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Lipid-based core-shell nanoparticles: Evolution and potentialities in drug delivery

Virginia Campani, Simona Giarra, Giuseppe De Rosa*

Department of Pharmacy, Università degli Studi di Napoli Federico II, Via D. Montesano 49, 80131 Naples, Italy

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ABSTRACT

Over the last decade, impressive progress in the field of nanomedicine has led to the development of novel biomaterials and nanotechnology platforms. However, lipid-based nanovectors, i.e. liposomes, combining safety, versatility and delivery efficiency, remain the most "popular" approach. Lipids, especially charged lipids, have been used to design nanoparticles characterized by a core-shell structure. In these nanoparticles a lipid shell interacts with a core based on different biomaterials. Drugs characterized by a net charge can be condensed in the core, which is then covered by the lipid shell. This approach has been investigated in relation to the delivery of different active molecules, among them macromolecular drug, e.g. nucleic acids, and small molecules, e.g. bisphosphonates. This review reports the progress that has been made in the development of this technology and its potential applications in drug delivery.

1. Introduction

In the last ten years the number of published scientific studies in the field of nanomedicine has sharply increased leading to the development of different "families" of nanovectors tailored to meet specific requirements in drug delivery and targeting. Different biomaterials have been proposed depending on the drug and on the biomedical target. Moreover, the combination of different biomaterials, as well as the structure of the nanovectors, represents a further level of complexity.

Despite the number of nanotechnology-based platforms for drug delivery currently available, the number of clinical studies focused on these formulations is still very limited [1,2] with few products on the market [2,3]. The majority of studies do not go beyond the preclinical stage [1,4], remaining limited to laboratory scale. In many cases, the design of the nanotechnology based formulations has produced promising results in vivo, but is not suitable for clinical and industrial development. Other issues in the

Abbreviations: NPs, nanoparticles; siRNA, small interfering RNA; miRNA, microRNA; DC-Chol, 3b(N-(N¢,N¢-dimethylaminoethane)carbarmoyl)-cholesterol; DOPE, dioleoylphosphatidylethnolamine; DMRIE, 1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide; DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; Chol, cholesterol; DSPE-PEG, 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000; NGR, aspargine–glycine–arginine pepetide; DOX, doxorubicin; DSGLA, N,N-distearyl-N-methyl-N-2[N′-(N2-guanidino-L-lysinyl)] aminoethylammonium chloride; PTX, paclitaxel; VEGF, vascular endothelial growth factor; VAP, vapreotide; BBB, blood brain barrier; Tf, Transferrin; BMVECs, murine brain microvascular endothelial cells; U87, human glioblastoma cells; LPC, cationic liposomes; EGFR, epidermal growth factor receptor; MCF-7, human breast cancer cells; PPD, PEG-peptide-DOPE ternary conjugate; MMP, matrix metalloproteinase; pDNA, plasmid DNA; DPPE, dipalmitoylphosphatidylethanolamine; PC, phosphatidylcholines; PS, phosphatidylethanolamine; RAW 264.7, mouse macrophage cell line; HA, hyaluronic acid; CaP, calcium/phosphate; ZOL, zoledronic acid; Pgp, P glycoprotein; MDR, multidrug resistant; DOPA, dioleoylphosphatidic acid; DOPC, dioleoylphosphatidylcholine; PEI, polyethylenimine; MCF-7, Human breast adenocarcinoma cell lines; GBM, glioblastoma; rPAA-Chol polymer, poly (amidoamine); T7, HAIYPRH; mPEG-PLA, poly(ethylene glycol)-block-polylactide; BHEM-Chol, N,N-bis(2-hydroxyethyl)-N-methyl-N-(2-cholesteryloxycarbonylaminoethyl) ammonium bromide; PLA, polylactide; PLGA, poly(D,L-lactide-co-glycolide; CTAB, hexadecyltrimethylammonium bromide; EPC, ethylphosphocholine; PBAE, poly(β-amino-ester); PEI, polyethilenimine; DODMA, 1,2-Dioleyloxy-N,N-dimethyl-3-aminopropane

* Corresponding author.
E-mail addresses: virginia.campani@unina.it (V. Campani), simona.giarra@unina.it (S. Giarra), gderosa@unina.it (G. De Rosa).

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clinical and industrial development of nanovectors are the difficult scale-up and the poor chemical and physical stability of the formulation during storage (i.e. aggregation of the nanovectors, degradation of the biomaterials, leakage of the encapsulated drug).

The use synthetic or polymeric components to deliver active molecules remains controversial due to their obvious limitations in term of systemic toxicity and high cost of production [5]. In the field of nanomedicine, lipid and mainly phospholipid-based delivery systems are certainly the most investigated platform due to their biocompatibility, biodegradability, very low toxicity and versatility [5–9]. Thus, lipid vesicles have been proposed to deliver both lipophilic and hydrophilic drugs by different routes of administration [6,10]. Liposomes can be considered the first generation of lipid nanocarriers, with several formulations already in clinical practice. Marketed formulations based on liposomes have been successfully used for the delivery of anticancer, antimicrobial, anaesthetic agents and vaccines [11].

