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REVIEW

Nanomaterials in controlled drug release

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Abstract In past years with the advances of chemistry and material sciences, the development of nanotechnology brought generations of nanomaterials with specific biomedical properties. These include the nanoparticle-based drug delivery, nanosized drugs, and nanomaterials for tissue engineering. The present article focuses on the use of nanomaterials in controlled drug release. The applications of nanomaterials with nano-enabled drug release characteristics brought many benefits when compared to the traditional (bulk) materials. We discuss the current advances and propose some future directions for the technology development.

Keywords Drug release · Nanomaterial · Nanoparticle · Gel · Colloid · Drug delivery · Self-assembly

Nanomaterials include all kinds of materials with at least one of the dimensions in the scale of 100 nm (Suri et al. 2007). In recent decade, nanomaterials expanded greatly due to the fast development of techniques in material science, and most bulk materials could be processed in order to acquire nano-features. Generally, nanomaterials include fullerene, nanoparticles, colloids, and nano-gels, which have different applications in various areas. In the present article, we would like to focus on nanoparticle and nano-gel-based control of drug release.

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Nanoparticles

In past decade, drug delivery made with nanoparticles or nanovesicles has brought great commercial benefits in the industry, with 24 products exceeding 5 billion US dollar sales (Huynh et al. 2009; Jatariu et al. 2009; Kateb et al. 2010; Provenzale and Silva 2009).

Variety of nanoparticles

The idea of nanoparticle emerged in 1970s as the delivery substrate for anticancer drugs and vaccines. Various nanoparticles since then were designed and developed, including poly(ethylene oxide)-poly(L-lactic acid)/poly(b-benzyl-L-aspartate), poly(lactide-co-glycolide)-[(propylene oxide)-poly(ethylene oxide)], polyphosphazene derivatives, poly(ethylene glycol)-coated nanospheres, azidothymidin (AZT)/dideoxycytidine (ddc) nanoparticles, poly (isobutylcynoacrylate) nanocapsules, poly(g-benzyl-L-glutamate)/poly(ethylene oxide), chitosan-poly(ethylene oxide) nanoparticles, methotrexate-o-carboxymethylate chitosan, solid lipid nanoparticles (SLNs), and so on (Blasi et al.

2009; Caruso et al. 2010; Chekhonin et al. 2009; Fonseca et al. 2009; Gilmore et al. 2008; Graf et al. 2009; Huynh et al. 2009; Jatariu et al. 2009; Kaur et al. 2008; Khalil and Mainardes 2009; Ljubimova et al. 2008; Mistry et al. 2009b; Modi et al. 2010; Namdeo et al. 2008; Shilpi et al. 2007; Tosi et al. 2008; Wong et al. 2010). Further to these polymer nanoparticles, there are metal-based, lipid-based, and biological nanoparticles. These different surface modifications could result in different interacting efficiency between the nanoparticles and cells, suggesting the diversity of applications (Table 1).

Drug release from nanoparticles

There are several basic approaches to control drug release from nanoparticles. First, the different affinities of nanoparticle surface molecules to different cells and tissues lead varies targeting efficiency, suggesting a targeted drug delivery effect. Therefore, the local drug concentration could be significantly higher in the regions of interest, especially when the nanoparticles were further coated with antigen-recognized antibodies. Secondly, the biodegration of nanoparticles would vary due to the different natures of the materials, the diverse biodegrading activity of enzymes among tissues, and the co-applied adjuvants. Thirdly, it would be ideal to design multi-layer nanoparticles with adjustable degrading curve, with a controlled drug release (Denora et al. 2009; Huynh et al. 2009; Jatariu et al. 2009). Adjuvants could be further combined to regulate the release of specific drugs from the nanoparticle when needed.

Administration routes of nanoparticles

Many routes of administration of nanoparticles are available, such as oral delivery, inhalation, transdermal, implantation, and injection. Inhalation was generally used to treat diseases relevant to respiratory systems, while the olfactory nerve could also mediate the direct drug delivery from the nasal epithelium into the brain, without crossing the blood–brain barrier (Al-Ghananeem et al. 2010; Ali et al. 2010; Jogani et al. 2008; Kumar et al. 2009; Mistry et al. 2009a; Nochi et al. 2010; Patel et al. 2009). The idea originated from the observation that some viral infections can propagate into the brain through the olfactory nerve, and some metal dusts were found in the olfactory bulb of mine workers (Charlton et al. 2007; Oberdörster et al. 2004). Now, the nasal drug delivery was recognized as a routine route of drug administration, even for some diseases of the brain (Betbeder et al. 2000; Fisher and Ho 2002; Patel et al. 2009). This requires the small sized nanoparticles to be transported by the olfactory nerve; and more important, any potential biohazards could lead to serious effects of the central nervous system functions. The application requires cautious evaluation before any drug could be adopted clinically for nasal-brain delivery.

