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Nanotechnology in Drugs Delivery

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Abstract: 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. Cyclodextrins have been used for two purposes: as a solubilising agent of paclitaxel, which it is a very lipophilic compound, and for their ability to disturb and inhibit the activity of the intestinal P-gp. The oral bioavailability of these cyclodextrin-poly(anhydride) nanoparticles was about 80%. This fact would be due to the combination of both bioadhesive and inhibitory properties of these nanoparticles.
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Keywords: Nanotechnology, Delivery, MTC, RNA

I. INTRODUCTION

Oral chemotherapy is a key step towards "Chemotherapy at Home", a dream of cancer patients, which will radically change the clinical practice of chemotherapy and greatly improve the quality of life of the patients. In the current regimen of chemotherapy, the anticancer drugs are administered through iv. injection or infusion.

Such a way causes high peak above the maximum tolerable concentration (MTC) of the drug in the plasma and then fast excretion of the drug from the circulation system, resulting in a limited area-under-the-curve (AUC), which is a quantitative measurement of the therapeutic effects, and a large part of AUC would be associated with high drug concentration above MTC, thus causing serious side effects. Instead, oral chemotherapy could maintain a sustained moderate concentration of the drug in the circulation to achieve a prolonged exposure of cancerous cells to the drug as well as to avoid high peak above MTC.

This theme issue includes a number of invited reviews that address important aspects of the use of principles of bionanotechnology in drug delivery and modern therapeutics. Special emphasis was placed by the invited authors to outline the importance of biomimetic systems and intelligent substrates in truly innovative drug delivery systems. 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. Nanotechnology often is associated with parenteral drug delivery, particularly for anticancer therapies, but it also has applications in oral drug delivery. Some recent developments show the potential of nanotechnology through this route of administration.

Researchers at the Georgia Institute of Technology (Georgia Tech) and Emory University recently developed a novel approach for delivering small bits of genetic material into the body to improve the treatment of inflammatory bowel diseases, according to an Oct. 10, 2010 Georgia Tech press release. Delivering short strands of RNA into cells has potential therapeutic applications, but delivering them into targeted cells in a living organism has been an obstacle.

In their work, the researchers encapsulated short pieces of RNA into engineered particles called thioketal nanoparticles and orally delivered the genetic material directly to the inflamed intestines of animals. "The thioketal nanoparticles we designed are stable in both acids and bases and only break open to release the pieces of RNA in the presence of reactive oxygen species, which are found in and around inflamed tissue in the gastrointestinal tract of individuals with inflammatory bowel diseases," said Niren Murthy, an associate professor in the Wallace H.

Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, in the Georgia Tech press release. This work was done in collaboration with Emory University Division of Digestive Diseases professor Shanthi Sitaraman, associate professor Didier Merlin, and postdoctoral fellow Guillaume Dalmasso.

II. DRUG ADHESION AND DIFFUSION

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 are a significant focus of recent research.

Professor Matthew Tirrell of the University of California at Santa Barbara provides an excellent review of this subject, while Professor Mark Byrne of Auburn University concentrates on configurational biomimetic imprinting processes of important analytes on intelligent gels that can lead to the preparation of new biomaterials that not

onlyrecognize the analyte but also act therapeuticallyby locally or systemically releasing an appropriate drug.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]. There is a variety of microelectronic devices that have been studied for controlled drug delivery systems [1].

Adhesion and diffusion of the drug in the mucosal microenvironment of the GI tract is another problem for oral chemotherapy. Before the drug molecules reach their final destination (e.g., the blood system, the lymphatic system, the target tissue or cell), it must go through the stomach, the lumen of the intestine, the mucus layer coating the intestinal epithelium, and finally the epithelium itself. The human intestinal epithelium is highly absorptive and is made up of the villi that vastly increase the total surface area of the epithelium available for absorption of the drug in the GI tract, which could be as large as approximately 400 m2. Absorptive enterocyte cells and mucus secreting goblet cells cover the villi, which are interspersed with follicle associated epithelium (FAE). These lymphoid nodules, Peyer's patches, are covered with microfold cells (M cells) specialized for antigen sampling. M cells are significant for drug delivery [29] since they are relatively less protected by mucus and possess a high transcytotic activity .

