), mechanical properties of dental materials and ceramics processed through colloidal routes (post-doctoral work at ETH Zurich), and porous inorganic materials obtained using microfluidic techniques (post-doctoral work at Harvard University).

CONFERENCE

19th International Symposium on Microencapsulation

Discretization of Materials to Improve Added Value: Targeting - Controlled Release - Increased Availability - Shelf Life

Pamplona (Spain), September 09-11, 2013

The International Society on Microencapsulation is pleased to announce the 19th appointment of its symposium. The International Symposium on Microencapsulation has become a very well known scientific symposium related to the preparation, properties and uses of small particles; from conventional microcapsules to all other small particulate systems including micelles, polymers or self assembling structures that involve preparative manipulation. This time the meeting will try to focus on relevant uses of these devices for industrial, pharmaceutical, biotechnology, cosmetic and food applications. We believe that this important event will be a unique opportunity to share experiences and solve current problems and challenges in practice.

This 19th Symposium will take place at the Congress Auditorium of the University of Navarra in Pamplona, from the 9th to the 11th of September 2013. Please do not forget these dates and mark them clearly in your agenda.

http://www.symposiummicroencapsulation2013pamplona.com

ARTICLE

MICROFLUIDIC GENERATION OF NANOFIBRILLAR MICROGELS

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INTRODUCTION

Cell fate is influenced by multiple external cues, including exposure to soluble growth factors, interactions with neighboring cells, and biophysical properties of the surrounding extracellular matrix (ECM) (A. Atala, 2008). Understanding and reproducing the properties of cellular microenvironment is vital in tissue engineering, wound healing and treatment of diseases. Over the past several years, three-dimensional (3D) culture in hydrogels made from synthetic and natural polymers has gained great interest in biomedical research, as it offered the ability to analyze of a variety of factors that determine cell fate in complex natural ECM. Furthermore, the encapsulation and subsequent cell culture of cells in micrometer-size hydrogel modules or microspheres (microgels) acting as 3D microenvironments offerred control over the shear forces imposed on cells, the ease of cell visualization, and the transport of oxygen, nutrients and growth factors to the encapsulated cells.

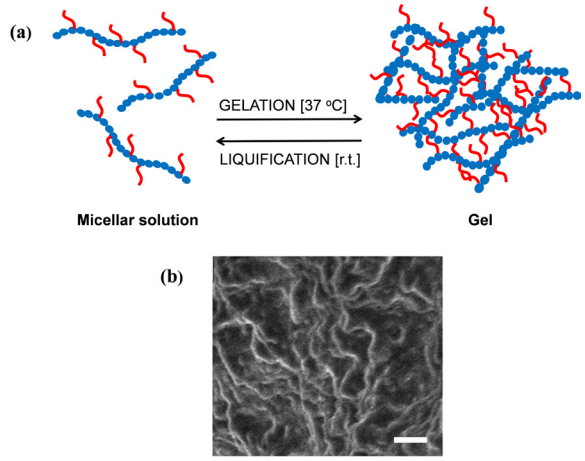

Figure 1. (a) Schematic of temperature mediated formation of the hydrogel from worm-like micelles. The blue and red colours correspond to the polystyrene core and the poly(N-isopropylacrylamide) corona of the micelles, respectively. (b) Representative images of the hydrogel structure. The scale bar is 5 μm.

Physically crosslinked hydrogels formed by biopolymers provide a biocompatible, non-cytotoxic cellular environment, yet, natural polymers vary in composition and molecular weights, depending on the polymer source. The utilization of synthetic polymers enables a systematic control of their composition and molecular weight, however chemically mediated gelation process poses the requirements of mild crosslinking chemistry, without compromising cell viability (M. P. Lutolf and J. A. Hubbell, 2005).

MICELLAR GELS AS 3D MICROENVIRONMENTS

Physical gelation of synthetic polymers is conceptually and practically appealing, as it combines the advantages of biopolymers and synthetic polymers and enables concomitant encapsulation of cells under close-to-physiological conditions. Self-assembly of block copolymers (Winnik et al. 2010) offers a very promising approach to producing artificial cellular microenvironments. It is currently well-established that micelles of block copolymers organize in networks (micellar gels), due to the association governed by, e.g., hydrophobic forces, hydrogen bonding or electrostatic interactions between one of the blocks of the copolymer. The reversible nature of association offers the possibility of tuning the dynamic interactions between the cells and their microenvironment by local degradation and remodelling of the matrix by the cells. Furthermore, the utilization of stimulus-responsive hydrogels that dissociate 'on demand' helps to solve some of the technical challenges in post-culture cell analysis. For example, 3D gels may scatter light, which makes it difficult to analyze embedded cells by conventional microscopy. Post-culture digestion of gels with the release of cells is a beneficial for the subsequent characterization of cells by e.g. fluorescence-activated cell sorting. Finally, hydrogels formed by cylindrical micelles (versus spherical micelles) have the structure that may mimic the nanofibrillar morphology of natural ECM (Figure 1). While the self-assembly of peptide amphiphiles in nanofibrillar gels showed great promise as an artificial scaffold for directed cell differentiation (Stupp et al. 2004), the formation of synthetic, block copolymer hydrogels for their potential use as artificial ECMs has not been reported, although the recent work of Armes et al. 2012 showed the feasibility of this approach.

GENERATION OF NANOFRIBILLAR THERMOREVERSIBLE MICROGELS BY USING MICROFLUIDICS

Recently, microfluidics (MFs) offered a very promising route to the generation of large libraries of cellular microenvironments with controllable, yet, tunable dimensions, compositions and physical properties that can be used to study a complex relationship between a large ranges of chemical compositions and biophysical properties of microgels and cell fate. In the present contribution, we report MF preparation of nanofibrillar temperature-responsive microgels derived from worm-like polymer micelles, and demonstrate a model system that can be used for the encapsulation and on-demand release of the encapsulated cells (Kumacheva et al. 2013).

We generated microgels from aqueous solutions of worm-like micelles of the temperature-sensitive poly(N-isopropylacrylamide)-block-polystyrene copolymers (Figure 2). Precursor droplets were generated by MF emulsification of the micellar solution in a PBS buffer at room temperature (below the low critical solution temperature of the poly(N-isopropyl acrylamide) and subsequent gelation of the droplets by increasing their temperature above the gelling temperature of 28 °C.

