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HEPARIN-BASED NANOPARTICLES: A SUMMARY OF THEIR USES

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Abstract

For every review it always shows the deals with nanoparticles for and to be synthesized using heparin and dependent nanoparticles. Such nanoparticles have been widely studied since a

long time ago, obtaining satisfactory outcomes. An expressive visually shows these nanoparticles with excellent good comparative characteristics, and since heparin is produced in the human body within the mast cells, this makes these nanoparticles useful for future applications like imaging, disease and cancer treatment, and antibacterial activity. They can also be used for applications that are not oriented directly to the medical and biological areas such as in the case of analyte detection in aqueous solution, although such studies are very few. These nanoparticles synthesis is mainly through wet chemistry methods, using heparin that could have been modified or not.

Keywords: Unfractionated Heparin, Nanoparticles, Proteins and Polysaccharides

Introduction

Nanoparticles are defined as dispersions of particles or solid particles with nanoscale sizes. There are different nanoparticles types; they can be classified as nanopores, nanotubes, quantum dots, nanoshells, dendrimers, liposomes, nanorods, fullerenes, nanospheres, nanowires, nanobelts, nanorings, and Nano capsules. Such categories are pretty general and are based on dimensionality, morphology, composition, uniformity, and agglomeration [1].

Nanoparticles have been widely studied for many years and they have also generated an intense scientific interest due to a wide variety of potential applications in biomedical, optical, and electronic fields. Nanoparticles have drawn attention based on the few properties they exhibit like their surface to mass ratio and the reactivity of their surface [2]. In general, metal nanoparticles are prepared by top-down or bottom-up approaches; such methods are useful for obtaining nanoparticles which are good in their particle size and particle size distribution but because most of the reactants used are hazardous, there are times in which they are not useful for certain further applications, so another step has to be performed to modify their surface, which also implies an extra cost and use. Thereupon, another pathway has to be found to carry out the synthesis procedure to avoid these problems [2]. Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides, and synthetic polymers. The selection of material depends on factors such as (a) required size of nanoparticles; (b) aqueous solubility and stability; (c) surface characteristics as charge and permeability; or (d) degree of biodegradability, biocompatibility, and toxicity [3, 4].

Glycosaminoglycans are biomaterials also known as mucopolysaccharides or polysaccharides, such as heparin, keratan sulfate, chondroitin sulfate, heparan sulfate, and hyaluronic acid. They are usually composed of a repeating disaccharide unit along their structure. In such disaccharide units, which are variable according to the glycosaminoglycan being referred to, the amino sugar is always hexosamine, either D-glucosamine or D-galactosamine, mostly in the N-acetylated form; the other monosaccharide is mainly D-glucuronic acid or L-iduronic acid, except of keratan sulfate, in which D-galactose replaces the uronic acid [5]. In the specific case of heparin, it is composed of repeating units of 1→4 linked pyranosyl uronic acid and 2-amino-deoxyglucopyranose (glucosamine) residues. The uronic acid is composed of L-idopyranosyluronic acid (L-iduronic acid) and D-glucopyranosyluronic acid (D-glucuronic acid) and it possesses a high negative charge [5–7].

Heparin was discovered in 1916 in Toronto, Canada, by Jay McLean under the guidance of William H. Howell. Later, heparin has been extensively studied and commercialized and even nowadays there are several aspects about it that are to be disclosed. Heparin is mainly used as an anticoagulant and antithrombotic in medicine, although it is used and still studied for other uses in other therapeutic fields as well, for example, wound healing, burn injury treatment, inhibition of inflammation, and metastatic spread of tumor cells [8–11]. Also, it is found within the human body and of animals [12], specifically, in the mast cells granules where it interacts with histamine, proteases, and inflammatory mediators. It can also be synthesized synthetically [6].

