The future of intelligent therapeutics

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Abstract

Smart delivery in response to recognition of undesirable biological compounds calls for advanced designs of drug delivery carriers. Recognitive proteins and protein binding domains reveal molecular architectures with specific chemical moieties that provide a framework for selective recognition of a target molecule in aqueous environment. Developments of particular interest to the field will have a wide and far reaching impact and will cover intelligent biomolecule-modulated drug and protein delivery, nano-scale patterning and recognition of biological molecules for micro-diagnostic devices, and site or ligand-specific interaction with cells and tissues.

Introduction

Recent advances in the discovery and delivery of drugs to cure chronic diseases are achieved by combination of intelligent material design with advances in nanotechnology. Since many drugs act as protagonists or antagonists to different chemicals in the body, a delivery system that can respond to the concentrations of certain molecules in the body is invaluable. For this purpose, intelligent therapeutics or "smart drug delivery" calls for the design of the newest generation of sensitive materials based on molecular recognition.

Biomimetic polymeric networks can be prepared by designing interactions between the building blocks of biocompatible networks and the desired specific ligands and by stabilizing these interactions by a three-dimensional structure. These structures are at the same time flexible enough to allow for diffusion of solvent and ligand into and out of the networks.

Synthetic networks that can be designed to recognize and bind biologically significant molecules are of great importance and influence a number of emerging technologies. These artificial materials can be used as unique systems or incorporated into existing drug delivery technologies that can aid in the removal or delivery of biomolecules and restore the natural profiles of compounds in the body.

Nanoscale Structures in Intelligent Therapeutics

In recent years, there has been considerable work in preparing materials and finding new uses for nanoscale structures based on biomaterials. Uses such as carriers for controlled and targeted drug delivery, micropatterned devices, systems for biological recognition, have shown the versatility of these biopolymeric materials as indicated by Langer and Peppas [1].

Of specific interest to us are applications requiring the patterning of vinyls, methacrylates and acrylates during reaction allowing for the formation of nanoscale three-dimensional structures. These micropatterned structures may be used for a host of applications including cell adhesion, separation processes, the so called "factory-on-a-chip" microscale reactors, and microfluidic devices.

Electronic devices have now reached a stage of dimensions comparable to those of biological macromolecules. This raises exciting possibilities for combining microelectronics and biotechnology to develop new technologies with unprecedented power and versatility. While molecular electronics use the unique self-assembly, switching and dynamic capabilities of molecules to miniaturize electronic devices, nanoscale biosystems use the power of

microelectronics to design ultrafast/ultrasmall biocompatible devices, including implants, that can revolutionize the field of bioengineering.

Thus, in recent years we have seen an explosion in the field of novel microfabricated and nanofabricated devices for drug delivery. Such devices seek to develop a platform of well controlled functions in the micro- or nano-level. They include nanoparticulate systems, recognitive molecular systems, biosensing devices, and microfabricated and microelectronic devices.

For example, polymer surfaces in contact with biological fluids, cells, or cellular components can be tailored to provide specific recognition properties or to resist binding depending on the intended application and environment. Engineering the molecular design of biomaterials by controlling recognition and specificity is the first step in coordinating and duplicating complex biological and physiological processes. The design of surfaces for cellular recognition and adhesion, analyte recognition, and surface passivity encompasses a number of techniques such as surface grafting (ultraviolet radiation, ionizing radiation, electron beam irradiation). Certain techniques can change the chemical nature of surfaces and produce areas of differing chemistry as well as surfaces and polymer matrices with binding regimes for a given analyte.

In addition, biomimetic methods are now used to build biohybrid systems or even biomimetic materials (mimicking biological recognition) for drug delivery, drug targeting, and tissue engineering devices [2]. The synthesis and characterization of biomimetic gels and molecularly imprinted drug release and protein delivery systems is a significant focus of recent research. Configurational biomimetic imprinting of an important analyte on an intelligent gel leads to preparation of new biomaterials that not only recognize the analyte but also act therapeutically by locally or systemically releasing an appropriate drug.

