Lipid and Gold Nanoparticles in Medicine

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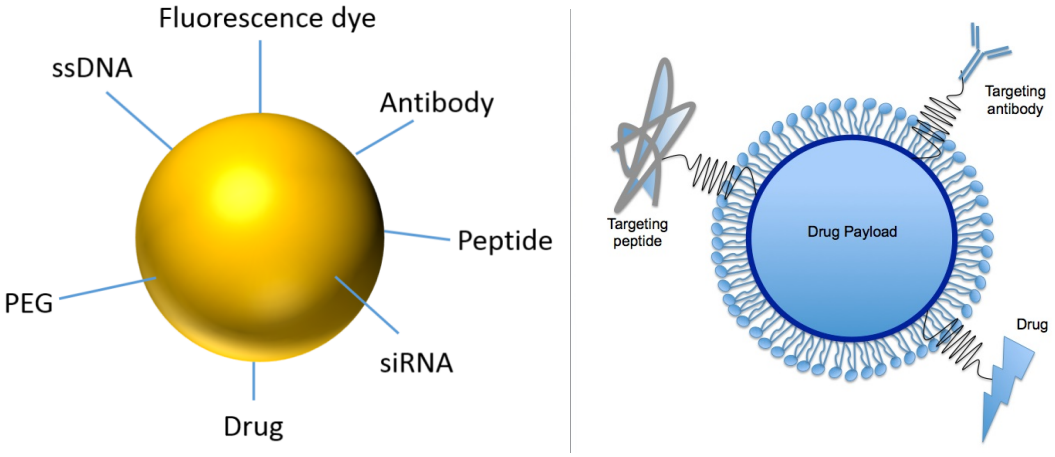
Abstract

The use of nanoparticles in the field of medicine, and more specifically drug delivery is a topic of high interest in today's world. The promise of specific, targeted, and rate controlled delivery of medicine is one that cannot be overlooked. Much work has been done in this field to look into the safety and efficacy of nanoparticles as drug delivery systems, showing promising results. However, as with any technology, there remain some hurdles that must be navigated such as polydispersity, and aggregation. In this paper, the topic of gold and lipid nanoparticles as drug delivery systems is outlined and discussed.

1 Introduction

Nanoparticles are simple structures of nanometer size that can range anywhere from a few nanometers, to hundreds of nanometers. A more rigid definition of this class of materials is any structure with a total radius of < 100nm.[1] The term nanoparticle includes a variety of shapes including rods, spheres, crystals, and more. Beyond this, nanoparticles can be made of a variety of materials, including but not limited to metals, lipids, and polymers.[1] These particles are highly tunable and as such, the physicochemical properties can be controlled to a significant degree. Once the concept of ligands is introduced, the possible applications of nanoparticles become endless. For this study on nanoparticles as medicinal delivery systems, gold nanoparticles (AuNPs) and lipid nanoparticles (LNPs) will be the topic of focus.



(a) (b)

Figure 1: (a) Schematic of a Gold Nanoparticle with Ligands.[11] (b) Schematic of a Lipid Nanoparticle with Ligands and Drug Payload.[12]

In terms of biomedicine, both forms of NP are desirable as they are biologically inert, as well as being more simple to synthesize, as compared to other targeted drug delivery systems.[2],[3] AuNPs provide further benefits such as facile functionalization - the addition of ligands - and ease of imaging.[3] LNPs on the other hand, are somewhat more difficult to image as gold scatters light and electrons to a much higher degree than lipids.

