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Micelles and nanoparticles for ultrasonic drug and gene delivery ☆

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Abstract

Drug delivery research employing micelles and nanoparticles has expanded in recent years. Of particular interest is the use of these nanovehicles that deliver high concentrations of cytotoxic drugs to diseased tissues selectively, thus reducing the agent's side effects on the rest of the body. Ultrasound, traditionally used in diagnostic medicine, is finding a place in drug delivery in connection with these nanoparticles. In addition to their non-invasive nature and the fact that they can be focused on targeted tissues, acoustic waves have been credited with releasing pharmacological agents from nanocarriers, as well as rendering cell membranes more permeable. In this article, we summarize new technologies that combine the use of nanoparticles with acoustic power both in drug and gene delivery.

Ultrasonic drug delivery from micelles usually employs polyether block copolymers and has been found effective *in vivo* for treating tumors. Ultrasound releases drug from micelles, most probably via shear stress and shock waves from the collapse of cavitation bubbles. Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genes *in vitro* and *in vivo*. The small packaging allows nanoparticles to extravasate into tumor tissues. Ultrasonic drug and gene delivery from nanocarriers has tremendous potential because of the wide variety of drugs and genes that could be delivered to targeted tissues by fairly non-invasive means.

Keywords: Targeted delivery; Polymeric micelles; Thermo-responsive polymers; Ultrasound; Non-viral gene transfection; Drug delivery; Nanoemulsions; Solid nanoparticles; Liposomes

Contents

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1. Introduction

Nanotechnology has finally and firmly entered the realm of drug delivery. Such is an obvious match — to combine the fields of medicine and therapeutic delivery with the up-and-coming universe of nanotechnology and nanoparticles. Although the cells themselves are larger than the usual size that demarks a nanoparticle, the targets of therapeutic drugs – the membrane protein complexes, membrane pores, organelles, ribosomes, chromosomes, and even DNA itself – are nanosized structures. Thus it is natural and expected that as the technology for nanoparticle manipulation and nanoscale visualization has matured, so has the technology to manipulate biology and drug carriers on the nanoscale to produce better health and life for humankind.

Time and space do not permit us to review all of the nanotechnology innovations that have been introduced into medicine during the past two decades. Instead the focus will be on the use of ultrasound and nanosized drug carriers to deliver drugs, genes, and other therapeutic agents specifically to their targeted sites in the body. Targeted drug delivery is essential to modern medicine in which specifically designed and effective drugs are employed to work on selected tissues, cells, and cellular structures. For example, in chemotherapy one often would like to deliver a fairly toxic chemotherapeutic agent directly to a target tissue or location instead of injecting it systemically into the whole body. Similarly in gene therapy for cardiac or brain tissues, it is essential to deliver the gene to that organ only, and perhaps to even a small volume within that organ. Not only does localized delivery use less of the often very costly drug or gene, but also such localized delivery spares the rest of the body from exposure to the therapeutic, resulting in fewer of the detrimental side effects that often accompany drug and gene therapy. In this review, the main modality of localized drug delivery is the use of focused ultrasound to effect drug or gene release at the target tissue, and to stimulate the targeted cells in a manner to render them more prone to drug or gene uptake, or more susceptible to therapeutic processes. This review presents those technologies that use ultrasound in combination with nanoscale therapeutics or therapeutic carriers such as micelles and other nanoparticles.

1.1. Ultrasound

Ultrasound (US) consists of pressure waves having frequencies of 20 kHz or greater. Most often the US is generated by piezoelectric transducers that change an applied voltage into mechanical displacement of a surface (the face of the transducer) that is in contact with water, gel, or some other media that can efficiently transmit ultrasonic waves. Usually the transducers are designed to couple the sound waves into body tissue, but not into air. Thus, the transducer must be placed in direct contact with tissue or skin, and the air in between must be excluded through the application of a fluid such as water or ultrasonic gel. Such a simple application has obvious advantages in that there is no surgery or other invasive procedures, thus eliminating pain and minimizing patient aversion to such therapies.

Like optical and audio waves, ultrasonic waves can be focused, reflected, and refracted through a medium [1–4]. Thus US can be carefully controlled and focused on the tumor site or a particular tissue volume within the body. As mentioned, such site-specific treatment is beneficial in drug delivery to localize the drug interactions to the target tissue only, thus sparing the body from deleterious side effects.

Although often compared to light waves, US is a very physical phenomenon; the pressure waves constituting US actually cause a compression and expansion of the transmitting medium, and there is a slight oscillatory displacement of the medium as the pressure waves pass through. This movement creates forces that physically push and stress cells and tissues, but not with sufficient force to disrupt cell membranes, unless gas bubbles are present [5–7].

Another difference between ultrasonic sound waves and light waves is the amount of absorption or scattering that occurs as