Nanoimprinting and Therapeutics

The design of a precise macromolecular chemical architecture that can recognize target molecules from an ensemble of closely related molecules has a large number of potential applications [3]. The main thrust of research in this field has included separation processes (chromatography, capillary electrophoresis, solid-phase extraction, membrane separations), immunoassays and antibody mimics, biosensor recognition elements, and catalysis and artificial enzymes. Nanoimprinting creates stereo-specific three-dimensional binding cavities based on the template of interest. Efforts for the imprinting of large molecules and proteins have focused upon two-dimensional surface imprinting, a method of recognition at a surface rather than within a bulk polymer matrix. More recently, by using an epitope approach and imprinting a short peptide chain representing an exposed fragment of the total protein, three-dimensional imprinting of proteins within a bulk matrix has been successfully prepared.

There is a variety of microelectronic devices that have been studied for controlled drug delivery systems [1]. Sensors represent another area where microfabrication and nanotechnology for drug delivery can be important. For example, scientists are building capacitor-based sensors which have been tested in vitro in model blood vessels. One concept is to implant such systems in small animals to measure blood pressure during cardiovascular studies. In another case, small sensors are being used to measure intraocular pressure for glaucoma patients. For *in vivo* sensors, issues of biocompatibility will be important, and packaging issues may become significant. To address such issues, in one case an electrochemical sensor array was developed to put inside a biocompatible tube which can be monitored by telemetry. This sensor was designed so that it could monitor such substances as pH, carbon dioxide and oxygen.

Another interesting approach involves the development of microfabricated microneedles. This type of approach can have a remarkable effect in enhancing the delivery of drugs without causing significant pain to the patient. Microneedles are able to do this without pain because they don't penetrate deep enough into the skin layers that contain nerves, but are able to penetrate far enough into the skin for the therapeutic compounds to enter the center of circulation.

There are numerous techniques for microfabrication of patterned polymer surfaces and microchips for drug delivery. While silicon has been the choice material for much of the research done with MEMS, the methacrylates and acrylates provide a rapid and inexpensive base for future work. Several applications have already been suggested including patterned surfaces for cell adhesion, biosensors, microfluidic devices, and arrays for chemical screening. Initial work has been directed at creating a microfluidic pump directed by oscillating electrical current. It is possible for pH sensitive hydrogels to be created that deswell when connected to an external electrical source.

The development of nanoparticulate systems for drug delivery applications has taken a level of sophistication never before seen in the field of drug delivery [4]. Using intelligent polymers, it is now possible to design new devices for *intelligent therapeutics*. Such systems can be employed for auto-feedback drug delivery, whereby the hydrogel will be connected to a biosensor and will respond to fast changes in the external biological conditions. This idea may be used to develop novel insulin delivery systems. Another particularly novel use of these systems is for the release of human calcitonin.

Nanoparticles and Intelligent Therapeutics

New promising methods of delivery of chemotherapeutic agents using nanoscale structures have been recently reported. For example, biorecognition of various sugar-containing copolymers can be used for the release of chemotherapeutic agents.

Particles in the submicron range possess very high surface to volume ratios thus allowing for intimate interaction between the surface of the particles and the gastro-intestinal mucus. Additionally, carriers in the particulate form should be able to diffuse further into the mucus layer enabling them to reach the cells of the epithelial layer. The particle size and surface properties, namely, their relative hydrophobicity, are the main factors affecting the particles' effectiveness in prolonging their transit time in the GI tract and protecting the active agents from degradation.

An alternative method of targeting drugs to specific sites is by use of bioadhesive and mucoadhesive nanostructures. Such systems usually consist of hydrogen-bonded structures such as poly(acrylic acid)-based hydrogels which adhere to the mucosa due to hydrogen bonding and/or polymer chain penetration into the mucosa or tissue. Linear polymeric chains can be added to PAA-based mucoadhesives either as free chains or as tethered structures to serve as mucoadhesion promoters.

These recent developments in the field of drug delivery could not be predicted twenty years ago when the emphasis of all controlled release work was on the "adjustment" of the drug release rate. But they could not have been possible without the integration of the field and without the contributions of many scientists and engineers from other areas. I hope you will enjoy this volume and that you will find its contributions thought-provoking.

References

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