2 Background

Ligands are molecules that are affixed to the surfaces of nanoparticles to stabilize them and alter their physicochemical properties. Due to the scale of the nanoparticles, they aggregate as the high surface area presents a state of higher energy, and thus they are intrinsically unstable.[2] Aggregation is the process by which many nanoparticles will "stick" to each other due to attractive forces, and will no longer retain the properties of a nanoparticle. Ligands are thereby added to the surfaces to prevent this. In the case of AuNPs, the ligands are attached via thiols, phosphates, and amines, as sulfur, phosphorus, and nitrogen exhibit attractive forces with the surfaces of AuNPs.[1] In the case of LNPs, they are stabilized with ligands as well, but are more commonly stabilized electrostatically, by introducing charge repulsion between the particles.[2]

Characterizing AuNPs is quite simple, as the gold centers are very dense, and because of this Transmission Electron Microscopy (TEM) is used to determine size and polydispersity. The LNPs are typically characterized via photon microscopy and zeta potential. In both cases, the ligands, and ligand coverage can be determined via thermogravimetric analysis, and quantitative proton or carbon NMR.

Given the incredible versatility and surface properties of these AuNPs, biomolecules and medicinal molecules can be affixed to their surfaces. In the case of LNPs, these molecules are loaded within the particles themselves.[2],[4] Another structure of interest is gold nanoshells (AuNSs), made of a thin shell of gold onto which ligands can be attached.[4] These AuNSs are capable of being 'activated' by near infrared lasers (NIRs) as they possess resonance frequencies at these wavelengths allowing for the rapid and efficient conversion from light to heat, allowing for the use of photo-thermal therapy.[1],[4] This NIR wavelength property is desirable as water and biological fluorochromes have very low absorption coefficients in this range (Fig. 2).[4]

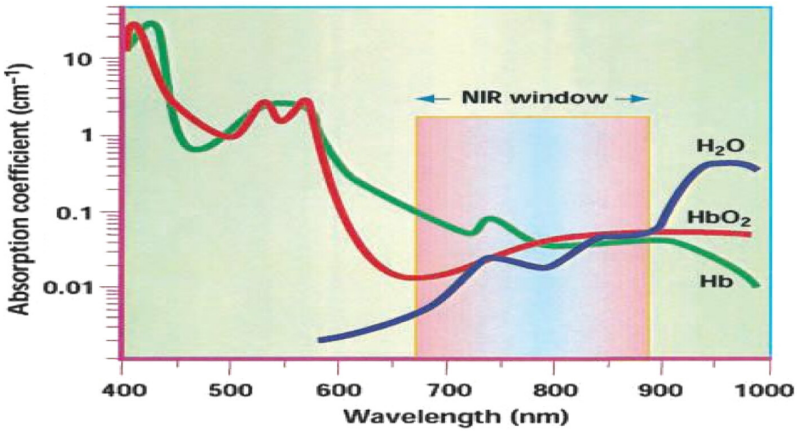


Figure 2: Absorption Spectra of Water, HbO_2, and Hb. NIR region highlighted. Adapted from [1].

With carefully selected targeting ligands, NPs can be directed towards a site of interest. By changing the ligands one can alter the NPs' affinity towards different biochemical environments.[2] The exact mechanism by which AuNPs enter cells is not fully understood, but involves the endocytosis - the process by which foreign bodies enter a cell - of the nanoparticles, which has been shown to occur even with large biomolecules such as proteins and antibodies as ligands.[1] LNPs are taken into the cells by phagocytosis,[5] which is a type of endocytosis. As compared to AuNPs ligand exchange drug delivery, a LNP's drug loading and release profile is dependent on the crystalline structure and melting point of the lipid.[5]

3 Fabrication and Synthesis

There are two methods by which one can synthesize AuNPs. Top-down, and bottom-up. The top-down method involves the abrasion of bulk material into fine particles. The bottom-up approach is rooted in self assembly, and involves the chemical synthesis of AuNPs. There are many available synthesis methods, all of which provide different sizes of AuNPs based on reaction conditions. Most commonly, gold chloride salts are introduced to a reducing agent, which reduces the gold from Au(III) to Au(0). The gold atoms then aggregate to form nanoparticles, and the resulting nanoparticles are stabilized by ligands in solution.[6]

