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Review article

A close collaboration of chitosan with lipid colloidal carriers for drug delivery applications

Loïc Bugnicourt, Catherine Ladavière*

IMP, UMR CNRS 5223, Université Claude Bernard Lyon 1, Domaine Scientifique de la Doua, Bâtiment POLYTECH, 15 bd André Latarjet, 69622 Villeurbanne Cedex, France

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ABSTRACT

Chitosan and lipid colloids have separately shown a growing interest in the field of drug delivery applications. Their success is mainly due to their interesting physicochemical behaviors, as well as their biological properties such as bioactivity and biocompatibility. While chitosan is a well-known cationic polysaccharide with the ability to strongly interact with drugs and biological matrices through mainly electrostatic interactions, lipid colloids are carriers particularly recognized for the drug vectorization. In recent years, the combination of both entities has been considered because it offers new systems which gather the advantages of each of them to efficiently deliver various types of bioactive species. The purpose of this review is to describe these associations between chemically-unmodified chitosan chains (solubilized or dispersed) and lipid colloids (as nanoparticles or organized in lipid layers), as well as their potential in the drug delivery area so far. Three assemblies have mainly been reported in the literature: i) lipid nanoparticles (solid lipid nanoparticles or nanostructured lipid carriers) coated with chitosan chains, ii) lipid vesicles covered with chitosan chains, and iii) chitosan chains structured in nanoparticles with a lipid coating. Their elaboration processes, their physicochemical characterization, and their biological studies are detailed and discussed herein. The different bioactive species (drugs and bio(macro)molecules) incorporated in these assemblies, their maximal incorporation efficiency, and their loading capacity are also presented. This review reveals the versatility of these assemblies. Depending on the organization of lipids (*i.e.*, nanoparticles or vesicles) and the state of polymer chains (*i.e.*, solubilized or dispersed under the form of nanoparticles), a large variety of drugs can be successfully incorporated, and various routes of administration can be considered.

1. Introduction

Drug delivery systems aim to deliver drugs to their sites of action within an organism, with the goal of achieving a therapeutic outcome. Among the different systems developed over the past six decades [1], those based on polymers or lipids have been widely examined and have demonstrated promising results in the literature [2].

Among the various biopolymers investigated, chitosan (CS) has been shown to be very interesting for such applications. This is a well-known natural polysaccharide composed of both 2-acetamido-2-deoxy-β-D-glucan and 2-amino-2-deoxy-β-D-glucan units. Its biocompatibility and non-toxicity have been proven many times [3–5]. Chitosan is generally produced from chemical or enzymatic deacetylation of chitin, one of the most abundant natural polymers present in the cuticles of arthropods, and the endoskeletons of cephalopods. It has been extensively studied owing to its promising results in many biomedical applications as solution, hydrogel, or particle [6].

Concerning lipid colloids, they have been among the first developed nanovectors [7]. Liposomes are the first nanomedicine delivery system to make the transition from concept to clinical application, and they are now an established technology platform with considerable clinical acceptance [8]. An emerging novel class of colloids (based on lipid components other than phospholipids), solid lipid nanoparticles (SLN), and more recently, nanostructured lipid carriers (NLC), have also attracted special interest during last few decades.

Nevertheless, despite these encouraging results obtained with chitosan and lipid-based colloids, several drawbacks have been pointed out. The main problem is the sudden release of drug from carriers once they are administered in the human body, limiting the efficiency of these systems. Another problem can also be the difficulty to incorporate any drugs in each of these vectors due to their lack of chemical compatibility. To overcome these limitations, assemblies have been developed to combine the advantages of various chemical and physicochemical features. Chitosan and lipid colloids have therefore been

* Corresponding author.
E-mail address: Catherine.Ladaviere@univ-lyon1.fr (C. Ladavière).

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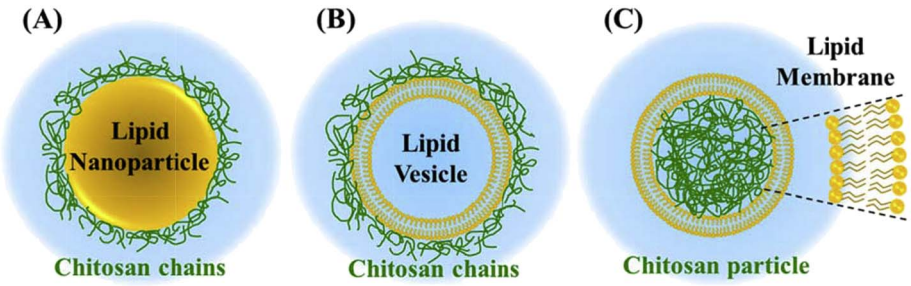

Fig. 1. Nano-sized «chitosan chains/lipids» assemblies considered in this review.

associated to afford new relevant drug nanovectors with unique properties. In this context, the aim of this review is to describe these "chitosan/lipid" associations, and more specifically those between i) lipid nanoparticles or vesicles, and ii) non-chemically modified chitosan solubilized (individual polymer chains) or dispersed (nanoparticles of polymer chains) (Fig. 1). In each of these cases, a special attention is given on their elaboration and characterization, on the interactions which govern them, and finally on their biomedical applications in the drug delivery area.