The reported method offered the following novel and potentially useful features: (i) The thermoreversible nature of the copolymer provided three crucial advantages. First, a low viscosity of the micellar solution allowed its stable MF emulsification at room tem-

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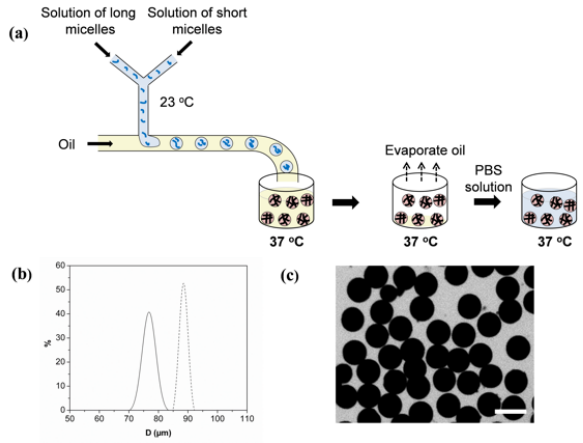

Figure 2. (a) Schematic of MF preparation of thermoreversible micellar microgels. (b) Distribution of the diameters of droplets (dotted lines) and of the corresponding micellar microgels (solid lines). (c) Typical optical microscopy images of the microgels generated. The scale bar is 100 μm. The particles were imaged and analyzed at 37 °C.

perature, which is a typical challenge for moderately concentrated polymer solutions. Second, polymer gelation occurred at a physiological temperature. Third, following incubation at 37 °C, the microgels could be readily liquified by cooling the system below its gelation temperature and releasing potential species (Figure 3). To mimic the temporary encapsulation of cells within the thermoreversible hydrogel, we encapsulated 6 μm-diameter poly(methyl methacrylate) microbeads coated with a fluorescent dye fluorescein isothiocyanate ((FITC) in the gel formed by short micelles and studied microbead release upon cooling the gel (Figure 4). The microgels had a nanofibrillar morphology and the porosity on the scale of cellular processes. (ii) The utilization of MFs provided the capability to generate microgels with narrow size distribution and at relatively high (10 s^{-1}) frequency of microgel formation, as well as the ability to vary microgel composition in a high-throughput manner.

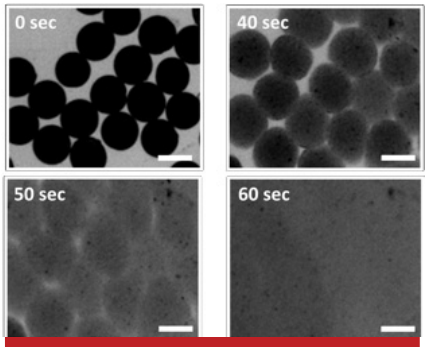

Figure 3. Optical microscopy images of the microgels undergoing dissolution in PBS solution at 25 °C. The scale bar is 100 μm

CONCLUSIONS

The reported microgels exhibit several advantageous features such as the nanofibrillar structure and rapid, reversible sol-gel transitions under near-physiological conditions. Hydrogel dissociation demonstrates the concept of post-culture cell release for further characterization. The ability to form microgels by the MF method offers two other potentially useful characteristics such as the narrow microgel size distribution and a short dissociation time. Our work offers a new concept for the generation of dynamic artificial three-dimensional microenvironments for studies of cell fate.

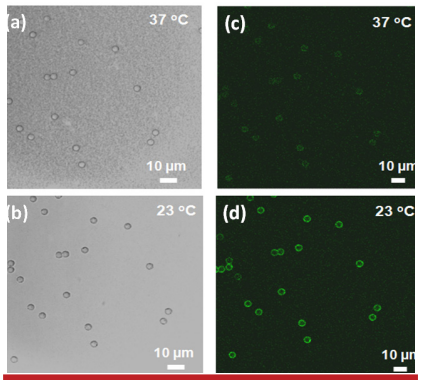

Figure 4. Transmission (a,c) and fluorescence optical microscopy images (b,d) of FITC-coated microspheres in the gel (a,b) at 37 °C and in the liquid state at 25 °C (c,d). The scale bar is 10 μm.

REFERENCES

1. A. Atala, Principles of Regenerative Medicine, Second Ed., Academic Press, Burlington, 2008.
2. M. P. Lutolf, J. A. Hubbell, Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering, Nat. Biotechnol., 2005, 23, 47-55.
3. A. Winnik, Nanofiber micelles from the self-assembly of block copolymers, Trends Biotechnol., 2010, 28, 84-92.
4. G. A. Silva, C. Czeisler, Kr. L. Niece, E. Beniash, D. A. Harrington, J. A. Kessler, S. I. Stupp, Selective Differentiation of Neural Progenitor Cells by High-Epitope Density Nanofibers, Science, 2004, 303, 1352-1355.
5. A. Blanazs, R. Verber, O. O. Mykhaylyk, A,. J. Ryan, J. Z. Heath, C. W. I. Douglas and S. P. Armes, Sterilizable gels from thermoresponsive block copolymer worms, J. Am. Chem. Soc., 2012, 134, 9741-9748.
6. D. Velasco, M. Chau, H. Thérien-Aubin, A. Kumachev, E. Tumarkin, Z. Jia, G. C. Walker, M. J. Monteiro and E. Kumacheva, Nanofibrillar thermoreversible micellar microgels, Soft Matter, 2013, 9, 2380-2383.

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Diego Velasco received his BSc degree in Chemistry at University of Cordoba, Spain. He did his Ph.D. in Polymeric Materials from the Complutense University of Madrid in 2011. His thesis was carried out in the Institute of Polymer Science and Technology (ICTP) and focused on the design of new stimuli sensitive polymers with applications in pharmacy and biomedicine. In 2011 he joined the group of Professor Eugenia Kumacheva as a postdoctoral fellow. His research interest lies in the use of microfluidic technology for the generation of microgels for cell encapsulation.

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Eugenia Kumacheva is the Canada Research Chair in Advanced Polymer Materials. She received her PhD degree in Physical Chemistry of Polymers at the Institute of Physical Chemistry (Russian Academy of Science). She did her postdoctoral research in Polymer Physics at the Weizmann Institute of Science. Since 1996 Eugenia Kumacheva has been a Professor in the Department of Chemistry at the University of Toronto. Her research interests include thin polymer films, polymer materials with structural hierarchy, synthesis of polymers in microfluidic reactors, conceptualization and design of polymer nanostructured materials, materials for 3D optical memory storage, optical limiting and switching, security documents, and delivery of anticancer drugs.

ARTICLE

MICROFLUIDIC FABRICATION OF SMART MICROCAPSULES WITH SQUIRTING RELEASE MECHANISM

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WHY SMART MICROCAPSULES WITH SQUIRTING RELEASE MECHANISM ARE NEEDED?

In biomedical fields, microcapsules are widely investigated as effective drug delivery carriers for the treatment of diseases such as cancers or tumors. Because most anticancer drugs have harmful side effects to the normal tissues, the most ideal delivery carriers should be able to transport and release the anticancer drugs specifically to the targeted tumor site without drug leakage during the transport process. For stimuli-triggered site-targeting delivery systems, the delivery triggered by physical contact may not be practicable in human body, and delivery triggered remotely is more preferable. Furthermore, some biological tissues present diffusion obstacles for drugs and/or their surrounding media are quite viscous, in which situations higher initial momentum for the drug delivery is very important for achieving a desired wide distribution of drugs at the targeted site. Therefore, smart microcapsules with squirting release mechanism, which can protect drugs before desired delivery and trigger the delivery with a large initial momentum only at diseased tissue by certain local physical or chemical signals, would be very useful for efficient therapy of a range of diseases including cancers and other site-specific diseases.

HOW TO DESIGN SMART MICROCAPSULES WITH SQUIRTING RELEASE MECHANISM?

