Journal of Drug Delivery Science and Technology 32 (2016) 256–269

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Some recent advances on liposomal and niosomal vesicular carriers

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ARTICLE INFO

Article history:
Received 31 July 2015
Received in revised form
1 October 2015
Accepted 11 October 2015

Keywords:
Liposomes
Niosomes
Drug delivery
Drug targeting

ABSTRACT

Efficient and safe drug delivery has always been a challenge in theraphy and diagnostics. The use of nanotechnology, as well as the development of nanocarriers for drug delivery, received great attention according to the evidence that they can theoretically act as “magic bullets” capable to hit the target cells while sparing normal tissues and organs. Since 1980 the formulation of vesicular carriers became a tool to improve drug delivery. Liposomes and niosomes are self assembled nanocarriers obtained by hydration of amphiphilic molecules and appropriate amounts of cholesterol. Vesicular carriers can be unilamellar or multilamellar, are suitable as carriers of both hydrophilic and lipophilic drugs and are able to deliver drugs to the target site.

The vesicle properties are specifically dictated by size, shape, and surface chemistry which are able to modify the intrinsic pharmacokinetics of the drug and, eventually, drug targeting to the pathological areas.

This up-to-date review deals with the importance of various vesicular carriers in drug delivery with particular emphasis on innovative liposomes and niosomes developed at the Department of Drug Chemistry and Technologies at “Sapienza” University of Rome.

1. Introduction

The exploration of colloidal systems, i.e., systems containing nanometer sized components, for biomedical applications was launched already more than 50 years ago [1–3] and efforts to explore colloidal (nano) particles for drug delivery date back to the mid 70's [4]. More recently, the merger of nanoscience with medicine quickly fostered the conceptualization of nanomedicine. The adoption of nanoscience terminology by pharmaceutical scientists resulted in the advent of nanopharmaceuticals.

According to Rivera et al. [5] nanopharmaceuticals are defined as “pharmaceuticals engineered on the nanoscale, i.e., pharmaceuticals in which the nanomaterial plays a pivotal therapeutic role or adds additional functionality to the previous compound”. Even if Rivera's observations were mostly related to nano inorganic drugs rather than to liposomes, which are carriers for drugs, the common feature between nanodrugs and nanovectors is the scale: nanomedicine could be defined as the use of nanoscale or nanostructured materials in medicine that, according to their structure, have unique medical effects and provides unique characteristics to the pharmaceutical form [6]. Therefore nanocarriers offer an innovative approach to drug delivery, providing a range of features including cargo protection, increased dose delivery to target sites, enhanced drug transport through various biological membranes or prolonged and controlled drug release. Actually, the complexity of the overall human body and the healthy protective mechanisms in the body may lead to ineffective drug treatments. Consequently, the development of biologically functional nanocarriers that incorporate drugs to selectively bind and target specific cells becomes crucial.

Ideally, a drug delivery system (DDS) could be engineered to obtain the following set of properties: (1) long half-life in the body; (2) target to the site of the disease; (3) drug release as a response to local stimuli of the pathological site, such as intrinsically abnormal pH values or temperature, or to externally applied heat, magnetic field, or ultrasound; (4) enhanced intracellular delivery of drugs and genes; (5) encapsulation of a reporter (contrast) component

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http://dx.doi.org/10.1016/j.jddst.2015.10.008
1773-2247/

supplying a real time information about the DDS biodistribution and target accumulation.

There have been many attempts to functionalize and design nanocarriers so as to increase their efficacy; nevertheless, although the criteria for a successful nanocarrier are quite numerous, only few nanocarriers have actually shown significant clinical potential and practical application. Among commercially available nanopharmaceuticals, vesicular carriers (e.g. liposomes) are anyhow present in quite a large number [7,8].

Vesicular carriers have unique properties such as nanoscale size, high surface-to-volume ratio, and favorable physico-chemical characteristics. They have the potential to modulate both the pharmacokinetic and pharmacodynamic profiles of drugs, thereby enhancing their therapeutic index. Loading of drugs into vesicles can increase *in vivo* stability, extend blood circulation time, and allow controlled drug release altering the biodistribution of drugs.

Among the various peculiar characteristics that vesicles can acquire, one of the most attractive is the stimuli-responsive property.

Generally, the application of a stimulus causes structural or conformational changes in amphiphilic molecules, tuning the responses of the systems, including capture and release of chemicals, chemical reactions, and morphology transitions. Therein, much effort has been directed to the development of smart vesicles that respond to internal or external stimuli, in particular, pH, temperature, redox conditions, ultraviolet light and magnetic fields either reversibly or irreversibly [9].

