Scientific and Clinical Applications of Magnetic Carriers

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IN MEMORY OF PROFESSOR JOHN UGELSTAD

Professor John Ugelstad passed away on the third of April 1997 at the age of 76 after a long fight against cancer.

We think that everyone who knew Professor Ugelstad or initially met him in 1996 at the first international Scientific and Clinical Applications of Magnetic Carriers meeting in Rostock will agree that he would be honored to be remembered as he appears here. After a wonderful dinner at hotel Neptun high above the Baltic Sea, not only was he the first to dance but did so with the only other meeting participant who had a physical disability—an act that captured the essence of who he was as a human being.

Professor Ugelstad was an excellent scientist and a warm and supportive man, who devoted his life to bridging the gap between basic research and industrial realization. After completing a dissertation on the reactions between amides and aldehydes, he graduated from the Department of Industrial Chemistry at the University of Trondheim, Norway and spent several years conducting research in the United States, Europe, and Israel. He then was appointed to a professorship in the Department of Industrial Chemistry at the University of Trondheim. During his tenure, he worked on many projects, one of them being the emulsion polymerization of poly(vinyl chloride), which led to new industrial processes that have placed PVC materials in the daily lives of people everywhere.

His fame, honors, and international awards, however, stem mainly from his pioneering work in developing monodisperse polymer particles and inventing the method for preparing magnetizable polymer particles. This work led to numerous important applications in the fields of molecular biology, medicine and biotechnology. Examples of applications are cell separation, DNA technology, immunoassays and selective enrichments of micro-organisms, many of which are covered in this book.

Professor Ugelstad's work did not end with his retirement—he continued as professor emeritus and kept working as hard as before. The Rostock conference was his last, and we will all remember the excellent review he gave on the preparation and application of monodisperse magnetic carriers. When we asked him to review the same area for this book, however, he declined because he thought he had already written enough reviews. He wanted to present original work—and he did, as readers will find in Chapter 2.

Professor Ugelstad's fundamental work lives on in this book; his scientific legacy will continue to inspire anyone who seeks to understand polymer emulsification processes and the nature and broad applications of monosized particles.

PREFACE

The discovery of uniform latex particles by polymer chemists of the Dow Chemical Company nearly 50 years ago opened up new exciting fields for scientists and physicians and established many new biomedical applications. Many *in vitro* diagnostic tests such as the latex agglutination tests, analytical cell and phagocytosis tests have since become routine. They were all developed on the basis of small particles bound to biological active molecules and fluorescent and radioactive markers. Further developments are ongoing, with the focus now shifted to applications of polymer particles in the controlled and directed transport of drugs in living systems.

Four important factors make microspheres interesting for *in vivo* applications: First, biocompatible polymer particles can be used to transport known amounts of drug and release them in a controlled fashion. Second, particles can be made of materials which biodegrade in living organisms without doing any harm. Third, particles with modified surfaces are able to avoid rapid capture by the reticuloendothelial system and therefore enhance their blood circulation time. Fourth, combining particles with specific molecules may allow organ-directed targeting.

The development of magnetically responsive microspheres has brought an additional driving force into play. Magnetic forces can be used *in vitro* to direct the particles so that they (re)move bound cells and molecules, and *in vivo* to target and hold the magnetic carriers at anatomical sites with restricted access. These possibilities form the basis for well established biomedical applications in protein and cell separation. Additional modifications of the magnetic particles with monoclonal antibodies, lectins, peptides or hormones make these applications more efficient and also highly specific. The combination of these two advantages made the magnetic microspheres' application so successful in molecular and cell biology, advancing both basic studies and clinical practice. The purification of bone marrow cells from contamination with tumor cells using so-called immuno-magnetic beads, for example, has become a well established routine method in clinical therapy.

Newly developed surface modifications of biodegradable magnetic polymer particles resulted in longer circulation times and brought renewed interest in Paul Ehrlich's ideas of directed *in vivo* drug delivery (the "magic bullet"). Their success depends on a large extent on the construction of strong magnets, able to produce high magnetic field gradients at the target site. The currently available inhomogeneous fields are only strong enough for the manipulation of particles against the diffusion and blood stream velocities found in living systems over a distance of but a few millimeters from the sharp edge of the magnet poles. Efforts to enhance the local inhomogeneous fields in deeper regions of the body must also be pursued, by, for example, the implantation of ferromagnetic materials near the target.

Even with stronger magnets, one important problem remains and must be overcome: How can we deliver most of the magnetic carrier to the target area and avoid normal tissue (especially the liver)? The circulation time depends reciprocally on the particle size, whereas the magnetic susceptibility of the individual particle is directly proportional to the size. Size and magnetic properties must therefore be optimized carefully to decrease the unspecific, reticuloendothelial system uptake and to prolong the circulation time. This will provide a maximum time span for the extraction and concentration of the magnetic particles in the target area.

Aside from solving the magnetic targeting problems, intense efforts are ongoing in the development of biocompatible magnetic carriers for the directed transport and controlled release of drugs or radionuclides, for use as sources of local temperature increase (hyperthermia), and for local contrast enhancement in MR imaging. The ideal magnetic carrier is different for every application. New possibilities in design, preparation methods, materials and modifications will in the future lead to more proposals for their use.

The development and application of magnetic carriers is an interdisciplinary field that critically depends on the collaborative efforts of many different professions. Physicians who need new methods of delivering highly toxic compounds to tumors must specify the patient group which would most benefit from such an approach. Engineers and physicists must provide powerful and matching magnet setups. Chemists, pharmaceutical and basic scientists must devise the best magnetic carrier for the application. Finally, imaging specialists must provide methods of monitoring the fate of the magnetic drug, ideally online, thus guaranteeing that the magnetic carriers reach the target in the right amounts.

In order to discuss all these aspects of the biomedical applications of magnetic particles, we organized the first International Conference on "Scientific and Clinical Applications of Magnetic Carriers" in Rostock, Germany, in September 1996. The special atmosphere at this meeting and the interest of all participants in the new aspects of preparation, modification and application of magnetic particles inspired us to edit this book. Our intention was to publish more than just the normal proceedings of a conference. We wanted to provide more of a text book containing a current summary of the knowledge in our field. This book thus covers the basics of how to prepare and apply different kinds of magnetic microspheres and reviews concepts and promising applications. It also contains many original, never before published contributions. The chapters were chosen so as not to duplicate each other and are written by internationally recognized scientists, physicians and engineers. We would like to thank all the authors and participants of the meeting for their contributions.

Magnetic carriers are now established for in vitro work in the laboratory as well as for *ex vivo* work in bone marrow purification. Modern clinical trials are currently being performed, and we believe that this modern field of interdisciplinary research and development for the health of human beings stands at the beginning of rapid advancements. We are looking forward to the next International Conference on "Scientific and Clinical Applications of Magnetic Carriers" which will take place in Cleveland from May 28–30, 1998 and hope that, in the meantime, this book will provide for interesting and enjoyable reading.

Wolfgang Schütt, Rostock, Tokyo
Urs Häfeli, Cleveland

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