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The Spherulites® : an innovative encapsulation system for active ingredients

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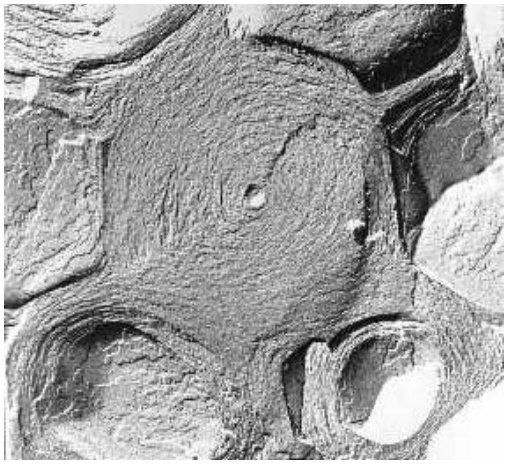
Background

Liposomes and lipidic vesicles are widely studied as drug delivery systems for anticancer drugs, protein and peptide delivery and vaccine. Despite the tremendous activity devoted to these developments since the 60's, only few liposome based drugs are actually on the market. The main drawback of this concept has been due to difficulties to industrialize the manufacture of liposomes and their lack of stability and reproducibility.

Definition

Spherulites® have been discovered during academic research at a CNRS (Centre National de la Recherche Scientifique) laboratory working on physics of liquid-crystal.



CryoTEM photograph of a spherulite™ before dispersion (T. Gulik, CNRS)

Spherulites® are multilamellar microvesicles (from 0.1 to 10 µm), with an internal structure of concentric spherical bilayers made of water and amphiphile, created by the controlled shearing of liquid-crystalline phases. As the initial step is a lamellar liquid-crystalline phase at thermodynamic equilibrium, the resulting structure is highly uniform both inside each vesicle and among the whole sample. This leads to a high stability of the vesicles and a high reproducibility of the manufacture process, at any industrial scale.

Main characteristic

Due to their unique structural properties and mode of manufacture, Spherulites™ are exceptionally suited to numerous applications: in protection, prolongation, enhancement of bioavailability, administration through alternate route, or vectorization of active substances.

The main asset of the Spherulites® are:

- High stability, and protection of the incorporated molecule against enzymatic degradation
- Ability to incorporate both hydrophilic and lipophilic active molecules with high encapsulation yield
- Manufacture without use of organic solvents and with little stress (pressure, shear, temperature) allowing the encapsulation of fragile molecules like proteins

For pharmaceutical applications Spherulites® are manufactured starting from already approved components, therefore limiting the toxicological issues. The final dosage can be either liquid (a dispersion of Spherulites® in aqueous medium) or solid, after freeze-drying, spray-drying and other solid dosage manufacturing process.

Twelve patent family are protecting the technology and its applications, eleven of them dealing with pharmaceutical applications. Five of them are now issued in Europe and six in the US.

Applications

The technology is already marketed in cosmetic and veterinary fields and is under development in pharmacy, for vaccine, peptide and protein delivery and oncology.

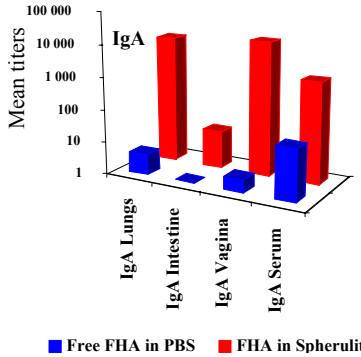
Dermatology

Spherulites® are used for two main effects in dermatology. A reservoir effect is obtained using cationic additives among the components of the amphiphilic membrane. This positively charged vesicles interact with the negatively charged protein of the skin or of the hair in order to increase the contact time of the active ingredient with the targeted site of administration.

The other effect is linked to the capability of the Spherulites® to co-encapsulate absorption enhancers together with the active ingredient. The nature of the amphiphiles constituting the vesicle and the addition of specific enhancers allow to tailor the penetration capability of the active ingredient. An antiviral drug based on this concept is under development.

Vaccine

Encapsulation of antigens in Spherulites® leads to very high titers of antibodies in mice immunized by parenteral route. Spherulites® act as potent delivery systems for systemic responses. Moreover Spherulites™ are able to



IgA antibody response in serum and mucosal sites after intranasal immunization with 3.2µg FHA incorporated in spherulites™ or free.

elicit a balanced response with a potentiation of IgG2a antibodies in accordance with higher IFN-γ production by splenocytes

Intranasal administration of antigen within Spherulites® induced specific IgA antibody responses not only in lungs but in other distant mucuous sites *i.e.* in intestine and vagina. Moreover, nasal administration of Spherulites® generated both IgA and IgG antibodies in serum indicating that Spherulites® can also be used for inducing systemic responses by a non invasive way.

Peptide & proteins delivery

Peptide and proteins are fragile molecules quickly degraded in human body, especially in the gastro-intestinal track. Tremendous effort are made to find a non invasive method of delivery of these potent drugs. Spherulites® are well designed for the delivery of these molecule as their structure allow to protect them from enzymatic degradation.

A 12 amino-acids peptide, with a 3 min half-life in blood stream has been successfully formulated as a suspension for SC injection with a release time of 6 hours. This allows the switch from a continuous infusion to three SC injections a day.

Anticancer drugs delivery

Oral delivery of anticancer drug is one of main challenge of today pharmacy. The main issues to face are the poor and variable bioavailability of these drug when administered through oral route. Spherulites® have been used to solubilize highly insoluble anticancer drugs like campthotecin derivatives, therefore providing an aqueous pharmaceutical vehicle for these molecules.

References:

O. Diat, D. Roux, F. Nallet, "Effect of shear on a lyotropic lamellar phase", *J. Phys. II France*, 3, 1427-1452 (1993)

T. Gulik, J..C. Dedieu, D. Roux, C. Degert, R. Laversanne, "Freeze-fracture electron microscopy of sheared lamellar phase", *Langmuir*, 12, 4668 (1996)

O. Diat, D. Roux, R. Laversanne, "Process for the preparation of microcapsules or liposomes with controlled size" International patent to Capsulis WO93/19735, priority FR 9204108

R. Laversanne, C. Degert, D. Roux, "Method for making a product adhere to a surface" International patent top Capsulis WO98/46199, priority FR 9704548

P. Mahy, B. Delord, J. Amédée, O. Freund, D. Roux, R. Laversanne, S. Gaubert, D. Kaiserlian, "Antigen vectors in the form of multilamellar vesicles and compositions containing antigens encapsulated in these vesicles" International patent to Capsulis WO99/16468, priority FR 9712085

O. Freund, J. Amédée, D. Roux, R. Laversanne. "*In vitro* and *in vivo* stability of new multilamellar vesicles" *Life Sciences*, 67, 2000, 411-419