Heparin is also known as unfractionated heparin (UHF); it is polydisperse, mostly obtained from porcine and bovine mucosa and has been normally utilized for the treatment and prevention of thrombotic events. Heparin is composed of molecular chains of varying lengths from 2000 to 40,000 kDa; its use is restricted to an in-hospital setting, where its dosage can be strictly supervised. On the other hand, low molecular weight heparins (LMWHs) are smaller chains of UFH that can be obtained by various chemical and enzymatic depolymerization processes, and their weight ranges from 2000 to 15000 kDa. They have reduced inhibitory activity against thrombin and they exhibit more predictable pharmacokinetic properties compared with UFH. Other subcategories of LMWH involve low and ultra-low molecular weight heparins (ULMWHs) [13].

Apart from its noble anticoagulant properties, heparin and its derivatives can interact and modulate proteins involved in different biological process such as inflammation and angiogenesis [14]. Still, its mechanisms of action are still under debate. Furthermore, heparin broader use is still impaired due to its strong anticoagulant activity and hemorrhagic complications [15, 16]. This work is devoted to review research on heparin-based nanoparticles for different applications.

Heparin-Based Nanoparticles

Heparin has been used in nanoparticle synthesis procedures since some time ago. Heparin-based nanoparticles own enhanced properties when heparin is integrated to them because of its biological properties [17, 18]. Some works are related to synthesis with no specific applications, the synthesis procedure is proposed only, and some other works aim to mention the potential ones as follows.

Nobel metal nanoparticles, for example, gold and silver [19–22] and metal oxide ones [23]; conjugates: silica [24] and chitosan [25, 26]; and poly(lactide-co-glycolide) [27], complexes [28, 29], and magnetic particles have been synthesized using heparin [30]. When it comes to specifics and applications, the most relevant works are related to the health field, especially cancer treatment, imaging, and detection [31], and they are many and varied taking advantage of heparin uses as an anticoagulant for treatment and prophylaxis of various thromboembolic disease processes, to maintain anticoagulated states in patients on extracorporeal circulation or hemodialysis and to help maintain patency of indwelling vascular catheter [32].

Cancer Diagnosis and Therapy

Cancer is a quite spread disease nowadays. It was the leading cause of death worldwide, accounting for 8.8 million deaths in 2015 [33]. Therefore, there is an increasing necessity for the development of treatments beside the ones already available, which are surgery, chemotherapy, radiation, and targeted, photodynamic, and immunotherapies. There are some other procedures which include stem cell transplants, hyperthermia, photodynamic and photothermal therapies, blood transfusion and donation, and laser treatment [34].

To understand how cancer develops, it has to be mentioned that healthy cells usually divide in an ordered way and they die when damaged or worn down but when cells divide and grow uncontrollably, they continue forming new ones that replace the normal cells leading to the growth of a tumor. Cancer cells can spread to other parts of the body and infect them, too [35]; therefore, early detection is necessary to avoid it.

Nanoparticles have been studied since some years ago to detect and treat cancer [36, 37]. Work has been devoted to use heparin as a part of a multifunctional nanosystem [38] to detect and treat cancer since it is a biocompatible substance and it is well absorbed by the body due to its biological interactions with proteins, growth factors, chemokines, cytokines, enzymes, and lipoproteins, involved in a variety of biological processes [14]. Also, previous studies have been on the usage of heparin alone on the treatment of cancer and the effects that heparin produces [39–42]. There is a list of drugs that are used for cancer treatment as stated by the National Cancer Institute [43]. Among them, doxorubicin, docetaxel (taxotere), paclitaxel (taxol), and sorafenib have been employed, for example, as part of nanosystems intended for therapeutic purposes. In all cases, after nanoparticle synthesis and the usual characterization (UV-Vis spectra and either TEM/SEM, DLS, or zeta potential), they are tested for cytotoxicity, biocompatibility, antiangiogenic effect, differentiation, drug loading efficiency, apoptosis analysis, cell uptake, and pharmacokinetics, among others. Next, some works devoted to this topic will be mentioned briefly.