Currently available anticancer drugs such as paclitaxel and carmustine are usually lipophilic molecules. Besides, some nanoparticles, such as proteins, liposomes and micelles, are promising candidates for targeting drug delivery systems, but they usually exhibit low physical and chemical stability. Therefore, design of smart microcapsules with squirting release mechanism for lipophilic drugs and nanoparticles is of great importance and necessity. Similar squirting release behaviours can be found in some plants in nature when they eject seeds from fruits for the widest possible distribution. For example, the ripe fruit of ecballium elaterium (Figure 1A), also called squirting cucumber or exploding cucumber, is highly turgid. On its own ripeness or being disturbed by

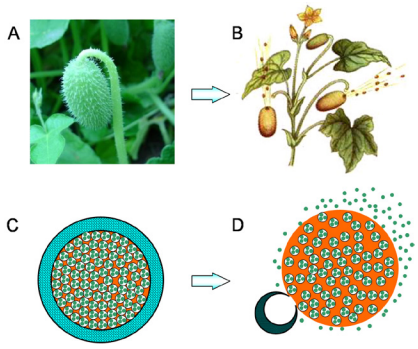

Figure 1. A) A picture of squirting cucumber; (B) Schematic illustration of squirting cucumbers ejecting seeds together with a stream of mucilaginous liquid; (C) A microcapsule with crosslinked smart hydrogel shell containing oil phase or nanoparticles in the inner water phase of W/O emulsion core; (D) Oil phase or nanoparticles together with the oil phase stream being squirted out from the microcapsule due to the dramatic shrinkage and sudden rupture of the hydrogel shell triggered by environmental stimuli [1].

sniffing animals or whatsoever, the ripe fruit squirts a stream of mucilaginous liquid containing its seeds into air for a considerable long distance by a sudden contraction of the wall of the fruit (Figure 1B). Inspired by the squirting cucumber, we design a novel family of smart microcapsules with squirting release mechanism (Figure 1C,D). The proposed microcapsule is composed of a crosslinked smart hydrogel shell with stimuli-responsive property, and encapsulates oil phase or water-based nanoparticles by dispersing the aqueous phase that containing nanoparticles into the oil phase core (Figure 1C). Upon recognizing environmental stimuli, the hydrogel shell shrinks rapidly, which results in a sudden increase of the liquid pressure inside the microcapsule because the oil phase in the capsule is incompressible. When the internal pressure increases to a critical value, the hydrogel shell ruptures suddenly due to its limited mechanical strength, at the same time the encapsulated substances are squirted out from the microcapsule together with the oil phase stream into the environment with a large momentum (Figure 1D), just like the seed-ejecting of ripe squirting cucumber.

MICROFLUIDICS TECHNIQUE PROVIDES AN EFFICIENT AVENUE FOR FABRICATING SMART MICROCAPSULES WITH SQUIRTING RELEASE MECHANISM

To fabricate smart microcapsules with squirting release mechanism, monodisperse multiple emulsions with precise control of interior structures are necessary as templates for synthesis. Recently, a novel type of scalable microfluidic devices that based on assembly of glass capillaries have been developed for generating monodisperse multiple emulsions with precise control of both the size and number of the inner droplets [2,3]. Figure 2 shows the schematic illustration of the fabrication of monodisperse O/W/O double emulsions in a capillary microfluidic device and the template synthesis of core-shell microcapsules with squirting release mechanism [3]. The microfluidic device is assembled as follows. The outer diameter of cylindrical capillaries is 1.0 mm, and the inner dimension of square capillary tubes is also 1.0 mm. The end of injection tube and transition tube are tapered by a micropuller and then adjusted by a microforge. Three cylindrical capillaries are respectively used as the injection tube, transition tube, and collection tube by aligning them coaxially inside the square capillaries. To prepare O/W/O double emulsions, the inner, middle and outer fluids are separately pumped into the injection tube, transition tube and collection

tube of capillary microfluidic device. Monodisperse O/W/O double emulsions generated in collection tube are collected in collection solution. After that, double emulsions in the collection solution are converted into microcapsules by polymerization of the aqueous middle layer into hydrogel shell. The polymerization can be initiated by certain methods, including oxido-reduction [2] and UV irradiation [3]. Because the structures of O/W/O double emulsions can be precisely controlled in microfluidics, the shell and interior structures of smart microcapsules with squirting release mechanism can be effectively controlled via microfluidics technique.

THERMO-RESPONSIVE MICROCAPSULES WITH SQUIRTING RELEASE MECHANISM

There are many cases in which environmental temperature fluctuations occur naturally and the environmental temperature stimuli can be easily designed and artificially controlled, thermo-responsive microcapsules with squirting release mechanism are desired for applications in these cases. With the above-mentioned microfluidics technique, smart microcapsules with thermo-responsive hydrogel membranes can be designed and fabricated with either O/W/O double emulsions or W/O/W/O triple emulsions as synthesis templates [2,3]. These microcapsules can be used for thermo-induced burst squirting release of lipophilic substances (Figure 2) [3], nanoparticles (Figure 3) [1], and/or both hydrophilic and lipophilic substances [2]. Usually, the thermo-responsive shells of these smart microcapsules are made of crosslinked poly(N-isopropylacrylamide) (PNIPAM) hydrogels. PNIPAM is a well-known thermo-responsive polymer with dramatic phase transition property when environmental temperature changes across its lower critical solution temperature (LCST). When the temperature is lower than the LCST, the PNIPAM hydrogel exhibits a swollen and hydrophilic state, while it shrinks dramatically and turns to hydrophobic when the temperature is higher than the LCST. In our microcapsule systems, the swollen and hydrophilic PNIPAM hydrogel membrane of the microcapsule can protect the encapsulated substances when the temperature is below the LCST. To ejecting the encapsulated substances into the environment with a large momentum, what we need to do is just applying a heat stimulus to increase the local environmental temperature above the LCST to cause the dramatic shrinkage of the PNIPAM hydrogel shell.

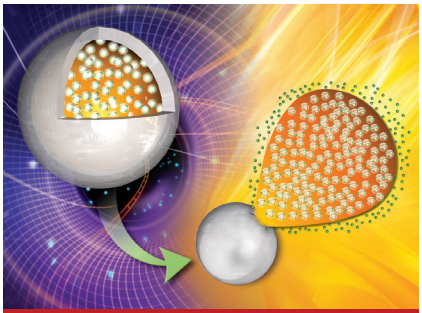

Figure 3. Thermo-triggered squirting microcapsule ejecting nanoparticles with a high momentum by the dramatic shrinkage and sudden rupture of hydrogel capsule membrane, just like a nanoparticle bomb [1].