Polymer toxicity is something we'll have to investigate further, but during this study, we discovered that thioketal nanoparticles loaded with siRNA have a cell-toxicity profile similar to nanoparticles formulated from the FDA-approved material poly(lactic-co-glycolic acid)," said Murthy in the press release. In the future, thioketal nanoparticles may become a significant player in the treatment of numerous gastrointestinal diseases linked to intestinal inflammation, including gastrointestinal cancers, inflammatory bowel diseases and viral infections, according to Murthy.

The traditional definition of nanotechnology speaks of ‘control of matter’. Many newly developed nanomedicines (e.g., targeted liposomes, polyplexes, nanotubes, modified/artificial viruses) can be designed to serve specific therapeutic purposes. Physicists, biologists, chemists, informatics experts, physicians, and pharmaceutical scientists all play a role in developing these ‘smart’ technologies for targeted delivery, for bio-imaging or for the development of new devices. In this context, as the first speaker (Daan Crommelin) proposed, the descriptor ‘smart’ technologies may be better than ‘nanotechnologies’, as in many cases the end product is in the micrometer range or larger and the feature that is of critical importance stands out not because of size but because of function. The speakers that followed indeed showed how smart these new nanotechnological approaches can be The notion that the era of nanomedicines started in the previous century is demonstrated when looking at the development of nanocrystal technology, discussed by Eugene Cooper. Rather simple wet milling techniques led to a decrease of the crystal size down to the hundred nanometer range. These dispersions are stabilized with surface active polymers. The oral bioavailability of nanocrystal based formulations of poorly water-soluble drugs has been clearly enhanced for some drugs. Poorly water-soluble nanocrystals were also used for parenteral injection of imaging material for CT scans.

The ‘nanocrystal story’ clearly shows that rather simple techniques can improve the performance of poorly water-soluble drugs dramatically, although the number of such drugs that are marketed is limited at this point.Recently, much attention has been focused on nanoemulsions and self-emulsified drug delivery systems (SEDDS) to improve the oral bioavailability of poorly water-soluble drugs. Nanoemulsions are non-equilibrium, heterogeneous systems consisting of two immiscible liquids in which one liquid is dispersed as droplets within the other liquid [58]. Self-nanoemulsified drug delivery systems are isotropic mixtures of oil, surfactant, co-surfactant and drug that form fine oil-in-water (o/w) nanoemulsions when introduced into aqueous phases under gentle agitation.

They are stabilized by an interfacial film of surfactant molecules with a droplet size typically less than 100 nm, which guarantees efficient absorption of oil droplets. These systems improve the oral bioavailability of poorly-water soluble drugs by different mechanisms including improved drug solubilisation and protection against physicochemical and enzymatic degradation. The skin is an organ where different nanotechnological approaches are being tested, which Gregor Cevc reviewed. Microneedles with different shapes and sizes, hollow or solid, biodegradable or non-biodegradable attract a lot of attention. In the case of ballistic injection systems, nanometer sized hard or soft (droplets) material is shot into the skin for intradermal delivery.

This concept is now in an industrial development phase for delivery of insulin or vaccines. Skin humidity is considered one of the many factors that cause the high variability of the results. The idea of using nanoemulsions or transformable lipid vesicles for short-lasting skin penetration through aqueous pores has been subject of a long and fierce controversy both regarding the efficacy and the physical mechanisms involved. Clinical studies show effectiveness for local analgesics and, bit by bit, the driving forces are being revealed.

III. CONCLUSION

Drug delivery across the various physiological barriers such as the gastrointestinal barrier for oral chemotherapy is a great challenge in drug design and drug formulation. The molecular basis of the GI drug barrier has been found mainly due to the overexpression of the multidrug efflux pump proteins, P-glycoproteins (P-gp) in the epithelial cell membrane. 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. Professor Lisa Brannon-Peppas offers an important review in this field.

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