Virus-based drug delivery

More arguments suggest that virus-based drug delivery could be categorized as a biological nanoparticle system. The viruses are with the natural infection routes and could have self-proliferation. Therefore, the utilization of any viral-based drug delivery should consider following aspects: selection of the proper virus to use; engineering of the virus to remove hazardous effects; packaging of the drug/gene sequences into the virus/viral protein-coated nanoparticle; activity and proliferation control following targeting. The main groups of viral vector include enveloped and non-enveloped groups. Enveloped viral vectors include retrovirus (RNA), lentivirus (RNA) and HSV-1 (dsDNA); non-enveloped viral

Table 1 Nanoparticles for controlled drug release and targeted delivery

Types	Source	Bio-compatibility	Controlled release	Targeting efficiency
Polymer	Chemical synthesis	Could be improved with surface modification	Yes	Depends
Metal	Mechanical	Low	Less easier	Low
Lipid	Chemical synthesis	Low	Yes	Low
Biological	Chemical synthesis or biological	High	Depends	Varies

vectors include AAV (ssDNA) and adenovirus (dsDNA) (Bok 2004; Fisher and Ho 2002; Fonseca et al. 2009; Heilbronn and Weger 2010; Poeschla 2003; Sleeper et al. 2009). These viral vectors are of different sizes, varied tissue inflammation reactions, different genome integration abilities, and diverse transfection efficiencies. One of the most widely used systems is the AAV-based drug delivery (Alexander and Hauswirth 2008; Buch et al. 2008; Grieger and Samulski 2005; Martin et al. 2002; Surace and Auricchio 2003, 2008), which is characterized by numerous successes in past decade.

Nano-gel

Microgels are known as intra-molecularly crosslinked macromolecules (ICM), which are formed through polymerization of precursors. Conceivably, the nanogels are polymerized from nano-scale precursors. Nano-level gels and colloids were widely adopted for drug delivery and tissue engineering. In some cases the nanogels contain nanoparticles, and are considered as a manner of nanoparticle delivery. Here we focus on nanofiber-formed nanogels, especially on nanoscaffolds. One of the most important nanogels is the self-assembly nanoscaffolds hydrogel.

Molecular self-assembly is a strategy in nanofabrication. The ideal molecules were designed and produced; under certain conditions, these molecules could aggregate into desired structures due to the molecular forces and shape-complementarity. The known weak interacting forces included Van der Waals, capillary, π–π, and hydrogen bonds. And the individual molecules would follow the order during self-assembly processes.

One example would be the self-assembly peptide nanofiber scaffolds. Because peptides are synthesized from amino acids, the degradation of the peptide-based scaffolds would lead to no immune response and side effects (Kopecek and Yang 2009; Zhao et al. 2010). Moreover, these reported self-assembly peptide nanofiber scaffolds are with high water content, mimicking the natural extracellular matrix, and have been shown to be useful in 3D cell culture, tissue repair, and regeneration (Collier et al. 2010; Ellis-Behnke et al. 2006a, b; Guo et al. 2007; Kopecek and Yang 2009; Ling et al. 2011; Zhao et al. 2010). One interesting application is to engineer the peptide molecules with side chains of pharmaceutical effects (Zhao et al. 2010), and the hydrogel during biological degradation will guide the drug release reactions. The other way is to mix drug particles, including nanoparticles, with the nanogels before administration. The attachment/interaction of drug particles to specific chains and bases in the nanogels could elongate the drug effect for a long period, and the drugs could be retained in the desired regions to treat.

Other than the peptide-based nanogels, many other types of nanomaterials in gel form were developed, including the fabrication of some microgels into nanoscale, such as the nano-collagen fibers. The acquirement of nano-scale characteristic could bring special characteristics to these bulk materials and remains to be one hot research topic currently.

Summary

In conclusion, the newly emerging nanotechnology has largely facilitated the drug delivery processes in many aspects of pharmacology. In the area of cytotechnology, nanoparticles and nanogels provide excellent testing tools to examine the efficiency and effectiveness of drugs, as well as potential toxicity in a high throughput manner. In the future, there will be more nanomaterials available for such applications.

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