

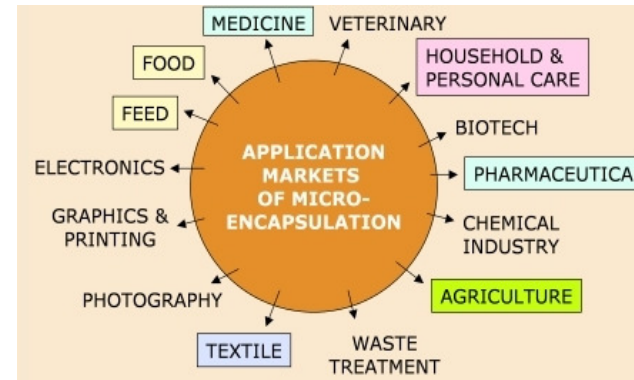
COST 865 Spring Workshop  
Luxembourg, 24./25. April 2009

## Multiscale requirements for bioencapsulation in medicine and biotechnology

Workgroup II, COST 865, presented by  
Marion Ansoorge-Schumacher (TU  
Berlin),



## Bioencapsulation in medicine and biotechnology



**Biotechnology:** Increase of cell density and productivity in cell fermentation, avoidance of washout of biological catalysts.

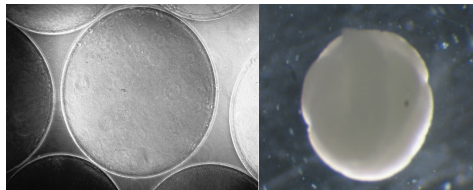
**Medicine:** Drug protection & deliverance; bio-artificial organs.

## Drawbacks to application of bioencapsulation



Why not more generally applied ?

- Considered low reproducibility
- Lab-to-Lab variations



**Pitfall until 2008:** Lack of documentation of production  
process and capsule properties

## Review on methods for characterisation of capsules



Review  
Multiscale requirements for bioencapsulation in medicine and biotechnology

Paul de Vos<sup>1,2</sup>, Marek Bučko<sup>3,4</sup>, Peter Gemeiner<sup>5,6</sup>, Marián Navrátil<sup>4,7</sup>, Juraj Švitel<sup>4,8</sup>, Marijke Faas<sup>9,10</sup>, Berit Løkensgard Strand<sup>11</sup>, Gudmund Skjåk-Bræk<sup>12</sup>, Yrr A. Morch<sup>13</sup>, Alica Vikartovská<sup>14</sup>, Igor Lack<sup>15</sup>, Gabriela Kollánková<sup>16</sup>, Gorka Orive<sup>17</sup>, Dennis Poncellet<sup>18</sup>, Jose Luis Pedraz<sup>19</sup>, Marion B. Ansoorge-Schumacher<sup>20</sup>

<sup>1</sup>University Hospital Groningen, Section of Medical Biology, Translational Biotechnology, Groningen, 37008 Groningen, The Netherlands  
<sup>2</sup>Institute of Chemistry, Center for Optics, Slovak Academy of Sciences, Dubravská cesta 9, 845 38 Bratislava, Slovakia  
<sup>3</sup>University of Jyväskylä, Faculty of Science, Department of Chemistry, PO Box 35, 40014 Jyväskylä, Finland  
<sup>4</sup>Institute of Chemistry and Food Science, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského 9, 812 19 Bratislava, Slovakia  
<sup>5</sup>Department of Food Science, Faculty of Science, University of Jyväskylä, PO Box 35, 40014 Jyväskylä, Finland  
<sup>6</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>7</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>8</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>9</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>10</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>11</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>12</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>13</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>14</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>15</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>16</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>17</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>18</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>19</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania  
<sup>20</sup>Department of Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy, Bucharest, Romania

**ARTICLE INFO**  
Article history:  
Received 16 October 2008  
Accepted 1 January 2009  
Available online xxx

**Keywords:**  
Microencapsulation  
Bioavailability  
Toxicology  
Biomedical polymers  
XPS (X-ray photoelectron spectroscopy)  
Microbiology

**ABSTRACT**  
Bioencapsulation involves the entrapment of tissues or biological active substances in semipermeable membranes. Bioencapsulation has been shown to be efficacious in mimicking the cell's natural environment and thereby improves the efficiency of production of different molecules and therapeutic agents. The field of application is broad. It is being applied in biotechnology and biomedicine. It is clinically applied for the treatment of a wide variety of infectious diseases. During the past decades many procedures to fabricate capsules have been described. Unfortunately, most of these procedures lack an adequate documentation of the characterization of the bioencapsules. As a result many procedures show an extreme lab-to-lab variation and many results cannot be adequately reproduced. The characterization of capsules can no longer be neglected, especially since new clinical trials with bioencapsulated therapeutic cells have been initiated and the industrial application of bioencapsulation is growing. In the present review we discuss novel approaches to produce and characterize bioencapsules in view of clinical and industrial applications. A dominant factor in bioencapsulation is selection and characterization of suitable polymers. We present the advantage of using novel high-resolution NMR for characterizing polymers. These polymers are applied for producing semipermeable membranes. We present the pitfalls of the currently applied methods and do recommendations for standardization to avoid lab-to-lab variations. Also, we compare and present methodologies to produce bio-compatible bioencapsules for specific fields of applications and we demonstrate how physico-chemical technologies such as FTIR, XPS, and TOPO-SIMS contribute to reproducibility and standardization of the bioencapsulation process. During recent years it has become more and more clear that bioencapsulation requires a multidisciplinary approach in which biomedical, physics, and chemical technologies are combined. For adequate reproducibility and for understanding variations in outcome of bioencapsules it is advisable if not mandatory to include the characterization processes presented in this review in future studies.

