Expert Opinion

The second annual symposium on nanomedicine and drug delivery: exploring recent developments and assessing major advances

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The meeting was dedicated to novel aspects of nanomedicine, including polymer drug delivery systems (DDS) and biomaterials. Self-assembled micellar DDS have been evaluated in terms of morphology, biological properties, and results of clinical trials. Important advances in the design of nanoparticles as DDS have been highlighted in various presentations. Unexpected issues of polymer-related biological effects, including gene expression, were stressed in relation to polymer DDS. Great potential of nanofabrication of biomaterials, and preliminary data on the design of polymer scaffolds were demonstrated in a number of reports. This symposium demonstrated how timely the development of nanosised DDS is, with advances in understanding the disease-related mechanisms, and outlined the major areas of application of nanomedicine technology.

Keywords: biomaterials, nanofibres, nanogels, nanomedicine, polymer micelles, polymer scaffolds

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1. Meeting summary

Historically, nanomedicine approaches have been first applied to drug delivery. The most advanced and close to clinical practice drug delivery systems (DDS) are liposomes, hydrophobic drug-encapsulating lipid containers of submicron size range. Many liposomal drug forms have entered clinical trials. However, there are many properties of liposomes that are poorly compatible with therapeutic applications, for example, preparation, suspension instability and dry storage incapability. Therefore, an active search for alternative drug carriers continues. Progress in the development and nanomedicine applications of polymer-based DDS was a major issue in the programme of the second annual symposium on nanomedicine and drug delivery held in Brooklyn, New York, USA. An important part of the meeting was focused on self-assembled micellar DDS and examples of their successful application as novel drug forms and in developmental therapies. K Kataoka (Tokyo University) has greatly contributed to the design of smart polymeric micelles as DDS for cancer chemotherapy, photodynamic therapy and gene therapy. Kataoka has developed an innovative micellar formulation of cisplatin (CDDP) based on poly(ethylene)glycol(PEG)–polyaspartate block copolymers that displayed sustained drug release and protection compared with injected cisplatin. As tumour vasculature is leaky, accumulation of the loaded micelles via enhanced permeability and retention (EPR) effect significantly enhanced efficacy of the therapy (4 – 5 injections twice-daily) expressed in the reduction of animal death to 10% in 30 days, in comparison with 100% mortality in 8 days for cisplatin alone. The second generation of micellar DDS has included stimulus-activated carriers, which are capable of enhancing intracellular drug release. Conjugation of adriamycin to a polymer, through pH-sensitive

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hydrazone linkage, was an efficient way to trigger drug release, following accumulation of drug-encapsulating micelles in endosomes with an average pH of 5. Another approach to drug activation, named photodynamic therapy, is based on novel photosensitisers and ionic dendritic porphyrins. Drug-loaded photosensitised micelles are able to release drugs after irradiation, markedly increasing drug cytotoxicity in cancer cells compared with free, or polymer drug formulation without irradiation [1,2].

An understanding of the structures formed by the self assembly of polymer molecules, and processes favouring specific architecture of particles, is of major interest in the development of polymer DDS. A Eisenberg (McGill University) has pioneered in this area and presented results of his studies on multiple morphologies of polymer micelles. Eisenberg described approaches to control micellar size, water content and polymer segregation by ensuring a slow, energetically preferred process of polymer chain distribution. Application of charged block copolymers of PEG-polyacrylate with different block lengths at low pH may result in the formation of hollow vesicles, which are able to encapsulate drug molecules in internal volume. In addition, triblock copolymers of poly(acrylic) acid, polystyrene and polyvinylpyridine form differently charged micelles at different pH, with positive surface charge in the presence of hydrochloric acid, or negative charge in the presence of sodium hydroxide. These data could be helpful in creating various polymer DDS; however, at present they have mostly a theoretical interest. [3,4].