One of the most common methods of synthesis is the Brust-Schriffin method as it provides thermodynamically stable and air stable AuNPs with tunable size and low polydispersity - the measured size distribution of the particles. The Brust-Schriffin method involves the transfer of $AuCl_4$ to a toluene phase using a phase transfer agent. The gold is then reduced using sodium borohydride ($NaBH_4$) in the presence of dodecanethiol ($CH_3(CH_2)_{11}$-SH), which acts as the stabilizing ligand.[6] After the AuNPs have been synthesized, it is facile to perform a ligand exchange reaction by introducing the AuNPs to different ligands in solution. Over time the surface composition of these ligands will equilibriate. Size and polydispersity of AuNPs are characterized using transmission electron microscopy (TEM).

Similarly to AuNPs, there are many methods to creating LNPs, all producing various sizes and size dispersions. LNPs are often composed of phospholipids, but novel research is exploring the idea of solid LNPs with even better properties for drug delivery.[2],[7] The most widely used method of LNP synthesis is sonication wherein the chemical bonds in the lipids are broken up via sonic waves such that they form LNPs. This affords downsides such as potential degradation of the LNPs, as well as contamination from the sonication needle. Some other synthesis methods include membrane extrusion wherein the lipid is forced through a nanoscale polycarbonate membrane to create micelles, and ethanol injection wherein a lipid ethanol solution is injected into a potassium chloride solution, inciting the formation of LNPs. An important downside to consider with the ethanol injection method is very high polydispersity (30 to 110 nm). This method cannot reliably produce uniform sizes of LNPs.[7]

The introduction of the biomolecules in the case of AuNPs can be done via ligand exhange. Typically, AuNPs will be stabilized with easily removed ligands such as alkyl thiols ($CH_3(CH_2)_n$-SH), dimethylaminopyridine, or citrate, to facilitate further ligand exchange. The AuNPs are introduced to a solution containing a ligand of higher affinity, and left until the exchange is complete, and then purified via chemical or physical methods. For AuNSs, the medicines can be used as the core of the AuNP, or once again as ligands. The LNPs are loaded with the medicine within the micelle, and have tempered release curves based on their physical properties, allowing for timed drug release.[2]

4 Discussion and Summary

Overall, the use of nanoparticles as medicinal delivery systems offers the promise of leaps and bounds in the field. The possibility of targeted and rate controlled release of medicines is incredibly important for efficacy and efficiency. This does however come at a cost. With our current technology, many NP vaccine delivery methods have been advanced to human trials,[8] but what does this mean in terms of widespread application? Given how sensitive these structures can be, how can we reliably state their efficacy and safety for biomedical use?

The immune system is a very fickle and particular thing. As tunable as these NPs are, achieving true monodispersity - that is, all particles having the same dimensions - is very difficult to achieve.[4] This inherent polydispersity is a challenge that must be overcome to be able to produce reliable, and safe medical products. Furthermore, the probability of the aggregation of these particles, and the effects thereof have not been studied in depth. There have been many studies showing that AuNPs and AuNSs are not cytotoxic - toxic to cells - but there is little proof that there are no long term effects.[9] LNPs, typically being larger than the AuNPs, also run the risk of being treated as foreign bodies by the immune system if they become too large.

There are many applications of NPs in the medical field. A prominent area of study for AuNPs and AuNSs that is ongoing is their use for cancer treatment. The method used for chemotherapy today is intravenous, which has many side effects as the medicine is cytotoxic and does not target only cancer cells. With the use of AuNPs, and AuNSs, the chemotherapeutic agents can be directed towards cancerous regions, and targeted with NIR lasers, providing a much safer way to deliver this treatment. Beyond drug delivery, AuNSs are capable of high efficiency transfer of energy from light to heat, and can therefore be used for photothermal ablation of cancerous cells.[10] In conclusion, there is much research that needs to be done, but NPs serve as a promising horizon for the future of drug delivery.

5 References

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