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Preface

The GTRV (Groupe Thématique sur la Vectorisation) is a mainly French-speaking special interest group bringing together scientists from both the public and private sectors who are working towards the development of innovative carrier systems for the delivery of biological substances and for imagery and diagnostics. It organizes a 3-day meeting every year. This Special Issue contains reports of work first presented at the meeting held in Paris in December 2006. The varied contents list reflects the multidisciplinary nature of the GTRV, embracing biophysics, chemistry, pharmacology, molecular biology, pharmaceutical technology and clinical medicine. Progress in this field depends on close collaboration between specialists in different areas.

The GTRV meetings always include several invited speakers, whose lectures touch on subjects related to drug delivery systems but come from a wide range of disciplines. This was the case for the presentation of Pr. Hervé This, who has pioneered the subject of "molecular gastronomy" which applies physical and chemical principles to food processing. In this issue, he presents formalisms to describe various culinary preparations which are multiphase systems. These formalisms could also be used for pharmaceutical formulations such as emulsions.

The other research papers in this special issue cover all the stages necessary to produce a new drug delivery system, from the production of active ingredients and polymers, through the formulation of preparations with specific physical and chemical properties, optimization of drug loading, pharmacokinetics and distribution to studies of efficacy *in vivo*. They show how such systems can be used to facilitate drug penetration across physiological barriers. Several articles stress the importance of the surface properties of the carriers in determining their biological fate.

Recombinant proteins have many potential therapeutic applications but their relative fragility and short half-lives necessitate appropriate drugs delivery systems. Garbayo et al. describe the large-scale purification of glial cell line-derived neurotrophic factor intended for encapsulation in microspheres which would provide sustained delivery after implantation in the brain of Parkinson's disease sufferers. Al Haushey et al. have used bovine serum albumin as a model protein to study the microencapsulation process in a screening approach.

Microspheres and microcapsules can provide sustained release, but sub-micron systems are required to provide true drug carriers that can be administered by a parenteral route. Two articles address fundamental issues in the formulation of nanoparticles. Choisnard et al. describe an enzymatic method for modifying β cyclodextrins by additional of alkyl chains to the secondary face. The resulting amphiphilic molecules can be used to form nanoparticles. One versatile methodology for preparing nanoparticles from a variety of starting materials is nanoprecipitation. Legrand et al. have made a detailed study of the influence of polymer properties in solution on the size and yield of polylactide nanoparticles by nanoprecipitation and conclude with some useful guidelines for formulation. On the other hand, systems with a hydrophobic liquid core, nanocapsules and nanoemulsions, may be more suitable for some active substances; Anton et al. have investigated some key parameters of the phase inversion temperature method for preparing such systems.

Controlling the rate of drug release is a crucial factor for the successful development of any type of delivery system. Sheikh-Hasan et al. have had the ingenious idea of incorporating drugs into nanoparticles before including them in microparticles, in order to reduce the burst release which often characterizes this type of system.

Liposomes, the earliest described form of colloidal drug delivery system, are not neglected by the GTRV membership. Lalanne et al. combine two drug delivery strategies: synthesis of lipophilic pro-drugs and encapsulation within liposomes, to improve the stability of didanosine, an antiviral nucleoside. A similar prodrug approach was adopted by Stella et al., to encapsulate a derivative of gemcitabine in nanoparticulate systems. These two articles open up interesting possibilities for the administration of nucleosides, which suffer from the twin disadvantages of instability in biological media and poor penetration into cells.

A physiological delivery system, low-density lipoprotein (LDL) has been chosen by Bonneau et al. for photosensitizers, another class of anti-cancer drugs that need to be delivered intracellularly. The authors have used a physico-chemical approach to measure the interaction of these molecules with LDL particles and have also studied the uptake of the resulting systems into cells by confocal microscopy.

Intracellular gene and oligonucleotide delivery is another technological challenge. In this issue, Vroman et al. describe the synthesis of PEG-bearing copolymers for DNA delivery, while Resina et al. have compared two strategies for the delivery of

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steric block oligonucleotides. Cationic lipids (lipoplexes) and peptide-based strategies were tested for their ability to correct splicing errors in transfected cells.

