

Polymers and gold nanoparticles: applications in innovative formulations

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Polymer conjugation and nanotechnology have emerged in the last decades as valuable tools to combine materials and molecules having diverse pharmaceutical and biological properties. Bioconjugation is actually deemed the foundation for nanoscience which has been playing a pivotal role in the investigation of novel biophysical phenomena, processes, materials and supramolecular assemblies. The outcomes of nanoscience have found application in many fields of life and health sciences. Furthermore, polymer conjugation technology allows obtaining materials at the macro scale which can be exploited for many biological uses: tissue support for regeneration, implantable devices, releasing matrices etc. The chemical combination of molecular modules with different physicochemical and biological properties may accomplish nanocarriers and matrices with complex architectures, “triggerable” behaviour under selected conditions, drug targeting to specific tissues, controlled release in selected body district or at defined rates.

Gold nanoparticles have been attracted attention as a novel platform for drug and gene delivery, biodiagnosis and many biomedical applications. In our research group we have decorated gold nanoparticles with thermoresponsive polymers to endow particles with temperature “switchable” hydrophilic/hydrophobic character. The specific response of such polymers promotes cell membrane permeation of nanoparticles under peculiar physio-pathologic conditions. In fact several disease sites, namely inflamed or cancerous tissues, have local temperature about 1.5-2 °C higher as compared to normal tissues. Thermosensitive polymers with low critical solution temperature (LCST) at 37°C were used for this purpose. Thermosensitive gold nanoparticles were found to be cell internalized within a very sharp temperature increase. Furthermore, active targeting was conferred by conjugating few targeting molecules on the particles surface buried among the thermosensitive polymer chains. This latter nanosystem has been found to disclose reversibly the targeting moieties at temperature above 37°C and act as “stealth” object at 37°C when the polymer is in the coil state. Thus, multimodal site selective recognition was exploited by combining the nanoparticle morphological surface changes induced by the temperature increase and the consequent exposure of the targeting moiety which can bind its physiologic target.

Stimuli responsive drug delivery systems were designed to exploit the lower pH which distinguishes

tumour tissues from normal ones. We have recently prepared a stimulus responsive supramolecular system based on the pH sensitive amphiphilic unimer stearyl-PEG-poly-sulfadimethoxine. This unimer assembles in 20 nm lipid core micelles which undergo macro-aggregation as the pH decreased from 7.4 to 6.5. The pH controlled aggregation promoted the selective cell uptake. Very limited cell association was found at physiologic pH. Furthermore, the micelles can be efficiently loaded with paclitaxel which follows the fate of the micelles when the pH decrease triggers their aggregation. Overall this data suggest this system is valuable for further development for site selective tumour drug delivery.

We have studied the preparation of hydrogels formed by cyclodextrins (CDs) and polyethylene glycols (PEG) for controlled drug release. PEG was used to endow matrixes with high hydrophilic character and with potential swellability in organic solvents. CDs were used to introduce hydrophobic nano-cavities in the hydrophilic network which can host hydrophobic drugs by forming inclusion complexes. CDs may also play a role in the stabilization of proteins. The combination of hydrophilic polymers and hydrophobic nano-containers, namely the CDs, allows this material to be loaded with both small drug molecules and proteins with biological activity. The composition of the new matrix in term of CD/PEG ratio dictates the drug loading efficiency and its release rate. Thus, the composition can be modulated according to the molecular weight and the hydrophilic/hydrophobic character of the molecule to be loaded. Overall these materials are promising for controlled release of both small molecules and proteins.

Solid nano- and micro-particles were obtained with lipids mixtures or biodegradable polymers by supercritical fluid processing or spray-drying technique. Particles with size ranging from 0.2 to 10 µm were obtained depending on the processing methods and the materials employed. The nano- and microsystems obtained displayed high versatility for the formulation of small drug molecules and biopharmaceuticals.

Solid lipid nanoparticles (SLN) are raising increasing interest for drug delivery and they have been shown to carry desirable properties for the formulation of therapeutic proteins and oligonucleotides. In our research group we have investigated SLN for polypeptides delivery. Homogeneous dispersions of insulin in lipid mixtures were processed by compressed CO₂ according to the patented Gas Assisted Micro Atomization (GAMA) technique, a modified PGSS process. The techniques

allowed obtaining particles with size in the range of 200-300 nm. The procedure was adequate for obtaining high product yield and high protein loading. The protein maintained its structural properties and biological activity and was released within three days.

PLGA microparticles were prepared by spray-drying procedure with the aim of obtaining a controlled release system for cytokines. Particles with 10 μm size were obtained. The stability of the particles in water and the release rate of the loaded biopharmaceutic were adapted by addition of PEG, lecithin and disaccharides in the formulation excipients. Preliminary studies showed that the loaded cytokine can be released from the particles for 72 hours in phosphate buffer. In vivo pharmacokinetic studies displayed that, after microparticles intraperitoneal administration, the cytokine is still found in the blood stream two days after microparticles administration, while the protein administered in buffer solution was undetectable after 24 hours. The therapeutic efficiency of the new cytokine formulation after intra-articular administration is under investigation.