G Kwon (University of Wisconsin, School of Pharmacy) presented recent advances in the development of polymer micelles and supramolecular core-shell structures. A drug could be bound in these structures to the core-forming part of the polymer, via degradable bonds. PEG-poly-L-lactate readily assembles into micelles that efficiently solubilise the anticancer agent paclitaxel. This system proved significantly less toxic compared with the commercial solubilising agent, Cremophor® EL (BASF Corporation), used in paclitaxel formulations. The micellar DDS has provided comparable anticancer effects in animal models, but was less toxic *in vivo*. Among other examples, amphotericin B, a drug for hospital-related fungal blood disease, can be efficiently encapsulated into PEG-poly(acyl)aspartate micelles, which results in a lower systemic toxicity. An antifungal activity of the encapsulated drug was the same as that of Fungizone®, but the formulation was significantly less toxic to erythrocytes at doses as low as 0.5 mg/kg [5,6]. Evidently, these biocompatible micellar DDS show great promise for fast clinical evaluation.

An interesting approach to drug encapsulation, described by K Ulrich (Rutgers State University of New Jersey), was developed in the area of biodegradable and biocompatible amphiphilic star-like macromolecules (ASM), with a well-defined core structure. The ASMs are built from a polyol centre block, connected to PEG molecules, and have a size of ≤ 20 nm. Two zones are formed: a drug-binding core, with a capacity as high as 30% by weight; and a PEG protective shield, which can be modified by folate for tumour targeting. The small size of the DDS may greatly enhance penetration of drugs into tumour vasculature. Another type of carrier, called amphiphilic scorpion-like micelles, with a crosslinked core, has been found to carry more drugs than non-linked micelles of the same size. The well-defined structure and low cellular toxicity of these carriers are 'beyond questioning' advantages of the type of DDS [7].

Several novel types of other DDS with well-defined structures were highlighted in the presentations of other participants and discussed. D Discher (University of Pennsylvania) described the preparation of worm-like micellar carriers and synthetic phages from PEG-phospholipid vesicles, by extrusion through a nanoporous filter. These structures, following intravenous administration, have shown an extended circulation in the blood and accumulation in the tumour site due to the EPR effect reaching a maximum at 48 h post-injection. In addition, a significant threefold increase of the accumulation was achieved by attachment of human transferrin receptor-specific peptides. These targeting peptides were selected by phage panning, and have a different binding site on transferrin [8]. Active targeting is certainly a method of choice to avoid nonspecific drug biodistribution, and shifts drug accumulation patterns in a desired direction, compared with passive (EPR) targeting.

Novel approaches to fabrication of polymer scaffolds and their applications in nanomedicine were analysed in a presentation by K Leong (John Hopkins School of Medicine). Leong described another type of biocompatible nanomaterial, polyphosphoester nanofibres, with a diameter of 0.2 – 1.3 µm obtained by electrospining. Galactose-derivatised fibres provide an excellent matrix for programmed alignment of endothelial cells and could be used for tissue engineering. The original approach to fabrication of nanofibres, by interfacial complexation of polyelectrolytes with opposite charges, was developed on the bases of water-soluble chitin as a positively charged biocompatible polymer and alginate, or hyaluronic acid as negatively charged ones. During this mild process many biological agents (i.e., drugs, proteins) could be encapsulated in these biocompatible nanofibres. The release of low-molecular-weight drugs is fast (100% in 2 h), due to the lateral diffusion of the drug, whereas proteins showed sustained release for up to 35 days, well explained by biodegradation of nanofibres matrix. Nanofibres formulated with growth factors and adhesion molecules may be combined for fabricating multilayers and networks with living cells [9,10]. The elegance of this approach makes it very attractive for the development of artificial tissues as a first step to organ design.

The presentation by A Kabanov (University of Nebraska Medical Centre) illustrated the importance of polymer genomics. Studying the side effects of many polymers generally regarded as safe substances is becoming a central issue in the development of polymer DDS. Using the example of Pluronic® (BASF Corporation) block copolymers for treatment of drug-resistant cancer and gene therapy applications,

Kabanov demonstrated that treatment by polymers affects not only the function of various cellular structures, such as membrane-related efflux transporters and mitochondria, but it also has a potent modulating effect on the expression of many genes. Concerning new promising polymer DDS, Kabanov referred to nanogel carriers developed with S Vinogradov (University of Nebraska Medical Centre) and mentioned their application for: oligonucleotide delivery to the CNS; systemic treatment of cancer by nucleoside analogues; and protein formulation. Nanogel carriers consist of a crosslinked network of neutral and chargeable (poly[acrylic] acid or polyethylenimine) polymers, include ≤ 95% water and are well-adopted for systemic administration. Kabanov mentioned a great potential of this type of nanosised DDS for the development of 'smart' carriers with triggered drug release [11,12]. Unique properties of the nanogel carriers, such as a simple drug encapsulation procedure and convenient lyophilised storage form, make them promising candidates for delivery of high-molecular therapeutics including DNA vaccines, plasmid DNA and bioactive proteins.

