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Effect of phosphorus dendrimers on DMPC lipid membranes

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ABSTRACT

Large unilamellar liposomes and multilamellar vesicles consisting of DMPC interacted with cationic phosphorus-containing dendrimers CPDs G3 and G4. DSC and ζ-potential measurements have shown that liposomal-dendrimeric molecular recognition probably occurs due to the interaction between the complementary surface groups. Calorimetric studies indicate that the enthalpy of the transition of the lipids that interact with CPDs is dependent on the dendrimers generation.

These results can be used in order to rationally design mixed modulatory liposomal *locked-in* dendrimeric, drug delivery nano systems.

1. Introduction

Dendrimers represent the fourth and most recent category of macromolecular architecture (Tomalia, 2005). Unlike linear polymers they have a well-defined structure that leads to low MW polydispersity index values. Dendrimers have attracted much interest since their discovery due to the specific structure which makes them suitable for a variety of biomedical applications (Klajnert et al., 2004, 2006; Smith, 2008; Svenson and Tomalia, 2005). They are small in size, while their low polydispersity can contribute to the reproducibility of their pharmacokinetic behavior (Klajnert et al., 2009). The use of dendrimers as modulators of the release rate of a drug incorporated into liposomes and the possible alterations of the drug bioavailability seems to be an attractive field for research (Gardikis et al., 2010). In the present work we especially focus on interactions between dendrimers and model lipid membranes. The findings from this study could prove helpful to rationally design new advanced liposomal drug delivery systems for bioactive molecules by combining dendrimeric and liposomal technologies.

We tested cationic phosphorus containing dendrimers for lipid membranes interaction. CPDs differ from the molecules described previously by Supattapone et al. (1999). They have a hydrophilic surface and a hydrophobic backbone which allows for efficient membrane penetration (Loup et al., 1999). Because of water-solubility most of the potential applications of phosphorus-containing dendrimers are related to biology. Phosphorus dendrimers are more stable then PAMAM dendrimers but less than PPI dendrimers (Caminade and Majoral, 2005; Solassol et al., 2004). Here we show that CPDs were able to change the properties of DMPC lipid membranes.

2. Experimental

2.1. Materials

Phosphorus dendrimers were synthesized by the Laboratoire de Chimie de Coordination du CNRS by group of Professor Majoral J.P. The main characteristics and synthesis of CPDs were described earlier (Caminade and Majoral, 2005). CPDs-G3, $C_{624}H_{1104}N_{183}Cl_{48}O_{42}P_{45}S_{42}$ (generation 3, 48 surface cationic end groups, MW: 16,280; diameter: 4.1 nm) and CPDs-G4, $C_{1296}H_{2256}N_{375}Cl_{96}O_{90}P_{93}S_{90}$ (generation 4, 96 surface cationic end groups, MW: 33,702; diameter: 5 nm), are presented in Fig. 1. Phospholipid: 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), was purchased from Avanti Polar Lipids and used without further purification. All other reagents used were of

Abbreviations: CPDs, cationic phosphorus-containing dendrimers; DMPC, 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine; DSC, differential scanning calorimetry; ΔH, main phase-transition enthalpy; LUVs, large unilamellar vesicles; MLVs, multilamellar vesicles; MT, endothermic main transition peak; G3, generation 3; G4, generation 4; PT, endothermic pre-transition peak; T_m, gel to liquid-crystalline phase transition temperature; $\frac{1}{2}\Delta T_p$, half width of the peak transition.

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Cationic carbosilane dendrimers–lipid membrane interactions

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ABSTRACT

The aim of this work was to study interactions between cationic carbosilane dendrimers (CBS) and lipid bilayers or monolayers. Two kinds of second generation carbosilane dendrimers were used: NN16 with Si–O bonds and BDBR0011 with Si–C bonds. The results show that cationic carbosilane dendrimers interact both with liposomes and lipid monolayers. Interactions were stronger for negatively charged membranes and high concentration of dendrimers. In liposomes interactions were studied by measuring fluorescence anisotropy changes of fluorescent labels incorporated into the bilayer. An increase in fluorescence anisotropy was observed for both fluorescent probes when dendrimers were added to lipids that means the decreased membrane fluidity. Both the hydrophobic and hydrophilic parts of liposome bilayers became more rigid. This may be due to dendrimers' incorporation into liposome bilayer. For higher concentrations of both dendrimers precipitation occurred in negatively charged liposomes. NN16 dendrimer interacted stronger with hydrophilic part of bilayers whereas BDBR0011 greatly modified the hydrophobic area. Monolayers method brought similar results. Both dendrimers influenced lipid monolayers and changed surface pressure. For negatively charged lipids the monitored parameter changed stronger than for uncharged DMPC lipids. Moreover, NN16 dendrimer interacted stronger than the BDBR0011.