Park et al. synthesized an amphiphilic conjugate made of heparin and deoxycholic acid within which doxorubicin was encapsulated in a two-step procedure intended for action on SCC (squamous cell carcinoma). Then, the as-produced nanoparticles were tested for toxicity (to assess their safety as a drug carrier), antitumor effect, and cytotoxicity. The conjugate was proved to have high loading efficiency and release promoting an elevated antitumor effect [44]. Khaliq et al. designed a composite system in which heparin was used to form the heparin/DOX/DEVD-S-DOX complex first. Then, Pluronic F-68 was used to form the composite and to stabilize it. The task of this system is to deliver doxorubicin and the DEVD-S-DOX in a specific tumor site, once being there DOX (doxorubicin) is exposed in the tumor cells triggering apoptosis that subsequently leads to the repetitive activation of caspase-3. Caspases are proteases that control the death and inflammation of cells; they execute apoptosis, and so in the case of this nanosystem, an amplified apoptosis is induced. Murine squamous cell carcinoma (SCC-7) cancer cells were used in this study [45]. Zhang et al. developed an interesting system which comprises two anticancer drugs, ATRA (all trans retinoic acid) and DOX (doxorubicin), the first one being conjugated to LMWH (low molecular weight heparin) and the second one loaded physically, such system was named as

DOX-loaded LMWH–ATRA. The most relevant assets in this work are that the cytotoxicity effect on epithelial MCF-7 cells used was maintained and they possessed much higher anticancer activity compared to the free drugs in solution and side effects were reduced [46]. Kim et al. conjugated LMWH (low molecular weight heparin) to (SA) stearylamine in order to create, first, a polymer that was used to synthesize self-assembled nanoparticles, and then, docetaxel was loaded within them. The cell lines used in the study were MCF-7 and MDAMD 231 (human breast carcinoma). From the results, it was concluded that heparin conserved 30% of its anticoagulant activity that the half-life of docetaxel was improved with the formulation used and the growth of the MDAMD 231 cell line was inhibited greatly [47]. In other studies, doxorubicin and letrozole were used to treat this cancer type, too [48–51]. In one study, doxorubicin was combined with curcumin to be delivered by heparin modified poly(L-lactide) grafted polyethylenimine nanoparticles [52]. Yang et al. worked on an immobilized chitosan/heparin Pluronic-coated system for the delivery of sorafenib in gastric cancers. The line cell used for the study was the BCG-823 (gastric adenocarcinoma). It was discovered that these nanoparticles worked better than sorafenib alone for inhibition of cancer cells [53]. Other studies related to gastric cancer were developed by Lai et al. [54].

There is more research that has been carried out concerning cancer but not only of the types already mentioned. For instance, as for liver cancer, Sun et al. synthesized heparin-coated gold nanoparticles for liver specific imaging through computed tomography in vivo [55] and Lin et al. made a combination of nanoparticles, Emodin-Loaded PLGA-TPGS and Heparin Sodium-Loaded PLGA-TPGS ones for chemotherapeutic purposes [56]; colon cancer (oral absorption mechanism and antiangiogenesis effect of taurocholic acid linked heparin docetaxel conjugates) [57]; lung, melanoma, and ovarian cancers [58–61]; melanoma [62]; and heart, spleen, lung, and kidney [63–65]. HeLa cells were also used for a study in which the synthesized nanoparticles did not show an apparent cytotoxicity indicating good biocompatibility [66].

Some research has been directed to coupling already existing therapies, photodynamic, photothermal, and chemotherapy with heparin-based nanoparticles [67] and photodynamic therapy [68–71]. Some studies have only proved that heparin-based nanosystems have potential as drug carriers but they do not focus on a specific cancer kind (heparin-based nanocapsules as potential drug delivery systems) [72]. There are other works related to potential drug delivery for cancer treatment, although they do not focus on a specific kind. They only point out biocompatibility as well as anticoagulant activity [73].

