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Review

Formation of artificial multicompartment vesosome and dendrosome as prospected drug and gene delivery carriers

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ABSTRACT

Extensive studies in the last fifty years on the development of multifunctional liposomes have improved their drug delivery potential. Specifically, they fulfill to a significant degree the requirements which an effective drug carrier should exhibit, *i.e.* biocompatibility, biodegradability, drug encapsulation and protection of the drug, targeting to specific cells, reasonable stability in the biological milieu, transport through cell membranes and controlled drug release. However, despite these properties which have been achieved to a significant degree through molecular engineering of the liposome bilayers, a universal liposomal carrier has not yet been developed since it is rather difficult for the above properties to be simultaneously fulfilled. For this purpose a multicompartmentalization strategy was applied through which liposomes encapsulating smaller ones in their aqueous core were prepared. Multicompartment systems have also been prepared by encapsulation of dendrimers in the aqueous core of liposomes. In this manner drug delivery systems were prepared providing a double protection to drugs encapsulated inside the core of the small liposomes or incorporated in dendrimers. The external liposomal bilayer is also susceptible to multifunctionalization while their drug release can more effectively been tuned compared to single-compartment systems.

Modular-type strategies have been employed for the preparation of these multicompartment systems. Thus, unilamellar liposomes and mono-dispersed dendrimers are selected as the drug delivery modules from which universal multifunctional and multicompartment drug delivery systems have been obtained *i.e. vesosomes*, which are liposomes encapsulating smaller liposomes and *dendrosomes*, which are liposomes encapsulating dendrimers. Examples of the application of drug and gene delivery employing vesosomes and dendrosomes as carriers are critically discussed.

Contents

1. Introduction

A significant number of nano-sized drug delivery systems has been developed for enhancing the therapeutic efficacy of certain drugs [1]. Among these systems are included self-assembled nanoparticles such as micelles [2,3], liposomes [4–8] and also polymeric nanoparticles [9–11] originating either from linear polymers [12,13] or branched dendritic polymers [14–20]. The most extensively investigated nanoparticles are liposomes which were first prepared in mid-sixties by Bangham et al. [21] and have managed to enter the pharmaceutical market primarily due to their biocompatibility and biodegradability. In the present review the term *liposome* is used for a spherical vesicle consisting of an aqueous core enclosed by one or more lipid bilayers, while the alternative term *vesicle* is used for certain, extensively used

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in the literature abbreviations such as LUV (Large Unilamellar Vesicle), GUV (Giant Unilamellar Vesicle), and SUV (Small Unilamellar Vesicle). Notable examples of approved liposomal drugs are the anticancer formulations Doxil® (a 80–120 nm liposomal formulation of doxorubicin), DaunoXome (a liposomal formulation of Daunorubicin of about 60 nm diameter) and AmBisome for infectious diseases (a 55–75 nm liposomal formulation of Amphotericin B). Also Lipoplatin™, liposomally encapsulated cisplatin, is in Phase III clinical trials for a variety of cancer indications, including non-small cell lung cancer (NSCLC).

Upgrading the efficacy of liposomal drugs has been achieved by molecular engineering of the external liposomal bilayer by the introduction of appropriate functional moieties, *i.e.* by applying the strategy of multifunctionalization [22–24]. Specifically, multifunctional liposomes have been prepared bearing targeting ligands, for instance folate [25,26], or antibodies [27] for binding to complementary cell receptors, and protective groups, for example poly(ethylene glycol) chains (PEG) [28,29] which prolong the circulation of the carriers in biological fluids, and molecular transporting moieties such as penetrating peptides [30,31] which enhance their transport through cell membranes, while molecular imaging modalities, such as MRI, CT, optical imaging (Bioluminescence and Fluorescence), SPECT and PET, can be employed to follow their intracellular fate *in vitro* and *in vivo* [32]. Furthermore, due to the structural features of liposomes, binding amplification to cell receptors will result through the so-called multivalent effect. Due to multivalency, more than one cell receptors can simultaneously be accessed by one nanoparticular carrier [33,34] and this greatly enhances the attachment of the carrier to cell.