1. Introduction

Very often it is not a problem to create a drug but to transport it into the cell. In the bloodstream drugs are exposed to many factors like peptides or enzymes which can destroy them or interact with them. For the drug to get into the right place in the body means that it has to pass membrane barrier and interact properly inside the cell. Many publications are devoted to the problem of drug carriers formation, synthesis and way of transport (Yokoyama, 2005; Xiaopeng et al., 2007; Sahoo et al., 2008; Chen et al., 2008; Bronich, 2010; Yuan et al., 2010). Drug carriers are substances that could solve many problems in drug delivery. Those molecules should be able to improve the delivery and the effectiveness of drugs. Moreover, drug carriers are used to reduce cytotoxicity and improve drug metabolism (Petzinger and Geyer, 2006; Dong et al., 2010). They are exerted in a controlled-release technology to prolong *in vivo* drug actions (Jansen et al., 1994; Chen et al., 2008; Nanjwadea et al., 2009). Nowadays there are few systems of drug transport like liposomes, albumin microspheres, bioconjugates, virosomes or dendrimers (Bhardwaj and Burgess, 2010; Anada et al., 2009; Thakkar et al., 2005; Lua et al., 2002; Daemen et al., 2005; Najlah and D'Emanuele, 2006). Dendrimers are quite a new class of globular polymers and because of their properties they generate high interest. Among their possible biomedical applications are drug transfer or serving as DNA carriers. It is possible either by encapsulation in their interiors or by bonding to the surface groups.

For the efficient transport of a medicine a drug carrier has to pass through the cell membrane. Cell membranes are complex structures made of lipids and proteins. To understand how dendrimers can cross this barrier, first it is necessary to understand interactions between these molecules and lipid bilayers. Model membranes like liposomes are excellent research models for experiments because of their simple composition, easy preparation and a good enough time stability. In the literature there are numerous studies on interactions between mostly polyamido amine (PAMAM) dendrimers and liposomes (Ottaviani et al., 1998,1999; Castile et al., 1999; Purohit et al., 2001; Hong et al., 2004, 2006; Mecke et al., 2004, 2005a,b; Klajnert and Epand, 2005; Lee and Larson, 2006; Klajnert et al., 2006; Gardikis et al., 2006; Yan and Yu, 2009; Kelly et al., 2008, 2009; Ionov et al., 2010; Smith et al., 2010; Wrobel et al., 2011; Tiriveedhi et al., 2011; Ionov et al., 2011). Dendrimers can either pass through the lipid bilayer or dendrimers-lipids micelles are

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Interaction of Cationic Phosphorus Dendrimers with Lipid Membranes

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ABSTRACT

Large unilamellar liposomes and multilamellar vesicles consisting of DMPC interacted with cationic phosphorus-containing dendrimers CPDs G3 and G4. DSC and ζ -potential measurements have shown that liposomal-dendrimeric molecular recognition occurs due to the interaction between the complementary surface groups. Calorimetric studies indicate that the enthalpy of the transition of the lipids that interact with CPDs is dependent on the dendrimers generation. These results can be used in order to rationally design mixed modulatory liposomal locked-in dendrimeric, drug delivery nano systems.

Keywords: Dendrimer, lipid membrane, dendrimer/membrane interaction.

1.INTRODUCTION

Dendrimers represent the fourth and most recent category of macromolecular architecture [1]. Unlike linear polymers they have a well-defined structure that leads to low MW polydispersity index values. Dendrimers have attracted much interest since their discovery due to the specific structure which makes them suitable for a variety of biomedical applications [2-5]. They are small in size, while their low polydispersity can contribute to the reproducibility of their pharmacokinetic behavior [6]. The use of dendrimers as modulators of the release rate of a drug incorporated into liposomes and the possible alterations of the drug bioavailability seems to be an attractive field for research [7]. In the present work, we especially focus on interactions between dendrimers and model lipid membranes. The findings from this study could prove helpful to rationally design new advanced liposomal drug delivery systems for bioactive molecules by combining dendrimeric and liposomal technologies.

We tested cationic phosphorus containing dendrimers for lipid membranes interaction. CPDs differ from the molecules described previously by Supattapone et al., [8]. They have a hydrophilic surface and a hydrophobic backbone which allows for efficient membrane penetration [9]. Here we show that CPDs were able to change the properties of DMPC lipid membranes.

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Interaction of cationic phosphorus dendrimers (CPD) with charged and neutral lipid membranes

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ABSTRACT

Despite the rapid development of modern pharmaceutics, delivery of drugs to sites of action is not always effective. The research on new targeting delivery systems of pharmacologically active molecules is of great importance.