2. «Chitosan chains/lipid nanoparticles» assemblies

Solid lipid nanoparticles and nanostructured lipid carriers were considered as alternatives to classical liposomes in drug delivery area for several administration routes. SLNs have been the first to be described in 1991 by Mulher et al. [9]. Then, in early 2000, NLCs were developed as second generation of SLNs to modulate their physical state and drug loading capacity [10–12]. Both carrier types are based on solid lipids, however, they can be distinguished by their inner structure. SLNs consist of pure solid lipids (including high-melting point glycerides or waxes), while NLCs contain additional liquid lipids (spatially incompatible) leading to imperfections in the crystal lattice. This less ordered structure in matrix produces an improvement of drug loading (*vs* SLNs which crystallize in a perfect crystalline lattice that allows smaller space for the incorporation of drugs), and a decrease in the drug expulsion from the matrix during storage period. The lipid nanoparticles can be up to 1000 nm in size, and have the advantages to be biocompatible, scaled up, and easily sterilized. However, similar as for the emulsions, the lipid nanoparticles lack of stability due to unexpected growth. The adsorption of chitosan chains on their surface is therefore an interesting solution to overcome this drawback (Fig. 1A). The presence of chitosan chains leads to an increased stability of SLNs and NLCs, as well as an improvement of their bioadhesion (due to CS mucoadhesive [13] and absorption enhancing properties). Note that similar interesting properties provided by a surface adsorption of CS chains have also been demonstrated for inorganic or polymer particles (*e.g.*, silver [14,15], tungsten trioxide [16], PLGA [17], PMMA [18,19], PIBCA [20,21], silica [22,23]).

2.1. Elaboration of assemblies

The elaboration of «chitosan chains/lipid nanoparticles» assemblies usually consists in the previous synthesis of lipid nanoparticles, and then, the adsorption of CS chains to their surface. The SLNs elaboration techniques have been widely described by Mehnert and Mader [24]. Briefly, these methods start with the solubilization of solid lipids in an organic phase (such as dichloromethane or chloroform) [25]. This phase is then used for the preparation of an «oil in water» emulsion by sonication or mechanical stirring. Surfactants (*e.g.*, Poloxamer [25], Tween®80 [26], see Table 1) are added to the aqueous phase in order to stabilize the emulsion, and prevent the agglomeration of oil droplets. After evaporation of the organic solvent, the SLNs can be removed. Other techniques allow avoiding the use of an organic solvent by heating above the lipid melting point before directly incorporating them into the aqueous phase at high temperature. The mixture is then emulsified by sonication at high temperature as in the previous method [27].

To synthesize the «chitosan chains/lipid nanoparticles» assemblies, the SLN dispersion (previously formed) is transferred in an aqueous solution of CS and surfactants. An elaboration in one-step of these «core-shell» assemblies has also been described by directly adding CS chains to the aqueous phase of the first emulsion. Ying et al. [28] added a cross-linking agent (glutaraldehyde) to improve the association of CS chains with SLNs. Very recently, Ebrahimi et al. [29] proposed to replace glutaraldehyde by sodium tripolyphosphate (TPP), an ionic cross-linking agent generally considered as safe, in order to gelify chitosan chains onto the surface.

In the context of drug delivery applications, hydrophobic drugs have been previously solubilized in the organic phase [28,30,31]. For instance, curcumin (a naturally occurring polyphenolic compound) which exhibits pleiotropic health benefits against various diseases but restricted clinical applications due to its poor water solubility, has been efficiently dispersed into SLNs (Fig. 2) [31].

Encapsulation of hydrophilic drugs is more difficult, and requires the formation of a first «water in oil» emulsion. The hydrophilic molecules are in the aqueous phase, and lipids of SLNs constitute the organic phase. The resulting emulsion may then be used as organic phase for the elaboration of nanoparticles [25,32].

Concerning NLCs, their surface coating has also been achieved by unmodified chitosan. Note that chemically-modified chitosan (*N*-(2-hydroxy)propyl-3-trimethyl ammonium chitosan chloride [33], thiolated chitosan by the covalent binding of *N*-acetyl-l-cysteine with chitosan [34], oleoyl-quaternized-chitosan [35], *N*-trimethyl chitosan [36]) has also been used but this is not addressed in this review. As for the SLNs, the NLCs were firstly pre-prepared by heating (above their melting point) the mixture of solid and liquid lipids (see formulations in Table 1), until a clear and homogeneous phase was obtained. Then, a primary «oil in water» emulsion was formed by homogenization (by melt-emulsification and ultra-sonication techniques) of lipid melt in the aqueous phase (containing surfactants, Table 1), preheated at the same temperature. The hot emulsion was then cooled in an ice bath and homogenization was continued until the NLCs were formed. Finally, the formed NLCs were coated with chitosan chains. The nanoparticles were added dropwise to a chitosan solution under continuous agitation at room temperature. After the coating, the NLCs were usually washed by centrifugation. Note that a lyophilisation process of the resulting CS-coated NLCs dispersion (*e.g.*, by using trehalose as cryoprotectant) can be carried out [37,38].

2.2. Characterization of assemblies

The surface modification of SLNs was mainly demonstrated by the inversion of the surface charge and the increase in size. Ying et al. [28] have observed a shift of zeta potential from −20 to +30 mV after modification by CS chains. A non-negligible increase in size was also detected (from 84 to 270 nm, with a quite correct polydispersity index,