Disease Treatment

There are some works on heparin-based nanoparticles, which has been focused on other disease types, for example, bacteria-provoked ones. The *Helicobacter pylori* bacterium was discovered by Warren and Marshall in 1982 from patients with peptic ulcer (*Helicobacter pylori*) [74]. It is a type of microorganism which enters the gastric mucosa and triggers its inflammation. It is responsible for the development of duodenal or gastric ulcers, gastric cancer, and gastric mucosa- associated lymphoid tissue (MALT) lymphoma [75, 76]. Heparin-based nanoparticles have been synthesized with the purpose of treating *H. pylori* producing complexes that attack this microorganism. For *H.*

pylori to be eradicated, the agent that is used to attack it has to penetrate the gastric mucosa layer and hold a certain concentration for antibacterial activity within a fixed amount of time. However, the available treatments cause undesired side effects such as bad mouth taste and nausea. Besides this, bacterial resistance is another issue due to patients leaving treatment too soon [77, 78]. Chang et al. synthesized a complex formed by berberine, chitosan, and heparin. Berberine is an alkaloid derived from the barberry plant and it is known to treat gastroenteritis and diarrhea; it has also been shown to inhibit *H. pylori*. Chitosan was employed in this work because of its biocompatibility and adhesion properties and heparin was used because of its ability to bind to cell receptors and to promote ulcer healing [79]. Lin et al. have developed works on this *H. pylori* treatment topic, too. In one of them, a chitosan heparin complex was developed to encapsulate and protect a drug from the gastric acids to treat the *H. pylori* infection specific sites. It showed good stability at 1.2–2.5 pH values and the latter was the follow-up drug model [80]. In another study, genipin was used. Genipin is a natural cross-linker, for its choleretic action in liver diseases and its inhibition of *H. pylori*. Their results showed that amoxicillin was successfully released in the specific site avoiding most of its contact with gastric acids, much better than in the previous work [81]. There are other more interesting works related to disease treatment using heparin-based nanoparticles as drug carriers for the treatment of specific illnesses. Ciprofloxacin is an antibiotic used to treat a variety of bacterial infections, for example, typhoid fever, diarrhea, intestinal infection, and pneumonia [82]. Kumara et al. came up with a ciprofloxacin loaded genipin cross-linked chitosan/heparin nanoparticle system to target enteropathogenic bacteria in a simulated gastrointestinal system [83]. Other systems have been developed for multipurpose treatment; Lembo et al.'s heparin nanoassemblies were based on the autoassociation of O-palmitoyl-heparin and a-cyclodextrin in water; it was found that they possessed antiviral activity against herpes simplex viruses of types 1 and 2 (HSV-1 and HSV-2), human papilloma virus 16 (HVP-16), and the respiratory syncytial virus (SRV) and that this antiviral activity was affected by the sulphation degree of heparin [84]. More research has been carried out on the treatment of antithrombosis [85] and some more on the development of nanosystems although without mentioning a specific disease to be treated, like in the case of stealth nanoparticles (PEGylated nanoparticles) (Heparin-Engineered Mesoporous Iron Metal-Organic Framework Nanoparticles: Toward Stealth Drug Nanocarriers) [86, 87].

Other Potential Applications

As it has been described so far, heparin-based nanoparticles are potential useful tools in the medicine area, specifically in the cancer and disease treatment area. Some more applications will be covered in this section. Most of them still have to do with the medical area but the studies are fewer than the ones mentioned in the previous sections. As for the rest, they are focused on antimicrobial activity, biosensing, and analyte detection. Medical imaging refers to different technologies used to view the human body to diagnose, monitor, or treat medical conditions. Each type of technology gives different information about the area of the body being studied or treated, related to possible disease, injury, or the effectiveness of medical treatment [88]. Nanoparticles have been engineered for this purpose to improve the technique [89]. In the case of heparin-based

