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Nanoparticles and vesicles: promising drug-delivery systems

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Abstract

The study of the interaction of drugs with receptors is a subject of great relevance, because it can be applied to the research of new drugs and to the interpretation of the related biological activities. In particular, one of the main challenges that researchers have to face is related to the delivery of the molecule. In the context of healthcare safety, a proper vehicle might indeed improve the targeted and selective absorption of the drug, thus reducing its side effects. Recently, two carriers have gained high attention among the scientific community: nanoparticles and vesicles. The first ones might be obtained from macrocycles such as calixarenes, whose great advantage is the possibility to make their lipophilic structure highly hydrophilic through appropriate functionalizations. The latter arise from phospholipids in natural vesicles or anionic or cationic surfactants in synthetic ones. The present mini-review explores these carriers having possible application in human healthcare.

The study of the interaction of derivatives with human receptors, especially DNA, is an interesting and up-to-date subject, principally for the potential pharmacological activity of DNA-binders. Being the carrier of the genetic information and playing a crucial role in the cellular growth and division, DNA is in fact a biological target of several drugs used for the treatment of various diseases (1). In this context, it is important to outline that different DNA-binding compounds, although interacting with the same target, may exhibit different therapeutic effects like, for example, anti-malarial, antitumor and anti-HIV (2–5). Delivering a drug is a key step in the pharmacodynamics of the molecule and this has aroused an increasing interest toward the development of appropriate vehicles. By means of a tailored vehicle, it is in principle possible to improve the healthcare safety for drug treated patients. In this context, vesicles and nanoparticles have been developed as promising new carriers. In the last decades, for example, calixarenes macrocycles have been widely used for the development of new drug-delivery systems, especially nanoparticles. One of the biggest advantage in their use, in fact, is the possibility to make their lipophilic structure hydrophilic through functionalization with several polar groups, such as sulphonates, phosphonates or amines (6). Moreover, due to the presence of two possible sites of functionalization, the lower

and the upper rims, calixarenes are also capable to form amphiphilic derivatives (7–10). Several calixarenes have shown both low cytotoxicity, both low immunogenicity (6,11–13): for example, a calix[4]arene phosphonate and a sulphonate one have the same cytotoxicity with respect to that of glucose (12–14).

Vesicles, instead, are self-organized structures constituted by a curved double layer of surfactant molecules, entrapping an inner water pool. In liposomes the monomer units are phospholipids, while in the synthetic vesicles these can be anionic or cationic surfactants. Depending on the preparation method (15–17), it is possible to obtain vesicle dispersions with different characteristics; for example, the formation of unilamellar or multilamellar vesicles can be favoured. An important property of vesicles is the tuneable fluidity of the double layer (18,19). The latter can assume various structures with different permeability and fluidity, depending on temperature. The open double layers and both the uni- or multilamellar vesicles undergo to very well defined structural changes at certain temperatures, called phase transition temperatures (20). The main thermotropic transition phase, interesting for both biological and technological possible applications, is that from the rigid state, commonly called "gel-like", to the fluid state, "liquid crystal-like" phase. It is important to emphasize that by modulating the fluidity of the vesicular nano-aggregate it is possible to modify the solubilisation ability of the phospholipidic double-layer and, consequently, to vary the reactivity of substrates (21–23). Furthermore, DNA is able to interact with liposomes and the supramolecular systems formed are commonly called lipoplexes. The formation of the DNA/Liposome supramolecular structures depends on several parameters, like for example the lipid nature and concentration, the lipid/DNA ratio, the contact time, the temperature and the nature of the reaction medium (24–26). The lipoplexes formed by the association of cationic surfactants and DNA are promising and efficient genic carrier systems (27–30). However, some cationic lipoplexes are also cytotoxic. To get round this difficulty, neutral lipid/DNA systems in the presence of bivalent metal cations have been recently considered (31). These ternary supramolecular systems, analogously to those formed by the cationic liposomes, resulted to be very stable.

In this respect, it is worth mentioning that the supramolecular systems, formed by both the cationic and the neutral liposomes, have been studied only in equilibrium conditions, whereas a few attentions have been devoted to the kinetics of lipoplex formation (32,33). In particular, it has been reported that the lipoplex supramolecular structures are time dependent, and this result puts limits on the transfection efficiency for genic therapy (34). As a consequence, the search of efficient supramolecular structures as alternative vehicles of genic material requires the design of novel systems that can be formed in short time and that are stable, highly compartmentalized and non cytotoxic. In this context, first row transition metal bivalent cations have been used as stabilizing agents of lipoplexes formed by neutral lipid/DNA systems (31). However, while numerous studies have been reported on the interaction of metal complexes with DNA in water solution, to our knowledge in the literature there are not studies on the interaction of metal complexes with DNA confined in nanoscopic biomimetic systems. The only possible exception is a study about the confinement effect in reverse micelles on the intercalation of a copper(II)-Schiff base complex into native DNA (35). The results of this study indicate the occurrence of dramatic structural changes of both the DNA and the metal complex-DNA system, when going from aqueous solution to the micellar phase. Finally, quantum-chemical, molecular mechanics or hybrid computational approaches are useful for assisting the molecular drug design and for studying the nature of the host-guest interactions occurring between the drug and the carrier (36–38).

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