Keynote

NANOTECHNOLOGY ADVANCES IN CONTROLLED DRUG DELIVERY SYSTEMS

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Nanomedicine is defined as the application of nanotechnology to achieve breakthroughs in healthcare. Major goals of nanomedicine in terms of controlled drug delivery, are the maximization of drug bioavailability and efficacy, the control of pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity and biorecognition as well as the overcoming of obstacles arising from low drug solubility, degradation, fast clearance rates, relatively short-lasting biological activity and inability to cross biological barriers (e.g., blood-brain barrier). The above goals are expected to be achieved, through the development of targeted drug delivery systems (DDS) that can be selectively delivered to specific areas in the human body. However, since drug characteristics differ substantially with respect to chemical composition, molecular size, hydrophilicity, bioavailability, optimum concentration range, etc., the essential characteristics that identify the efficiency of the DDS are highly complex [1,2].

Drug Delivery Systems: ***Polymer micelles***, formed by self-assembly of amphiphilic block copolymers in aqueous solutions, are rapidly becoming a powerful nanomedicine platform for therapeutic applications due to their small size, in vivo stability, and prolonged blood circulation times. Multifunctional micelles can be prepared through conjugation of targeting ligands to their shell aiming to induce specific targeting and uptake by the cells. Micelles with sensitivity to external stimuli can also be prepared in order to trigger drug release at the target site [3,4]. Research on liposome technology has progressed from conventional vesicles to "***second-generation liposomes***", in which long-circulating liposomes are obtained by modification of the lipid composition and functionalization of the vesicle surface by various molecules, such as glycolipids, sialic acid and PEG ("stealth" liposomes). "Stealth" liposomes can finally become targeted via conjugation of targeting ligands (e.g., monoclonal antibodies) [4,5]. ***Solid lipid nanoparticles (SLNs)*** have attracted increasing attention as efficient and non-toxic alternative lipophilic colloidal drug carriers. SLNs are made from solid lipids (e.g., triglycerides, fatty acids, etc.) and can be produced to incorporate either lipophilic or hydrophilic drugs [6]. ***Immunostimulating complexes (ISCOMs)***, i.e., matrix constructs incorporating antigen, saponin, cholesterol and phospholipids, can be rapidly incorporated into the membranes of cells and may promote endocytosis of antigen by dendritic cells, monocytes and macrophages [7]. Multifunctional ***dendritic polymers*** (i.e., dendrimers and hyperbranched polymers) can be synthesized in order to be applied as DDS through appropriate functionalization of their various surface terminal groups [8]. Drugs can also be succesfully encapsulated within ***nanoparticles (NPs)*** and/or be absorbed onto the particle surface and thus be protected against chemical and enzymatic degradation [1,4]. *Chitosan* is a mucoadhesive polymer that is able to increase cellular permeability and improve the bioavailability of orally administered proteins. It can be readily formed into NPs, where drugs can be entrapped [9]. *Poly(D-L-lactide-glycolide) (PLGA)* is a biodegradable / biocompatible polymer that has been used for the delivery of a wide range of bioactive agents. In order to improve PLGA properties, with respect to drug stability and release profiles, polymer degradation, etc., new PLGA derivatives have been developed. PVA-based branched polyesters bearing PLGA side chains (*PVA-g-PLGA*) have been synthesized to be used as parenteral protein carrier systems. Furthermore, sulfobutyl groups have been covalently attached to the PVA backbone to create polymers with negative charge (*SB-PVA-g-PLGA*) to be applied as nanoparticulate adjuvants for tetanus toxoid vaccines. Finally, positively charged copolymers have been synthesized by attaching amino groups (e.g., diethylaminopropyl amine (DEAPA)), to the PVA backbone (*DEAPA-PVA-g-PLGA*) to be used as adjuvants for DNA vaccination, and drug carriers [10].

Gold NPs represent highly attractive and promising candidates for drug delivery due to their size, controllable surface functionalities and drug release profiles [11]. The efficacy of *magnetic NPs* as targeted nanocarriers of therapeutic compounds has already been demonstrated in vivo [12]. *Clay minerals* are biocompatible cationic inorganic materials, which spontaneously form NPs in aqueous media that can undergo ion exchange with basic drugs in solution. Upon administration of the drug-loaded clay NPs, the drug is displaced by counter-ions from the biological medium and delivered to its site of action. *Polymer/clay nanocomposites*, a new class of hybrid systems in which inorganic NPs are dispersed in a polymer matrix, have recently received a lot of attention as potential controlled release systems [13]. The design of *mesoporous silica nanomaterials* for controlled drug and gene delivery applications has also received a lot of interest. In addition, the surface functionalization of silicas with photo- or redox-responsive organic groups, inorganic NPs, dendrimers and polymers has led to the development of stimuli-responsive controlled release systems [14]. *Liposome-NP hybrids* are promising candidates as nanoscale delivery systems for combinatory therapeutic-imaging modalities. Various types of NPs (e.g., iron oxide, silica, etc.) have already been encapsulated in liposomes to enhance their compatibility with the biological milieu as well as their pharmacological efficacy [15]. *Thiomer micro- and nanogels* are lately considered as promising drug carriers. Thiolated polymers or designated thiomers with improved mucoadhesive properties are synthesized by immobilization of sulhydryl-bearing ligands on the polymeric backbone of various polymers such as chitosan and poly(acrylates) [16].

An important scientific challenge to be met in the future is the development of synthetic nanometer sized delivery systems for therapeutic agents of increased complexity, able to tackle challenging diseases. For example: i) targeted delivery schemes that accumulate the therapeutic agent specifically on the diseased cells for cancer treatment, ii) targeted agents able to deliver a therapeutic payload, e.g., a drug that stabilizes the atheromatic plaque and prevents rupturing, iii) delivery of NPs that selectively attach to stem cell niches and release local stimulating factors for the treatment of musculoskeletal disorders, iv) nanocarriers with special surface properties able to cross the blood-brain-barrier (BBB) and v) formulations of insulin-containing NPs, designed to cross physiological barriers and release insulin in the blood-stream [2].

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