ones, some studies have been carried out with good results by using quantum dots (QDs) in in vitro studies to assess their interaction with different cell lines, first. For example, in the case of THP-1,A549 and Caco-2 cell lines, it is proved that the QDs show affinity for the nuclear compartment of fixed permeabilised THP-1 and A549 cell lines but that they also remain confined to the cytoplasm of fixed permeabilised Caco-2 cell lines. This study is particularly interesting because, among the disadvantages that QDs pose, they provoke thrombosis and cell death in in vivo studies, and these heparin-based gelatin QDs may be useful in the future because of heparin reducing the presence of thrombogenic complications [90]. In another study, the QDs were loaded in heparin-deoxycholic acid conjugates, their oral administration showed no significant toxicity showing that, like in the aforementioned study, the use of QDs is being much less limited. This study was carried out using a rat model [91]. In one more study, QDs were loaded in heparin-deoxycholic acid (DOCA) nanoparticles for the imaging of the gastrointestinal tract, which could be orally administered [92]. On the other hand, not only QDs have been used for imaging purposes, but also other conjugate types, for instance, folate-heparin ones which were loaded with fluorescent dyes within them for tumor imaging as well [93]. Heparin-based nanoparticles have also been included in labeling and targeting investigations. Cell labeling studies have been carried out using superparamagnetic iron oxide nanoparticles that are coated with heparin (HSPIO). These nanoparticles were conjugated to a collagen matrix of cell surface using a polymer linker which remained stable in in vivo conditions and used as a Magnetic Resonance Imaging (MRI) agent, offering an alternative to endocytosis [94]. As for targeting, GonÇalves et al. developed heparin-chitosan nanoparticles labeled with rhodamine activated derivative (5[6]-carboxy-X-rhodamine N-succinimidyl ester (ROX)). The entire system was named CHROX. It was used to target drugs in vivo to the sciatic nerve, and such system showed no inflammation issues and good biocompatibility, although the authors mention that nerve regeneration is the topic that will be a follow-up to this research [95]. Bone and tissue-oriented studies have been worked on, too, for example, bone formation [96] and scaffold [97]; tissue engineering [98]; and regeneration [99]. Some other potential applications that are understudied are as follows: antimicrobial activity [100, 101], glucose biosensing [102], analyte detection in solution using a colorimetric approach [103], and surface enhanced Raman spectroscopy [104].

CONCLUSIONS

The use of heparin-based nanoparticles is an important issue because although it is a material that was discovered many years ago, it has been improved and it continues to be studied to disclose its properties and structure. Additionally, new uses for it are being explored besides the antithrombotic and anti-inflammation ones. The most important and relevant applications are focused on the treatment of cancer and other diseases, followed by bone and tissue engineering, antimicrobial activity, biosensing, and detection. Therefore, the range of potential applications is large and tempting.

As for heparin-based nanoparticles impact, it has to be pointed out that heparin is a biocompatible material that can be obtained naturally and synthetically. Its derivatives are also

useful because they have been created to widen its uses in the medical area or to overcome disadvantages or perils. When used for nanoparticle synthesis, it can be chemically modified in several ways, for example, through conjugation and cross-linking to produce nanobiomaterials that can be potentially used for different applications giving them certain functionality for a specific purpose. Heparin can be used for nanoparticle synthesis without being modified at all, too. The studies that have been carried out in vitro and in vivo for medical applications show that in the near future these heparin-based products could be an excellent option for the development of other alternatives to treat, detect, and prevent diseases in human beings. On the other hand, as for imaging, detection, antimicrobial activity, and biosensing, despite the fact that there are a few studies, they are areas that can be worked on further in order to develop very useful materials. As for nanobiomaterials heparin-based nanoparticles could be integrated to already existing materials to improve their antibacterial and antifungal activities, especially because nowadays several microorganisms have developed a strong resistance to the available common antibiotics.

As for detection and biosensing, since heparin structure allows it to interact with other materials such as dyes and biomolecules, there can be a chance to boost the existing detection and sensing techniques available even at very low concentrations. The most relevant heparin-based nanoparticles are the conjugated and cross-linked ones because they are usually synthesized incorporating different materials, but each one of them has a defined role in the specific application, for example, adhesion, biocompatibility, cell uptake, and drug release. In the case of heparin, it is usually to promote angiogenesis control, antithrombic, and anti-inflammation activities.

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