These articles illustrate the ability of appropriately formulated carriers to transport drugs across the plasma membrane of cells. Another challenge is to cross epithelial and endothelial barriers, one of the most difficult being the blood–brain barrier. Jallouli et al. have attempted this using very small (60 nm) nanoparticles with varying surface charge, aiming to exploit physiological mechanisms of transcytosis. They present results obtained in a well established *in vitro* model.

The ultimate test of a drug delivery system is its performance *in vivo*. A thorough knowledge of the carrier's pharmacokinetics and distribution should be obtained before it can be used rationally for therapeutic or diagnostic purposes. With this in mind, Mougin-Degraef et al. have labelled liposomes with two different radioelements, allowing the both lipid bilayer and the aqueous contents to be followed reliably. These liposomes are destined for pretargeted immunotherapy; in which a bispecific monoclonal antibody is used to 'tag' tumour cells and promote binding of liposomes loaded with a high-energy isotope which are administered later.

Another method of directing liposomes to a target is to load them with magnetic particles; Plassat et al. have studied the pharmacokinetics and distribution of such "magnetoliposomes" in mice. They were able to avoid using radioactivity by labelling the bilayer with a rhodamine-tagged phospholipids and using the magnetic properties of the iron oxide particles to trace the liposome contents. As in the previous article, their results confirm the ability of surface-grafted poly(ethylene) glycol to delay the clearance of liposomes from the circulation; however, a difference was observed between unloaded liposomes and those containing iron oxide particles. Such magnetic carrier systems are potentially useful for both guided drug delivery and as contrast agents for MR imaging. In this issue, Boissière et al. propose a new hybrid carrier structure for maghemite based on alginate and silica. These particles have not yet been tested *in vivo*, but internalization by fibroblasts and release of an encapsulated marker has been demonstrated.

Amphiphilic cyclodextrins, as described in an article cited above, are another starting material for the preparation of nanoparticles. One advantage of this could be the encapsulation of a drug within the core of the cyclodextrin, thus allowing its release to be controlled. The article by Gèze et al. describes the biodistribution of such particles in rats. Not surprisingly, since their surface was not modified by hydrophilic chains, a rapid uptake into organs of the mononuclear phagocyte system was observed, as for other conventional colloidal carriers.

Lipid nanocapsules are the subject of the final full article in this issue. Lacoeuille et al. not only studied the biodistribution of these carriers but also tested the activity of encapsulated paclitaxel against hepatocellular carcinoma in rats. The animals treated with drug in nanocapsules showed a slightly improved survival compared to those treated with free drug solution. These nanocapsules showed long-circulating properties thanks to PEG chains carried by the surfactants used to formulate them.

This Special Issue ends with some technical notes that should provide some helpful information for formulators. They stress that stability, both before and after administration to the patient, is an essential property of a carrier system destined for therapeutic applications. Thus, Morand et al. show that the commercial AmBisome® formulation of amphotericin B liposomes has sufficient stability when reconstituted to be used in an eye drop formulation to treat fungal keratitis. Ciobanu et al. describe a new liposome formulation which they designate "layersomes". In this formulation, conventional liposomes are coated with layers of first a positively charged and then a negatively charged polymer. Release of a fluorescent marker shows increased resistance of the membrane after coating. The note by Forminga et al. reports that some lipophilic drugs can contribute to the stability of the emulsion formulations prepared with them. Finally, Callewaert et al. have assessed the resistance of different microsphere preparations to steam sterilization and lyophilization. The addition of alginate covalently linked to albumin improves the stability of the microspheres.

During the preparation of this Special Issue, Dr. Nathalie Ubrich, a member of the GTRV board, died after a long battle with illness. Nathalie was active in promoting the work of the GTRV, not least by taking care of its website. The quality of her scientific work can be judged by the article which she co-authored included in this issue. Prof. Philippe Maincent has contributed a tribute to her life and work. All the members of the GTRV would like to dedicate this Special Issue to the memory of Nathalie. We hope that by highlighting some key issues and by proposing some innovative solutions this document will be useful to the community of scientists working in drug delivery systems.

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