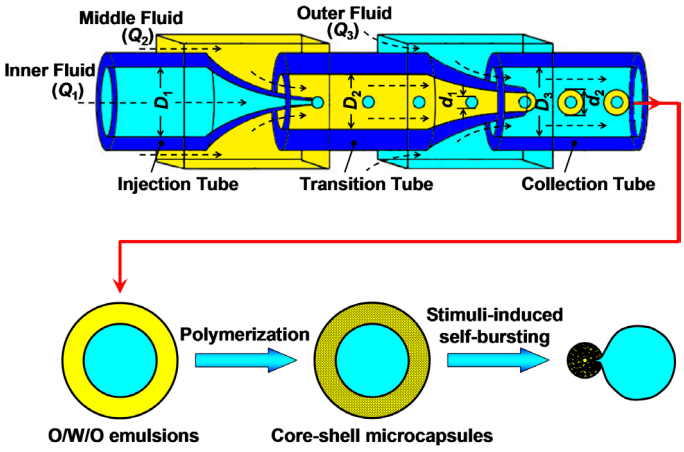

Figure 2. Schematic illustration of the fabrication of monodisperse O/W/O double emulsions in a capillary microfluidic device and the template synthesis of core-shell microcapsules with squirting release mechanism [3].

MOLECULAR-RECOGNIZABLE MICROCAPSULES WITH SQUIRTING RELEASE MECHANISM

Ion recognition and response are of fundamental importance in biological systems in nature, and also for a manifold of chemical, physical, biochemical and biomedical applications. Among physiologically important cations, strategies for K^+-recognition attract particular attention. At certain pathological sites in living organisms, serious cytoclasis or disabled K^+-Na^+ pump in cell membrane results in abnormal increase of extracellular K^+ concentration, which can be taken as an ion stimulus signal for designing self-regulated drug delivery systems. However, K^+-recognition in biomedical field is usually challenging due to interference arising from high Na^+ concentrations. Crown ethers are known for the unusual property of forming stable host-guest complexes with alkali metal ions. Although 15-crown-5 complexes best with Na^+ and 18-crown-6 favors K^+, a 2:1 "sandwich" complex of 15-crown-5 with K^+ is also well known. Recently, we have developed a novel K^+-recognition microcapsule that is able to translate the K^+-recognition into a squirting release function (Figure 4). The microcapsule membrane is composited of 15-crown-5 units as K^+ sensors and N-isopropylacrylamide (NIPAM) units as actuators. The LCST of PNIPAM-based polymer shifts negatively to a lower value when the 15-crown-5 units selectively capture K^+ ions to form "sandwich" complexes [4]. Therefore, at a designed operation temperature between the two LCSTs, due to the K^+-recognition, the microcapsule shrinks rapidly; at the same time the pressure in the oil core increases because the oil core is incompressible and can not pass through the hydrogel membrane

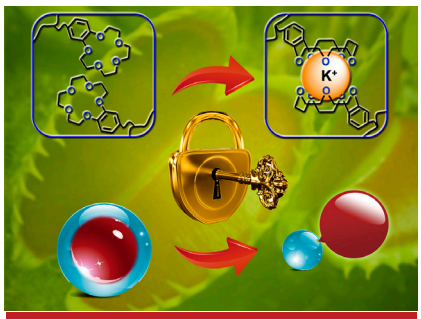

Figure 4. Schematic illustration of the concept of K^+-recognition microcapsule with a squirting release mechanism. The K^+-recognition-triggered volume shrinkage of the microcapsule membrane, which is due to the formation of a 2:1 "sandwich" complex of 15-crown-5 receptors with K^+ ions, results in a squirting release of the encapsulated oil core [4].

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via diffusion. When the internal pressure increases to a critical value, the capsule membrane ruptures suddenly due to its limited mechanical strength; as a result the encapsulated oil core squirts out.

CONCLUSIONS

We have succeeded in developing smart microcapsules with squirting release mechanism with the virtue of microfluidics technique. Microfluidics are efficient for generating highly controllable multiple emulsions, which are excellent templates for synthesizing core-shell microcapsules with squirting release mechanism. With smart microcapsules with squirting release mechanism as an advanced platform, stimuli-induced burst squirting release of lipophilic substances [3], nanoparticles [1], and/or both hydrophilic and lipophilic substances [2] can be effectively achieved. Various capsule shells can be designed and fabricated to respond to different stimuli, such as temperature [1-3], specific ions [4] and molecules [5]. Although our initial aim is to develop a new delivery system as a drug carrier, the proposed smart microcapsules with squirting release mechanism are not only limited in the pharmaceutical field. Our smart microcapsules with squirting release mechanism can also convert the variations of alcohol concentration into mechanical force [5]. Moreover, nanoparticle filled microcapsules has been utilized in fabrication of a tremendous array of materials, including inks, paints, personal care products and foods. We think that our smart microcapsules with squirting release mechanism can provide new characteristics to those functional materials.

ACKNOWLEDGEMENT

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REFERENCES

1. Liu L., Wang W., Ju X.J., Xie R., Chu L.Y. Smart thermo-triggered squirting capsules for nanoparticle delivery. Soft Matter, 2010, 6: 3759-3763.
2. Chu L.Y., Utada A.S., Shah R.K., Kim J.W., Weitz D.A. Controllable monodisperse multiple emulsions. Angew. Chem. Int. Ed., 2007, 46: 8970-8974.
3. Wang W., Liu L., Ju X.J., Zerrouki D., Xie R., Yang L., Chu L.Y. A novel thermo-induced self-bursting microcapsule with magnetic-targeting property. ChemPhysChem, 2009, 10: 2405-2409.
4. Liu Z., Liu L., Ju X.J., Xie R., Zhang B., Chu L.Y. K^+-recognition capsules with squirting release mechanisms. Chem. Commun., 2011, 47: 12283-12285.
5. Liu L., Song X.L., Ju X.J., Xie R., Liu Z., Chu L.Y. Conversion of alcoholic concentration variations into mechanical force via core-shell capsules. J. Phys. Chem. B, 2012, 116: 974-979.

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Dr. Liang-Yin Chu teaches and performs scientific research at Sichuan University in China, where he directs a talented research group with a diverse and interdisciplinary focus on the development of new materials, systems and technologies for membrane separation, microencapsulation, controlled release, drug delivery and microfluidics. He has authored and coauthored more than 300 refereed journal articles, 21 patents, 3 books and 12 book chapters. He was honored as a Distinguished Young Scholar by the National Natural Science Foundation of China in 2008, and a Distinguished Professor of "Chang Jiang Scholars Program" by the Ministry of Education of China in 2009.