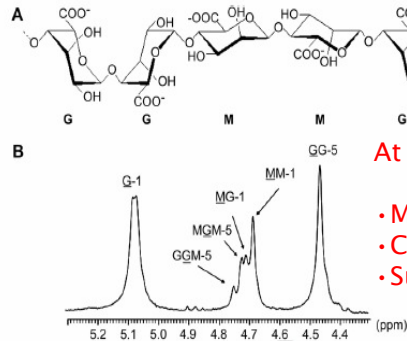
© 2009 Published by Elsevier Ltd.

Workgroup II,  
COST 865

# Polymers for bioencapsulation

## Selection of adequate polymer

- Support functional survival of cell (intracapsular compatibility)
- Compatible with exterior (recipient, fermentation)
- Mechanical and physical-chemical adequacy in specific application



At least documentation of:

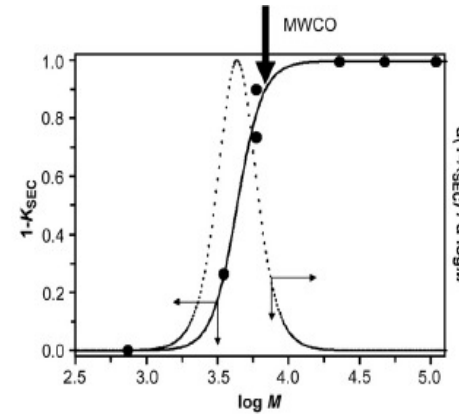
- Molecular weight average
- Chemical composition
- Substitutions with modifications

Fig. 1. Structure of alginate. A:  $\beta$ -D-mannuronic acid (M) and  $\alpha$ -L-gulonic acid (G), with most probable ring confirmation: M:  ${}^4C_1$  and G:  ${}^4C_1$ . B:  ${}^1H$ -NMR spectra of alginate from *L. hyperborea* stripe.

# Permeability properties

## Permeability properties

- Determines exchange, production, efficacy of system
- Determines survival of cells

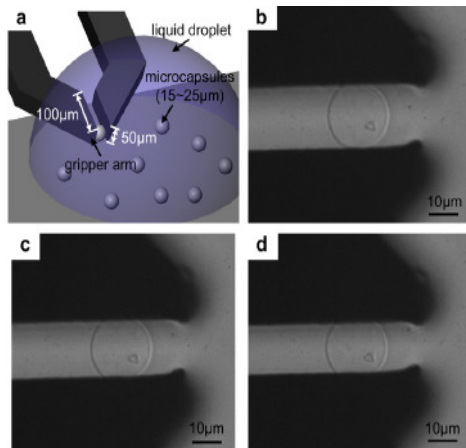


At least documentation of:

- Solutes applied (application dependent)
- Size exclusion chromatography most reproducible

# Mechanical resistance

## Determination of durability



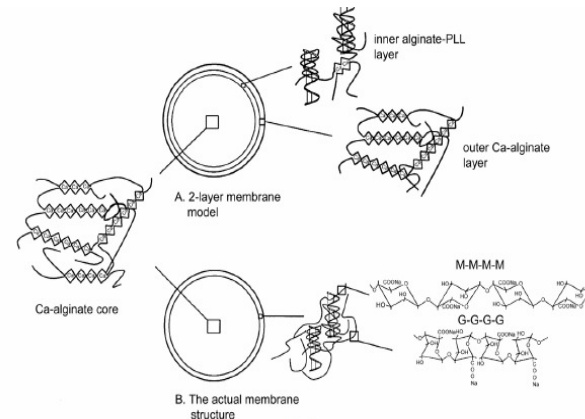
At least documentation of:

- Force required to acquire a fixed compression or implosion

# Surface properties

## Surface properties

- Determines functional performance in specific application
- Provides insight in actual structure of capsule

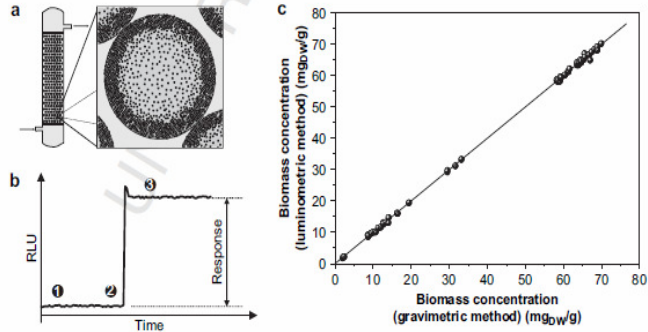


Recommendation:

- XPS, FTIR, or ToF-Sims before and after application

## Biocompatibility

- Intracapsular, functional survival of cells
- Extracapsular, maintenance of functional properties in application



Recommendation: Bioluminescence, viability monitoring; monitoring functional properties of membrane before after and during application

Every application requires a **specific adaptation** of the procedure, consequently every application requires an **unique capsule type**

**General technologies** to document capsule properties have been identified and **improve reproducibility**

Many novel **structural insights** have been gained by documentation and comparison