Surface properties such as surface charge of drug delivery particles frequently define their pharmacokinetic profile; hence the efficiency of drugs can be increased by application of nanoparticles having appropriate surface properties.

The aim of the present work was to study the interactions of cationic phosphorus-containing dendrimers (CPD) with model lipid membranes with no charge or bearing surface charge. The interactions of two generations of phosphorus dendrimers on the thermotropic behavior of model lipid membranes composed of DMPC (uncharged) or DMPC/DPPG (negatively charged) were studied using differential scanning calorimetry (DSC). The results of this study showed that CPDs can alter the thermotropic behaviour of the bilayer by reducing the cooperativity of phospholipids and this effect strongly depends on membrane surface charge. The information resulting from this study may be applied to the rational design of new drug carriers combining liposomal and dendrimeric technology.

1. Introduction

Dendrimers represent the so-called 4th architectural class of polymers and the newest category of drug delivery carriers [1]. They have a well-defined highly branched structure suitable for pharmaceutical applications [2–7]. They are synthesized by surrounding a core molecule with layers of branching elements. They are small in size, with low polydispersity which is a crucial factor to the reproducibility of the pharmacokinetic behavior of the encapsulated drug [8]. The use of dendrimers as modulators of the release rate of a drug encapsulated into liposomes and the possible alterations of the drugs' bioavailability seems to be an attractive field for research [9]. Differential scanning calorimetry (DSC) is an important technique to project the interactions between biomaterials or biomaterials and drug [9] and to design carriers based on the findings from their thermal behaviour. Recent published works on liposomes mixed with dendrimers as modulatory and controlled release drug delivery system (MCRS) [8,10,11], have shown that the mixed biomaterials should be studied using different physical techniques [i.e., Raman, photon correlation spectroscopy (PCS)] as well as thermal analytical techniques such as DSC, in order to investigate the kind of interactions between the materials of the system. In this study we focus on the interactions between cationic phosphorus dendrimers (CPD) with model lipidic membranes composed of dimyristoylphosphatidylcholine (DMPC) and of dimyristoylphosphatidylcholine with dipalmitoylphosphatidylglycerol (DPPG) (97:3 molar ratio) in order to collect data and to evaluate the changes of the thermal parameters of the system, for producing new and advanced mixed drug delivery systems which can modulate the release of the encapsulated drug. CPDs differ from the molecules described previously by Supattapone et al. [12], principally in their protonated tertiary amine end-groups. They have a hydrophilic surface and a hydrophobic backbone which allows for very efficient membrane penetration [13]. The findings from

Abbreviations: CPDs, cationic phosphorus dendrimers; Cp, heat capacity; DMPC, 1,2-dimyristoyl-sn-glycero-3-phosphocholine; DPPG, dipalmitoylphosphatidylglycerol; D:L, dendrimer:lipid molar ratio; DSC, differential scanning calorimetry; ΔH, main phase-transition enthalpy; MLVs, multilamellar vesicles; G3, generation 3; G4, generation 4; T_m, gel to liquid–crystalline phase-transition temperature; T_{onset}, temperature at which the thermal effect starts; $\Delta T_{1/2}$, width of the transition at half-peak height.

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Dendrimers as Delivery Systems in Gene Silencing Studies

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Abstract: RNA interference (RNAi) is a natural defence pathway in a variety of species, which leads to the posttranscriptional gene silencing - degradation of target messenger RNAs in a gene-dependent manner. This phenomenon has been employed to manipulate gene expression by introduction of small interfering RNA (siRNA) into the cell. Researchers are now developing RNAi-based interventions for the prevention and treatment of human diseases such as viral infection, tumors and metabolic disorders. However, RNAi-based drugs require usage of efficient carriers to permit the genetic material to cross the plasma membranes of target cells. In this review, we will define key terms of this breakthrough technology and mention some prerequisites of the RNAi-based therapy that must be fulfilled for this treatment to work. We will also point at some unique properties of dendrimers as carriers for targeting nucleic-acid materials and introduce carbosilane dendrimers that are currently being studied by our research team.

Keywords: Dendrimers, Carriers, RNA interference, Gene therapy, Biomembranes

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1. Introduction

Nano-sized particles exhibit unique chemical, biological, electrical and mechanical properties. Recently much attention has been devoted toward using nanotechnologies for medical application (nanomedicine), since there is a growing evidence that nanomedicine has the potential to cure diseases and repair tissues by manipulating individual cells at the molecular level. An experimental way of using nanotechnologies to treat or prevent disease is a gene therapy approach. The gene therapy is mostly aimed at replacing an abnormal disease-causing gene or inactivating a mutated gene that is not working properly (or at activating a gene that should work but it does not). The method requires using a carrier called a vector in order to bring the new gene into the body's cells [1].