EXIBITORS AT THE 16TH INDUSTRIAL SYMPOSIUM ON MICROENCAPSULATION, JUNE 25-27, MADISON, WI, USA

INDUSTRIAL NEWS

Appleton rebranding

Appleton Papers Inc known through its development and use of coating formulations, coating applications and Encapsys® microencapsulation technology is to change its name to Appvion, Inc. The change in name comes with a new look website http://www.appvion.com/.
More information can be found here: http://www.appvion.com/en-us/investors/Documents/Investors/Appleton%20Papers%20%20announces%20company%20name%20change%20to%20Appvion,%20Inc.pdf

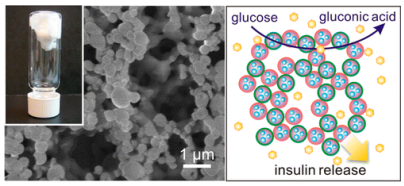
Eden Research plc announces EU approval granted for three actives

Eden specialize in natural terpene based crop protection products and use their own novel encapsulation process based on glucan particles or yeast cell walls for aiding the delivery of volatile actives in a number of product formulations. Eden report that approval has now been granted for the use of active components in their lead product 3AEY for fungicidal applications. Eden has a particular interest in targeting Botrytis particularly in fruit crops. http://www.edenresearch.com/html/news/press_releases/2013/20-05-13.asp
More information on their encapsulation technology can be found here http://patentscope.wipo.int/search/en/WO2005113128

Capsules incorporating phase change materials

KeepCool Ltd of Israel has shown a way how functional ingredients can be protected from high temperatures. The patent *"Layering and microencapsulation of thermal sensitive biologically active material using heat absorbing material layers having increasing melting points"* WO/2013/069021 describes a multi-layered capsule used to protect probiotic bacteria. A primary structure incorporating the probiotic bacteria is prepared and coated with multiple layers that are separated by a PEG layer and optionally an outer enteric coating.

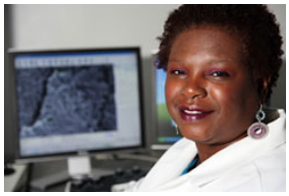
MIT treating Type I diabetes with nanospheres



Zhen Gu and colleagues at the MIT Department of Chemical Engineering and David H. Koch Institute for Integrative Cancer Research, together with researchers at Children's Hospital Boston, North Carolina State University and University of North Carolina at Chapel Hill, and Drexel University, Philadelphia, have treated Type 1 diabetes in a model system with a glucose responsive nanocapsule network. This is a fascinating piece of research utilizing an enzyme mediated release mechanism. Their paper Injectable Nano-Network for Glucose-Mediated Insulin Delivery is published in ACSNano

More information:
http://pubs.acs.org/doi/abs/10.1021/nn400630x

Enzyme triggered layer-by-layer nanocapsules



Mark Appleford and Marie-Michelle Kelley of The University of Texas at San Antonio have developed a novel drug delivery vehicle which is embodied in a new patent application "Logical Enzyme Triggered (Let) Layer-By-Layer Nanocapsules For Drug Delivery System". Capsules were composed of a core of calcium carbonate surrounded by single or multiple bilayers of polystyrene sulfonate and poly(aliylamine hydrochloride. Surface modification is proposed where enzyme cleavable conjugates are incorporated that can be tailored to specific drug targets which trigger release of the API.

The full-text of the patent can be found at
http://patentscope.wipo.int/search/en/WO2013043812
See also
http://utsa.edu/commencement/spotlight/spring2013/coe.html

New patent for a novel nutritional supplement to manage blood glucose levels

Response Scientific of Orlando, Florida, US, has been assigned a patent (8,420,125) developed by their scientists for a medical food or nutritional supplement for managing blood glucose levels and a method of manufacture. The nutritional supplement includes alpha-lipoic acid, linolenic acid, biotin, and coenzyme Q-10 at least one of which is microencapsulated with the components packaged for oral administration or formulated with a food product or in a cold drink.

The full-text of the patent at
http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,420,125.PN.&OS=PN/8,420,125&RS=PN/8,420,125

European Innovation Prize for French researcher

Professor Patrick Couvreur and team from Paris-Sud University in Paris win the inventor prize for their techonlogy of anti-cancer molecule nanoencapsulation, allowing to release precisely the drug inside the cancer cells while limiting the adverse effects.

More information (in French)
http://sciencesetavenir.nouvelobs.com/sante/20130528.OBS0942/des-nano-capsules-medicales-francaises-primees.html

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MICROFLUIDIC TECHNIQUE FOR MEASURING MICROCAPSULES

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INTRODUCTION

For liquid-filled artificial capsules, the membrane properties play an essential role in the control of the capsule deformation and possible breakup (to be induced or prevented depending on the application). But measuring the mechanical properties of the membrane is difficult as the capsules are typically small (from a few microns to a few millimeters), fragile and often highly deformable. We have designed a new technique that allows the measurement of the mean shear elastic modulus on a population of initially spherical capsules by coupling microfluidic experiments with a mechanical model. The experiments consist of flowing a capsule suspension in a small pore that has transversal dimensions comparable to those of the suspended capsules [1,2]. The hydrodynamic stresses and the constraints due to the channel confinement cause large deformations of the capsules. They are function of the flow strength and of the particle intrinsic physical properties such as the relative size compared to the channel section and membrane constitutive behaviour. The capsule deformation, volume and velocity can be measured simultaneously by means of image analysis. A sophisticated model of the flow of a capsule in a small pore then allows one to infer the membrane mechanical properties from the experimental results. The technique is hereafter illustrated on spherical capsules enclosed by a thin polymerized ovalbumin membrane.

PRINCIPLE OF THE MICROFLUIDIC TECHNIQUE

A dilute suspension of artificial capsules (mean radius a) in a viscous fluid (viscosity μ) is flowed at different flow rates in a cylindrical tube (radius h) or in a square section microfluidic tube (side $2h$). The micro-channels have a cross section comparable to the capsule dimension, i.e. $a/h = O(1)$. The deformation and velocity of one capsule are observed with a transmission microscope connected to a high resolution high-speed camera. Depending on the size ratio and velocity, slug or parachute profiles are observed as shown in Figure 1. The profile extraction is done with ImageJ. We then calculate the total length L of the profile, its axial length L_a and its surface S as shown in Figure 1. In a circular section, the initial radius of the capsule can be easily inferred from the deformed profile by assuming axisymmetry. In a square section pore, we determine an apparent radius a_{app} of the capsule as the radius of a sphere which has the volume $2Sh$. In order to analyze the experiments, a mechanical model of the set-up is needed.

MECHANICAL MODEL OF THE MOTION OF A CAPSULE IN A PORE

An initially spherical capsule (radius a) flows along the z-axis of a microfluidic channel with a square or circular cross-section (dimension $2h$) in the perpendicular xy-plane. The interior and exterior of the capsule are incompressible Newtonian fluids with the same density and viscosity. The thin membrane of the capsule is an impermeable hyperelastic isotropic material with surface shear modulus G_s and area dilatation modulus K_s. The bending resistance is neglected. The membrane constitutive law must be defined to account properly for the large deformation of the capsule. We have considered two laws, which have the same small deformation behaviour but which are either strain-softening (neo-Hookean law) or strain-hardening (Skalak type law) under large deformation. Apart from the capsule membrane mechanical properties, the two other main parameters of the problem are the size ratio a/h between the capsule initial radius and the channel cross dimension, and the capillary number $Ca = \mu V/G_s$, which measures the ratio between viscous and elastic forces, where V is the mean external undisturbed flow velocity along the z-axis of the channel. The flow Reynolds number is assumed to be very small, so that the internal and external liquid motions satisfy the Stokes equations. We assume that the membrane velocity is equal to the fluid velocity and that the elastic load on the membrane is due to the viscous traction exerted by the fluid flows.