The most important results of vesicle modification conferring stimuli-responsiveness include an increased stability and half-life of nanocarriers in the circulation, required biodistribution, passive or active targeting into the pathological site, responsiveness to local physiological stimuli such as pathology-associated changes in local pH and/or temperature. Furthermore, such smart systems can serve as imaging/contrast agents for various imaging modalities (gamma-scintigraphy, magnetic resonance imaging, computed tomography, ultra-sonography) [10]. Obviously for the preparation of such smart multifunctional pharmaceutical nanovesicles, chemical moieties providing specifically required individual properties must be simultaneously assembled in the same nanocarrier. Multifunctional pharmaceutical nanovesicles could provide almost unlimited opportunities in producing highly efficient and specialized systems for bioactive substances, genes and diagnostic agents [11–13]. However, such systems still represent a challenge in pharmaceutical technology and, although the approach is quite recent, it shows already a promising future.

Taking into account the reported properties, a preliminary question should be faced: can vesicular carriers be considered as "true" nanopharmaceuticals that meet the criteria of Rivera's definition [5]?

Here we try to answer this question by means of this review which discusses the importance of different vesicular carriers in drug delivery with particular emphasis on innovative liposomes and niosomes developed at the Department of Drug Chemistry and Technologies at "Sapienza" University of Rome.

Although the use of liposomes for drug delivery is certainly encouraging, liposomes still present some problems, i.e. storage stability (mainly related to oxidation processes) and leakage of encapsulated drugs. In addition, it should be also considered that synthetic phospholipids are usually expensive and, on the other side, natural phospholipids show a variable degree of purity [14]. An alternative approach to liposomes is the use of niosomes.

Niosomes are analogous to liposomes; in fact they can be prepared following the same procedures, under a variety of conditions, leading to the formation of unilamellar or multilamellar vesicular structures [15]. Moreover niosomes, like liposomes, are capable of encapsulating both hydrophilic and lipophilic drugs [16,17].

The composition, the mechanism of drug delivery, the methods of preparation as well as the characterization of vesicular carriers will be discussed. In particular the great effort spent on the characterization of vesicular systems will be reported (Table 1), according to the evidence that the physical-chemical characterization of nanovectors plays also a pivot role for their therapeutic applications and needs to be deeply investigated for an actual *in vivo* application of such nanoparticles and to tailor their targeting location after systemic injection. In fact, these parameters depend on the preparation procedures, compositions and surface features of the nanoparticles as previously reported [18,19].

An overview of liposome/niosome potential applications will be also provided together with future perspectives and challenges for the achievement of enhanced drug delivery and improved diagnostic applications.

1.1. Vesicles and pH sensitivity

For an appropriate control of vesicular *in vivo* properties, structure modifications are often used to achieve targeting to pathological organs or tissues and to impart sensitivity to stimuli which are specific of certain environments and/or pathological areas.

Different stimuli, intrinsically characteristic of the pathological areas or of the target tissue, could modify the properties of the drug-in-nanocarrier system, thus providing enhanced/controlled drug release, improved cellular drug uptake, controlled intracellular drug fate. Typical stimuli in pathological tissues include pH and redox conditions. For example, intratumoral pH value in solid tumors may drop to 6.5, because of hypoxia and massive cell death inside the tumor [28] and drops still further inside the cells, especially, within endosomes (5.5 and even below) [29].

pH-sensitivity was the first example of a stimulus-sensitivity used to appropriately modify drug/DDS behavior in the pathological areas with the decreased pH value or in the internalization pathway.

To obtain pH-sensitive niosomes, **C**holesteryl hemisuccinate (CHEMS), a pH-sensitive/responsive component, was incorporated into the nanocarriers and the cell internalization pathway was investigated in comparison to pH sensitive liposomes.

CHEMS shows the ability to acquire a lamellar organization after hydration in neutral or alkaline aqueous phase leading to a less "fluid"and to a thicker bilayer in pH-sensitive samples at neutral pH [30]. On the other side, Cholesterol (CHOL) forms monohydrate crystals in aqueous environment not influenced by pH variations [31]. At acidic pH, vesicular destabilization occurs due to protonation and/or dehydration of CHEMS polar headgroups [32].

In a first paper [33] it was possible to describe the cytoplasmatic delivery of a fluorescent probe, after cellular interaction with non-phospholipid vesicles and avoiding lysosomal degradation. This study led to positive results both in the pharmaceutical technology and in the biological areas. From the technological point of view, pH sensitive surfactant vesicles (SVs) made of Tween20/Cholesterol/Cholesteryl hemisuccinate were prepared. These pH sensitive niosomes were stable and able to maintain pH sensitivity in the presence of serum. The vesicular stability in serum could be related to the presence of polyethylene glycol units of the surfactant molecules on the vesicle surface. A following study allowed to clarify the mechanism of cellular interaction of neutral and pH-sensitive vesicle formulations, discriminating among fusion, clathrin-or caveolae-mediated endocytosis, phagocytosis and non clathrin–non caveolae dependent endocytosis. The obtained results imply that, as it occurs for liposomes, SVs were internalized by an energy-dependent process.