A similar DDS system was described in a presentation by J DeSimone (North Caroline State University). DeSimone reported synthesis of nanogel DDS made of a PEG-polyacrylate network with quaternised ammonium pendant groups. DeSimone highlighted major problems encountered on the way to application of the DDS, which are related to efficiency of intracellular drug release. In order to ensure, for example, an efficient release of antisense oligos from the nanogel, the carrier should be engineered to quickly disrupt endosomes, and then undergo degradation in cytosol. Another aspect of the PEG–acrylate network application discussed was nanofabrication of gel structures with controllable shapes. The author used a method of non-wetting imprint lithography on polytetrafluoroethylene templates to print PEG–polyacrylate nanoparticles, of any predesigned form and size (~ 0.2 µm). These nanogel particles were able to form secondary structures, such as rolls, and could be postsynthetically modified by targeting or active moieties [13]. It is not clear how this fabrication approach can be applied to the production of sufficient amounts of drug-loaded nanogel particles. However, DeSimone, has proposed them as an example of his developed methodology, which undoubtedly allows us to make a big step ahead to nanotechnology.

Another method of nanogel preparation was presented by K Levon (Poly University, Brooklyn), which focused on the preparation of multifunctional lipobeads and nanogels as carriers for small interfering RNA. This new class of drug carriers represents hybrid liposomes with supportive gel inside. Liposome reactor has been used to polymerise polyacrylate gels inside liposomes to produce particles with narrow size distribution, and then phospholipids can be removed by detergent. The technique can also be applied in the area of microassembling and constructing of stimuli-reactive carriers [14]. This interesting approach uses existing apparatus to produce biocompatible drug-loaded DDS and is well-adopted for fabrication of targeted nanocarriers.

The development of some nanogel systems has made a significant step in the direction of clinical trials. For example, E Turos (University of South Florida) described an interesting approach to preparation of polymer–drug conjugates and formulation of nanoparticles on their base. Microemulsion polymerisation of ethyl acrylate monomers and 1 – 15% antibiotic drug-binding acrylate monomer, was used to produce drug-loaded nanoparticles of 40 – 70 nm. Significantly more effective antimicrobial formulations of *N*-thiolated lactame and Cipro antibiotics have been obtained in the form of polymer nanoparticles [15]. Biodegradable bonds allow for sustained release of antibiotics *in vivo*, and their application to Phase I clinical trials makes these formulations one of the most advanced drug-encapsulating polymer DDS.

2. Expert opinion and conclusion

Summarising topics presented at this year's symposium, it becomes clear that DDS are indispensable for the application of poorly water-soluble drugs, easy biodegradable molecules, and compounds with high systemic toxicity. Drug transport across many biological barriers is sometimes hampered by cellular protective systems against exobiotics. Direct drug targeting, by conjugating the drug molecule with vector moieties, may be expensive and reduce drug activity. Therefore, submicron carriers, loading extensive amounts of drug, represent a better choice. Current DDS are based primarily on passive mechanisms of drug release, such as carrier biodegradation or dissociation of micelles. They are the most advanced and well-understood DDS, and several candidates for clinical trials have already been identified among these systems. However, first examples of the second generation of DDS have now appeared, including external stimuli-reactive carriers, which are capable of releasing drugs following irradiation, changes in pH or temperature. Biopolymer application to nanomedicine will also include self-assembling submicron structures or scaffolds with sustained release of drugs or biological factors necessary for cellular/tissue engineering. The significance of these approaches to nanofabrication of biocompatible materials cannot be omitted from the overall analysis of the current state-of-the-art in the nanomedicine area.

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