This problem represents a complicated fluid-structure interaction problem, where the fluid flows are governed by viscous effects and where the structure deformation may be large. In absence of an available analytical solution, a numerical solution must be sought. We solve the problem equations by coupling a boundary integral technique for the fluid flows to a finite element technique for the membrane mechanics. Details on the problem equations and their solution can be found in [3,4]. The advantage of the procedure is that only the boundaries of the flow domain (channel entrance and exit section, walls and capsule membrane) are discretized. The model inputs are the capillary number Ca, the size ratio a/h and the membrane law. The model outputs are the capsule centre velocity v_o, the steady deformed capsule shape, the additional pressure drop due to the capsule and the elastic stress distribution in the membrane. From the deformed profile, it is possible to compute the evolution of the total length L, of the parachute depth $L_p = L - L_a$ and of the apparent capsule radius a_{app} with size ratio a/h and Ca. The model also yields the elastic tension distribution in the membrane. If a failure criterion is known for the membrane, it is then possible to infer whether there is a risk of breakup.

All the following results pertain to an

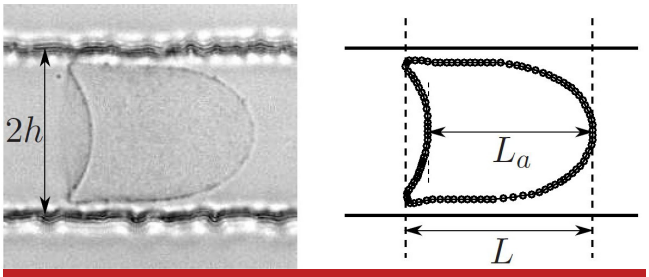

Figure 1 Capsule profile extraction from an experimental image. Images reproduced from [3]

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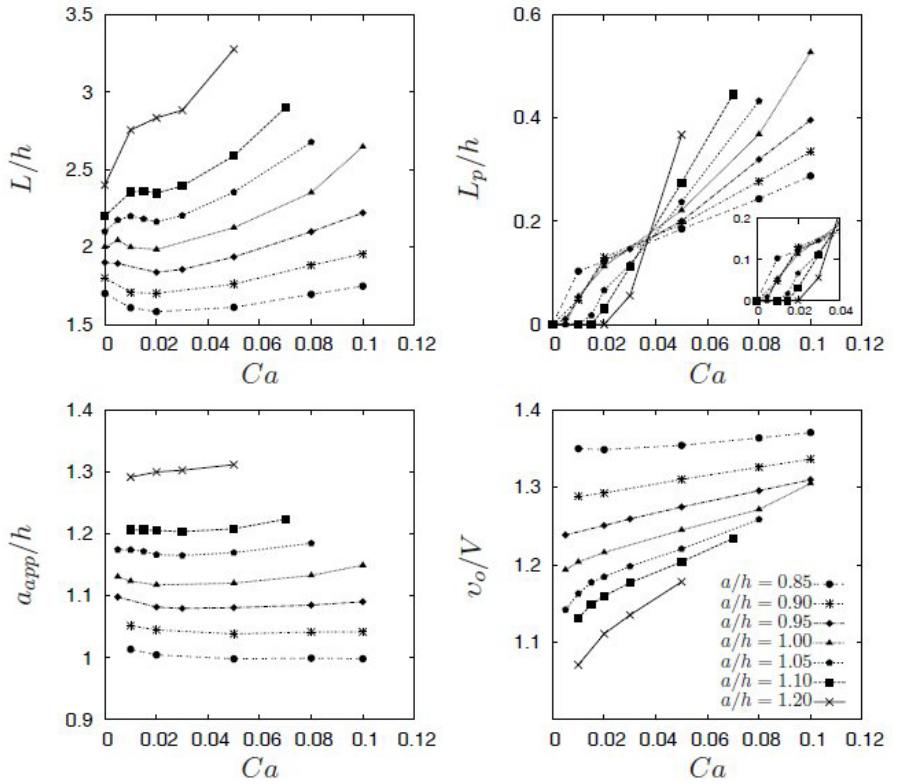

Figure 2. Charts of the deformation parameters for a capsule with a strain-softening membrane, flowing in a square section microfluidic pore. Images reproduced from [4]

equilibrium state, where the capsule is centred on the tube axis. At steady state, the membrane and the internal fluid are motionless. This means that the assumption of equal viscosity for the internal and external liquids does not limit the validity of the results: the viscosity ratio only influences the time the capsule needs to reach a steady state (this time increases as the internal viscosity increases). Furthermore, as the pressure inside the capsule is uniform, the curvature at the capsule upstream tip must be larger than at the rear to account for the viscous pressure drop in the lubrication film around the capsule. This explains why parachute or slug shapes are obtained. For a given membrane constitutive law, charts of the main geometrical parameters (L, L_p, a_{app}) and of the relative capsule velocity v_o/V are computed as functions of Ca for different size ratios. They are given for a strain-softening and for a strain-hardening law in the case of axisymmetric flow in a cylindrical pore [2]. The same charts have been recently published for the flow in a square section pore [3,4]. As an example, we show these charts in a square section tube for a strain-softening membrane in Fig. 2. One can see for instance that there exists a critical value of Ca for which $L_p > 0$, indicating the appearance of a parachute. The charts can be used to analyze experiments on flowing capsules and deduce the mechanical properties by inverse analysis.

EXAMPLE: CAPSULES ENCLOSED BY A POLYMERISED OVALBUMIN MEMBRANE

We illustrate the inverse analysis technique on artificial capsules with a polymerised ovalbumin membrane prepared using an interfacial cross-linking method [5]. The capsules (a = 31 ± 7 µm) are suspended in glycerin with a concentration 2.2% (viscosity µ = 0.7 Pa.s at 23°C). The suspension is injected into a square microfluidic tube (h = 27.4 ± 0.5 µm) by means of a syringe pump at different flow rates. A typical deformed profile is shown in Fig. 1. If one first models the capsule membrane as strain-softening, the charts of Fig. 2 can be used to determine which value of a/h and of Ca give the best correspondence between the experimental and numerical values of a_{app}, L and L_p. As a check, one can compare the experimental and numerical profiles obtained for these values of Ca and a/h and note that the superposition is very good as shown in Fig. 3. The velocity ratio v_o/V is deduced from the values of Ca and a/h, and hence the mean flow velocity V, since v_o is measured experimentally. It is then possible to infer the shear elastic modulus of the membrane $G_s = \mu V/Ca$.

We have analyzed a population of 18 capsules of different initial sizes, flowing through the square-section capillary tube at different flow rates. The mean elongation of each capsule is defined as the ratio between the profile perimeter and $2\pi a$. For a mean elongation ranging from 1 (no deformation) to 1.25, we find a constant value G_s = 0.036 ± 0.006 N/m, which is in agreement with former results on ovalbumin capsules prepared under the same conditions [2]. The same analysis with a strain-hardening law yields a value of G_s that decreases with increasing deformation. It thus seems that the cross-linked ovalbumin membrane is strain-softening rather than strain-hardening.