However, despite the use of multifunctionalization strategy which is applied to the liposomal bilayer for endowing liposomes with the above advantageous properties, the preparation of a universal drug delivery carrier has not yet been achieved since it is difficult to simultaneously fulfill all these requirements. In view of these hurdles, it is in order to further elaborate liposomes for obtaining an optimum universal liposomal-type carrier. For this purpose, simple drug delivery modules are prepared, the facile combination or interaction of which will provide systems exhibiting simultaneously most or all of the above properties which ensure effective drug delivery. Specifically, unilamellar liposomes and dendrimers, which are the mono-dispersed class of dendritic polymers, due to their structural features, size and facile functionalization, are selected as the drug delivery modules from which universal multifunctional and multicompartment [35–38] drug delivery systems can be derived. With the above delivery modules two types of nanoparticles which share the above properties have been obtained and specifically: Liposomes encapsulating smaller liposomes, named *vesosomes*, Fig. 1A, and liposomes encapsulating dendrimers, named *dendrosomes*, Fig. 1B.

In comparing vesosomes and dendrosomes it is assumed, in the first place, that the space occupied by each dendrimeric molecule represents a separate compartment of dendrosomal nanoparticle, in analogy with the encapsulated small liposomes inside the aqueous core of vesosomes. The external bilayer membrane of both nanoparticles is susceptible to functionalization affording multifunctional vesosomes and dendrosomes respectively. Regarding functionalization, these nanoparticles exhibit similar behavior, but this is not however the case concerning their other properties. Thus the size of dendrimers is in general smaller than that of encapsulated liposomes, which can also be strictly determined by an appropriate selection of dendrimeric molecular weights. Also, the size of dendrosomes compared to vesosomes is smaller and more easily tuned. Concerning drug loading in vesosomes, the drug is encapsulated inside the aqueous core of the small liposomes while for dendrosomes the possibility exists for covalent and non-covalent attachment to the dendrimeric scaffold, in this manner enhancing the flexibility of the latter carrier. Vesosomes consisting of liposomes of various sizes are biocompatible and biodegradable; the same properties should also be exhibited by dendrosomes through the selection of biocompatible and biodegradable dendrimers for encapsulation.

Lipid-based compartments encountered in this type of systems are primitively reminiscent of organelles in eukaryotic cells. They would therefore basically share certain structural analogies of biological cells and exhibit some analogous properties and interaction profiles. Thus, these multicompartment systems could be appropriate for modeling certain cell processes such as the evolution of eukaryotic cells, transport properties through bilayer membranes, development of nano-reactors [39,40] and application as a new generation of Drug Delivery Systems (DDS). The latter prospective application is the subject of the present review. These new drug delivery systems provide a double protection to encapsulated drugs, one being the bilayer of the encapsulated small liposomes while the other being the bilayer of the larger liposomes that enclose the smaller ones. In dendrosomes, encapsulated drugs except to the external bilayer protection, they are also protected due to their solubilization inside the nanocavities of dendrimers or due to conjugation to their scaffold. Another crucial characteristic of multicompartment systems is that a cocktail of drugs, which in certain cases consists of non-compatible drugs, can be encapsulated in the internal liposomal or dendrimeric containers. Also, drug release from these multicompartment systems can more effectively be tuned compared to single-compartment systems.

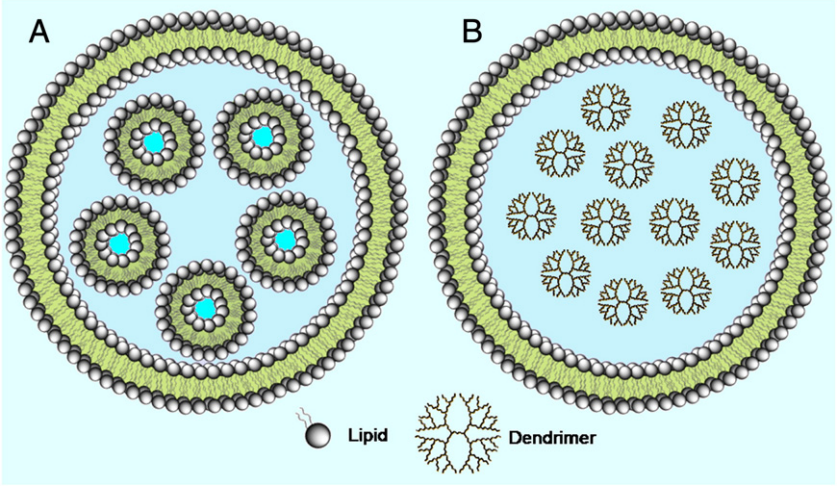

Fig. 1. (A) Vesosomes: Liposomes encapsulating small liposomes in their aqueous core. (B) Dendrosomes: Liposomes encapsulating dendrimers in their aqueous core.