Other families of lipid nanovectors have been proposed for drug delivery. For instance, solid lipid nanoparticles (SLNs) are delivery systems composed of a solid lipid core, generally based on glycerides, and stabilized by a surfactant coating [6,10]. SLNs are characterized by a core that remains solid at 37 °C, assuring nanoparticle stability in vivo. The techniques required to prepare SLNs are solvent-free, although high energy forces are often necessary [6]. Moreover, SLN are often characterized by low drug encapsulation efficiency as well as by premature, fast drug release [6,10,12]. Solid lipid nanocapsules (LNCs) can be considered a "second generation" of SLN, and consist, at room and body temperature, of a liquid lipid phase surrounded by a solid lipid shell. Compared to SLNs, LNCs are generally characterized by a higher encapsulation efficiency and finer control of drug release [13,14]. LNC have been successfully used as a drug delivery system for various applications and by different administration routes [14]. Recently, growing attention has been paid to lipid-based self-emulsifying drug delivery systems (SEDDSs) composed of a mixture of lipids, surfactant and co-surfactant able to emulsify in aqueous medium without the use of high energy forces. The resulting low production costs makes SEDDSs particularly attractive. However, their application has been proposed almost exclusively for the oral route [15–18]. Moreover, SEDDs, as well as SLNs and LNCs, are characterized by a lipid core, and are suitable for the encapsulation of lipophilic drugs in particular.

From a general point of view, lipid nanocarriers have been proposed for the delivery of drugs as which differ in terms of hydrophilicity/lipophilicity and molecular weight. Liposomal nanocarriers remain, in this context, the system with the highest versatility, due to the possibility to encapsulate lipophilic, hydrophilic molecules, independently of molecular weight. A great deal of work has been carried out to use lipid nanocarriers for the delivery of nucleic acids, i.e. small interfering RNA (siRNA) and microRNA (miRNA). These oligonucleotides are potentially useful for the development of novel therapies for the treatment of various diseases, but are also characterized by biopharmaceutical issues, thus requiring the development of delivery strategies [19,20]. In the case of liposomes, anionic molecules such as siRNA and miRNA have been efficiently encapsulated by using cationic lipids. Indeed, cationic liposomes have been used extensively in transfecting nucleic acid into cells and are the basis for a number of marketed commercial agents designed for in vitro experiments [21]. Liposomes based on cationic lipids have been used for local delivery of nucleic acid in humans. Encouraging results were found following nasal administration of DNA complexed with cationic liposomes in patients with cystic fibrosis [22–24]. DC-Chol (3b(N-(N′,N'-dimethylaminoethane)carbarmoyl)-cholesterol)/ dioleoylphosphatidylethanolamine (DOPE) cationic liposomes were also used in patients with different cancer types by injection directly into a cutaneous nodule, generating a strong local immune response [25]. Phase II of the clinical study demonstrated the usefulness of direct intratumoral injection with Allovectin-7, (a plasmid DNA encoding the genes HLA-B7 and beta2-microglobulin) complexed with a cationic lipid mixture, DMRIE (1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide) /DOPE [26]. Although cationic liposomes have also been used in clinical trials for chemotherapeutics, e.g. paclitaxel [27,28], lipoplexes are characterized by heterogeneous size distribution and their size is very sensitive to the experimental conditions used in preparation [29–31]. SLNs containing cationic lipid, e.g. DOTAP, or other cationic additives, e.g. cetyl trimethylammonium bromide (CTAB), have been proposed to complex miRNA to obtain efficient protection of the nucleic acid towards enzymatic degradation and enhanced RNA delivery [32,33]. Moreover, they aggregate in presence of serum, mainly following interaction with the serum components, especially albumin [34] with consequent aggregation of the complexes and rapid uptake by the Kupffer cells of the liver [35]. Following intravenous administration, nucleic acid/lipid nanoparticles complexes transiently accumulate into the capillaries of the lung, gradually redistributing to the liver, especially in the Kupffer cells [35,36]. The addition of PEGylated lipids to the complexes prevents the complex aggregation in serum, also providing stealth properties [37]. However, this approach has achieved only limited in vivo applications, likely due to the difficulty to control the size as well as the complex structure/morphology [38]. Higher in vivo stability has been achieved by replacing positively charged lipids with ionisable cationic lipids i.e. 1,2-dioleyl-3-dimethylammonium propane (DODAP), 1,2-dioleyloxy-N,N-dimethyl-3-aminopropane (DODMA). These nanovectors are known as stable nucleic acid lipid particles (SNALPs) [39,40]. The use of an ionisable lipid leads to neutral vesicles at physiological pH with higher physical stability and longer circulation time compared to cationic liposomes. [39,41]. Nowadays, different formulations based on ionisable lipids are under clinical trial [41,42].

Despite the huge number of studies and the encouraging results achieved over the last decade, the use of lipid nanocarriers in clinics remains in its infancy. Moreover, the use of lipid nanocarriers for the delivery of nucleic acids in clinical practice is still far off. Novel strategies to enhance the delivery efficiency are required as is greater effort in the design of strategies to facilitate the translation of these technologies from the lab to the large scale. In this direction, the core-shell nanoparticles, which has recently emerged for the delivery of different molecules, must be considered an opportunity. In this review, the peculiarities and the advantages of core-shell nanoparticles, compared to other lipid nanocarriers, are described and discussed. Special attention will be paid to the delivery of siRNA and miRNA, still considered an open challenge today. However, when worthy of note, novel applications of lipid core-shell nanoparticles for the delivery of other classes of drugs, i.e. peptides or small molecules, are outlined.