CONCLUSION

The present technique enables to infer plausible mechanical properties of an artificial capsule membrane from experiments, in which the capsule has to deform to flow inside a small pore with cross-dimensions of the same order as those of the capsule. The method is based on the coupling of experimental observations with a rigorous mechanical model of the system. The method works well, if the deformation of the capsule is large enough. Thus,

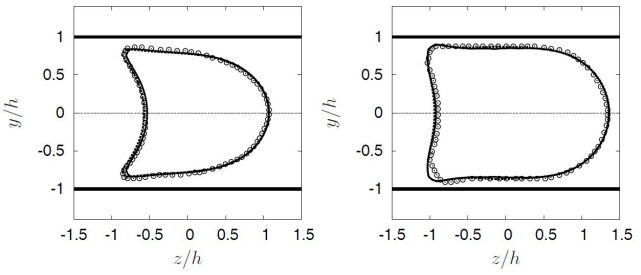

Figure 3 Comparison between extracted experimental profiles (circles) and numerical profiles (full line) obtained for a strain-softening law. Left: a/h = 0.9, Ca = 0.08; right: a/h = 1.1, Ca = 0.03. Images reproduced from [3].

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it is best to use a pore, such that the size ratio of the capsules is of order unity. Small capsules ($a/h < 0.8$) have to be flowed fast to be deformed with concomitant difficulties of observation leading to profile fuzziness. In order to reach large deformation, while keeping the capsule velocity moderate, a high viscosity suspending liquid is necessary. But the price to pay is that the high viscous pressure drop inside the micro-channel may lead to the destruction of the connections. The advantage of using a square-section channel rather than a cylindrical one is linked to the easy fabrication of microfluidic tubes of any size and to the easy connection with the propulsion device. Furthermore, this system can be built in a microfluidic fabrication device to monitor the properties of the capsules in situ [6]. We note that it is even possible to infer the large deformation behaviour of the membrane, at least to decide whether it is strain-softening or hardening.

REFERENCES

1. Y. Lefebvre, E. Leclerc, D. Barthès-Biesel, J. Walter, F. Edwards-Lévy Flow of artificial microcapsules in microfluidic channels: A method for determining the elastic properties of the membrane. Phys. Fluids, 20, 123102 (2008).
2. T. X. Chu, A.-V. Salsac, E. Leclerc, D. Barthès-Biesel, H. Wurtz, F. Edwards- Lévy Comparison between measurements of elasticity and free amino group content of ovalbumin microcapsule membranes: discrimination of the cross-linking degree. Int. J. of Colloid Interface Sci., 355, 81–88 (2011).
3. X.-Q. Hu, A.-V. Salsac, D. Barthès-Biesel Flow of a spherical capsule in a pore with circular or square cross-section. J. Fluid Mech., 705, 176–194 (2012).
4. X.-Q. Hu, B. Sévénié, A.-V. Salsac, E. Leclerc, D. Barthès-Biesel, Characterization of membrane properties of capsules flowing in a square-section microfluidic channel: effects of the membrane constitutive law, Phys. Rev. E, In Press (2013).
5. F. Edwards- Lévy, M. C. Andry, M. C. Lévy Determination of free amino group content of serum albumin microcapsules using trinitrobenzenesulfonic acid: effect of variations in polycondensation pH. Int. J. Pharmaceutics, 96, 85–90 (1993).
6. T. X. Chu, A.-V. Salsac, D. Barthès-Biesel, L. Griscom, F. Edwards-Lévy, E. Leclerc Fabrication and in situ characterization of microcapsule in a microfluidic system. Microfluid. Nanofluid., 14, 309–317 (2013).

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ARTICLE

MICROFLUIDICS: A NEW TOOL FOR TUNABLE RELEASE PROPERTIES OF DRUG LOADED POLYMER MICROBEADS

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INTRODUCTION

Pharmaceutically active ingredients can be administered orally, intravenously, intramuscularly or subcutaneously but oral administration remains the most physiological and convenient way of delivering drugs (Delie and Blanco-Príeto, 2005). One can develop systems that carry drug to a specific region within the gastrointestinal tract for a local or systemic action. Different dosage forms are used for oral administration but microparticles have certain advantages over single unit systems like less chance of dose dumping and local irritation, increased bioavailability, low dependence on gastric emptying time etc. Microencapsulation is used to develop microparticles where active materials are entrapped through the formation of thin coating materials for protection of drug, controlled release, reduced administration frequency, patient comfort and compliance (Khan et al., 2013). Conventional methods (emulsion solvent evaporation, emulsion solvent diffusion etc.) for microencapsulation show poor drug loading, polydispersity and batch to batch variation (Holgado et al., 2008). Microfluidics can be a suitable alternative to overcome these problems by producing microparticles having a very narrow size distribution (Serra and Chang, 2008).

MICROBEAD FABRICATION

A simple and low cost off-the-shelf co-axial microfluidic device (Fig 1) was used to synthesize copolymer microbeads with different ethyl acrylate (EA) and tripropylene Glycol Diacrylate (TPGDA, a difunctional monomer) weight contents, encapsulating a lipophilic model drug (ketoprofen). The monomer dispersed phase, admixed with the drug, was injected into a continuous phase (carob solution of 2150 cps viscosity) through a fused silica capillary (I.D. 50 µm) placed in an outlet PTFE tubing (I.D. 16 or 18 mm). Once monomer droplets are generated they are polymerized downstream by UV irradiation having and intensity of 140 mW/cm2 (Hamamatsu Lightningcure LC8) (Fig 1). Microbeads were then collected at the exit of the tubing and washed with distilled water, dried and stored in glass vials until further use.

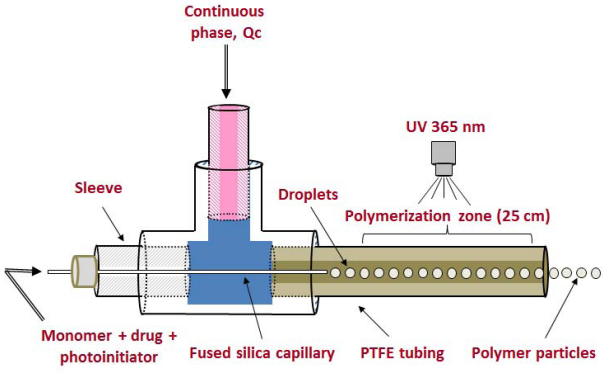

Figure 1. Schematic drawing of the microfludic setup.

Size analysis was performed by Hiris version 3 (R&D VISION) software and has shown microbead size decreased by increasing the ratio of continuous to dispersed phase flow rates (Qc/Qd) with coefficient of variation less than 5 % (highly monodispersed microbeads) for each formulation tested (different EA weight contents). In these conditions we operated in dripping mode (Fig 2.A). From optical and SEM microscopy each formulation produced spherical beads with uniform surface which gets rough with increasing content of ethyl acrylate.

