SMART4FABRY

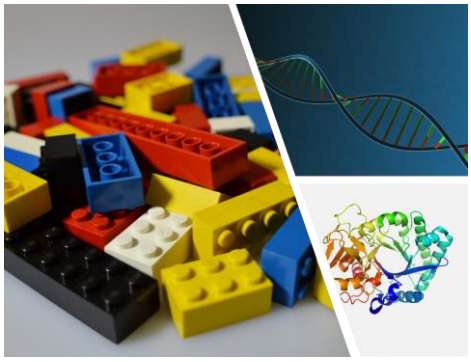
Smart Functional GLA—nanoformulation for Fabry disease

MOLECULAR SELF-ASSEMBLY

Molecular self-assembly can be defined as the autonomous and spontaneous organization of components into patterns or structures.

For being more illustrative, supramolecular chemistry can be described as a «Lego™ chemistry», in which each Lego™ brick represents a molecular building block and these blocks are held together by intermolecular interactions (non-covalent bonds) of a reversible nature, forming a more complex supramolecular entity, according to the intrinsic information contained in each component. Self-assembly can occur with components having sizes from the molecular to the macroscopic, when appropriate conditions are met.

An important interesting feature in this kind of interactions is that living cells self-assemble, offering countless natural examples of functional self-assembly. Many supramolecular species designed and developed in research have been inspired from biological systems found in nature. All these examples illustrate that self-assembly could be a practical strategy for making ensembles of nanostructures, becoming an essential part of nanotechnology. In this direction, the development of nanocarriers based on non-covalent self-assembly interactions, has become in the last years a focus of interest for researchers.



MANY EXEMPLES OF SELF-ASSEMBLY CAN BE FOUND IN NATURE

- Protein folding, in which a linear polypeptide chain is able to self-assemble in a mature protein, offering a well-defined tridimensional structure.
- Outer shell of typical viruses, as the tobacco mosaic virus (TMV). Many viruses show a protein capsid composed of multiple copies of coat proteins forming a determined geometry, i.e. rod-like structures in TMV.
- Nucleic acids, with the formation of double-stranded DNA by association of the pairing of nucleotides into two complementary chains of DNA.

PARTNERS

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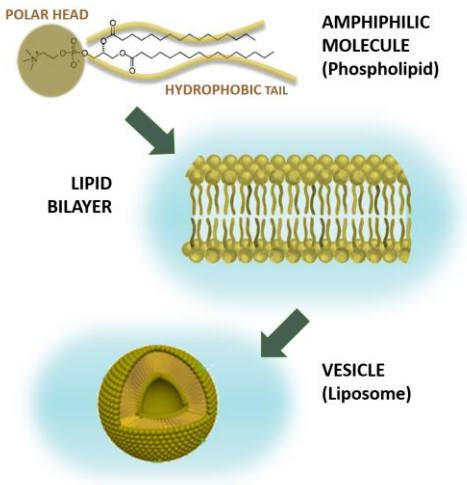
VESICLES: SUPRAMOLECULAR STRUCTURES FROM SELF-ASSEMBLED AMPHIPHILIC MOLECULES



Most of the self-assembling molecules used as monomers to produce vesicles (such as phospholipids and surfactants) show an amphipathic feature, usually composed by a hydrophilic ("water-loving") or polar head group and a hydrophobic ("water-fearing") or nonpolar part. They can spontaneously self-assemble in water forming ordered assemblies bounded by non-covalent interactions, resulting in structures with different morphologies and shapes, from spherical and rod-like micelles to amphiphilic bilayers. The morphology of the formed supramolecular entity can be considered by geometric consideration. In a first-order approximation, each monomer can be described by a packing parameter, that determines the preferred curvature of the structure formed.

SELF-ASSEMBLED NANOVESICLES FOR DRUG DELIVERY APPLICATIONS

Liposomes constitute an example of phospholipid self-assembly, forming a bilayer membrane closing an aqueous space. These systems become really interesting in the nanomedicine research field, since their amphiphilic nature allows the encapsulation of both hydrophilic and hydrophobic drugs, depending if they are encapsulated inside the aqueous space or entrapped into the membrane, respectively.

MANY LIPOSOME-BASED DRUGS ARE CURRENTLY AVAILABLE FOR HUMAN USE

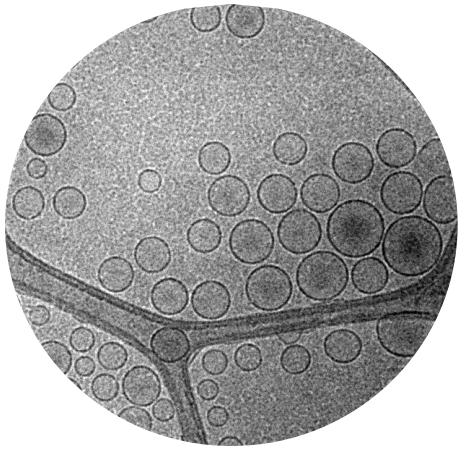
- Most of the liposomal drug formulations are administered by intravenous or intramuscular route.
- Doxil®, based on liposomal technology, was the first FDA-approved nanodrug (1995)

<15

Current clinically liposome-based products in the market

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 720942.

IMPORTANCE OF CONTROLLING THE SELF-ASSEMBLING PROCESS



Interestingly, the morphology of the final assembled structure is dependent not only on the composition and ratio of the involved molecules and geometry of the monomer, but also on parameters as the external environment, temperature or manufacturing process.

- In some systems, such as lipid-based quatsomes, the proportion of each membrane component determine the final structure. An equimolar proportion of the two components that form the membrane showed a pure vesicular phase. However, moving away from this equimolar ratio leads the formation of other self-assembled structures.

- Manufacturing process play a crucial role in the formation of vesicles. Structural differences are observed between systems prepared by DELOS-susp, a methodology based on the use of compressed CO_2 as a cosolvent, and conventional methods, like thin film hydration, in which more heterogeneous systems are obtained.

In conclusion, self-assembled processes become a very powerful tool in the nanomedicine field, as a strategy for building nanocarriers for drug delivery applications. However, knowledge and precise control on the supramolecular organization of the components become essential for obtaining robust and homogeneous nanoformulations, granting high-quality products, for fulfilling the requirements for preclinical and clinical stages.

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