FTIR spectra confirmed complete polymerization of comonomer droplets by observing the absorbance of acrylate double bond stretching and bending vibrations at 1636 and 808 cm-1 respectively. Pure ketoprofen showed ketonic and carbonyl peaks at 1659 cm-1 and 1692 cm-1 respectively. In FTIR spectra of microbeads one observed ketoprofen ketonic peak at 1659 cm-1 but could not see carbonyl peak corresponding to 1692 cm-1. This could be due to disruption of crystalline dimer as a result of the interaction between ketoprofen carboxylic group and carbonyl group of polymer. Afterwards carboxylic acid stretching vibration is shifted to higher wavelengths and is overlapped by strong ester vibrations of monomers at 1725 cm-1 (Fig 3). These results are further confirmed by DSC studies for which characteristic peaks of ketoprofen were not observed. DSC thermogram further indicates the conversion of crystalline form to amorphous form. These results were further confirmed by XRD where diffraction peaks of ketoprofen at 6, 14 and 18Ð are reduced in XRD patterns of all the formulations.

Low encapsulation efficiency was observed in pure poly(TPGDA) microbeads but was increased by increasing the amount of EA. It is believed that this results from the increase in the number of carbonyl groups in polymer chain with increased EA weight content. Here caroboxyl group of ketoprofen will interact with carbonyl group and will not

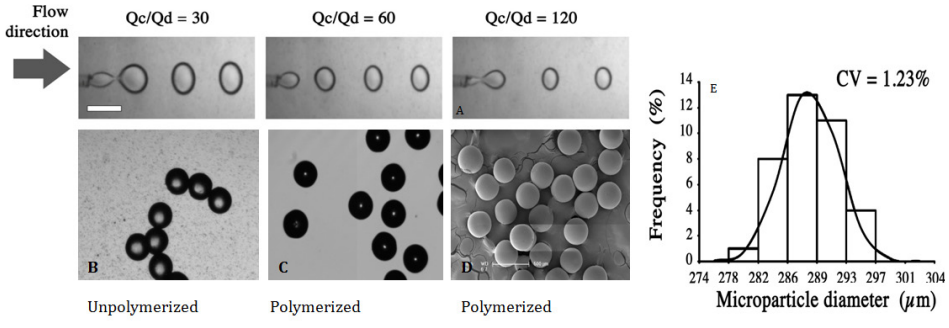

Fig 2: Snapshots of the droplet formation for different Qc/Qd ratio (Scale bar = 500 µm) (A). Optical images of unpolymerized droplets (B) and polymerized beads (C), SEM micrographs of microbeads (D) Typical microbeads size histogram for Qc/Qd=120 (E) (Adapted from Khan et al., 2013).

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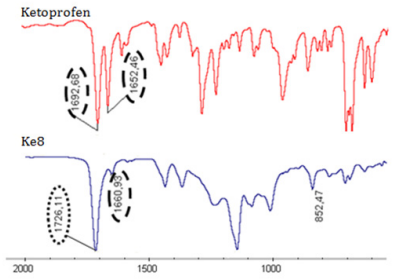

Fig3: FTIR spectra, stretching and bending vibrations of acrylate, stretching vibrations of ester (.....) and dimeric carboxylic and ketonic carbonyl group of ketoprofen (--). (Adapted from Khan et al., 2013)

diffuse to surrounding media having pH around 6 to 7 during polymerization. Encapsulation efficiency was higher in small size beads than larger which may be due to the fact that smaller droplet polymerizes faster than larger thus reducing the diffusion of ketoprofen.

Drug release studies were carried out in USP phosphate buffer solution of pH 1.2 and 6.8 and indicated that all formulations released a small quantity of ketoprofen at pH 1.2. At pH 6.8 the release rate depended on the concentration of EA and increased with an increase in EA weight content (Fig 4). Pure poly(TPGDA) microbeads forms a very dense polymeric network where dissolution media cannot access easily to dissolve and diffuse the drug. But when the concentration of EA is increased, it makes loose matrix that helps in faster imbibition of surrounding fluid and diffusion of ketoprofen. Furthermore one was able to improve the drug release by decreasing the size of microbeads (Fig 4).

CONCLUSION

Capillary-based co-flow microfluidic setup was found conveniently appropriate to encapsulate ketoprofen in monodispersed polymeric microbeads while starting from monomers. Inter-droplet distance, particle size and encapsulation efficiency was affected by the ratio of dispersed to continuous phases flow rates. Drug release from microbeads was also affected by the nature of monomers. Difunctional monomers tend to retard the release rate while addition of monofuntional monomer improves the release rate. Thus it was found that the developed microfluidic device can tune quite precisely the release properties of drug loaded polymer microparticles. In future, this setup could be used to encapsulate other hydrophilic or hydrophobic drug for desired applications.

REFERENCES

1. Delie, F., Blanco-Príeto, M., 2005. Polymeric Particulates to Improve Oral Bioavailability of Peptide Drugs. Molecules 10, 65-80.
2. Holgado, M.A., Arias, J.L., Cózar, M.J., Alvarez-Fuentes, J., Gañán-Calvo, A.M., Fernández-Arévalo, M., 2008. Synthesis of lidocaine-loaded PLGA microparticles by flow focusing: Effects on drug loading and release properties. International Journal of Pharmaceutics 358, 27-35.
3. Khan, I.U., Serra, C.A., Anton, N., Vandamme, T., 2013. Continuous-flow encapsulation of ketoprofen in copolymer microbeads via co-axial microfluidic device: Influence of operating and material parameters on drug carrier properties. International Journal of Pharmaceutics 441, 809-817.
4. Serra, C.A., Chang, Z., 2008. Microfluidic-Assisted Synthesis of Polymer Particles. Chemical Engineering & Technology 31, 1099-1115.

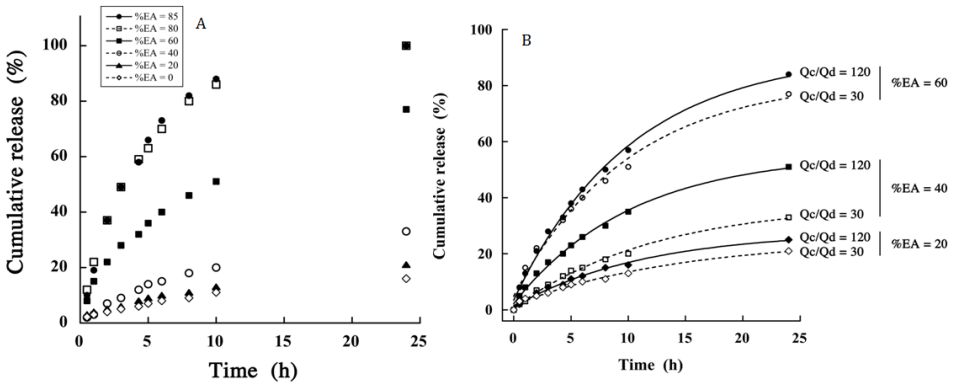

Fig4: Cumulative ketoprofen release of various ethylacrylate (EA) contents at pH 6.8 (A). Formulations prepared under various Qc/Qd showing different release profiles (B). (Adapted from Khan et al., 2013)

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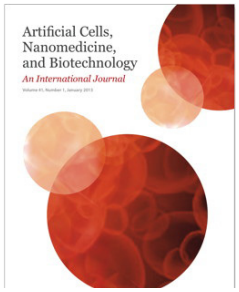
BIBLIOGRAPHY



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