Nano Today 15 (2017) 91–106

Contents lists available at ScienceDirect

Nano Today

journal homepage: www.elsevier.com/locate/nanotoday

Review

Evolution and clinical translation of drug delivery nanomaterials

Shabir Hassan[a,b,1], Gyan Prakash[a,b,1], Ayca Bal Ozturk[a,b,f], Saghi Saghazadeh[a,b], Muhammad Farhan Sohail[a,b], Jungmok Seo[a,b,c], Mehmet Remzi Dokmeci[a,b], Yu Shrike Zhang[a,b,*], Ali Khademhosseini[a,b,d,e,*]

[a] Biomaterials Innovation Research Center, Division of Engineering in Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA 02139, USA
[b] Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[c] Center for Biomaterials, Korea Institute of Science and Technology, Seoul 02792, Republic of Korea
[d] Nanotechnology Center, King Abdulaziz University, Jeddah 21569, Saudi Arabia
[e] Department of Bioindustrial Technologies, College of Animal Bioscience and Technology, Konkuk University, Seoul 143-701, Republic of Korea
[f] İstinye University, Faculty of Pharmacy, 34010, Zeytinburnu, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 19 April 2017
Received in revised form 15 June 2017
Accepted 27 June 2017
Available online 2 August 2017

Keywords:
Drug delivery
Inorganic nanomaterial
Polymeric nanomaterial
Liposomes
Clinical trials
FDA approval

ABSTRACT

With the advent of technology, the role of nanomaterials in medicine has grown exponentially in the last few decades. The main advantage of such materials has been exploited in drug delivery applications, due to their effective targeting that in turn reduces systemic toxicity compared to the conventional routes of drug administration. Even though these materials offer broad flexibility based on targeting tissue, disease, and drug payload, the demand for more effective yet highly biocompatible nanomaterial-based drugs is increasing. While therapeutically improved and safe materials have been introduced in nanomedicine platforms, issues related to their degradation rate and bio-distribution still exist, thus making their successful translation to clinical application very challenging. Researchers are constantly improving upon novel nanomaterials that are safer and more effective not only as therapeutic agents but as diagnostic tools as well, making the research in the field of nanomedicine ever more fascinating. In this review, the stress has been made on the evolution of nanomaterials that are under different stages of clinical trials or have been approved by the United States Food and Drug Administration (FDA).

Contents

* Corresponding authors at: Biomaterials Innovation Research Center, Division of Biomedical Engineering, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 65 Landsdowne Street, Cambridge, MA 02139, USA.
E-mail addresses: yszhang@research.bwh.harvard.edu (Y.S. Zhang), alik@bwh.harvard.edu (A. Khademhosseini).
[1] Equal contribution.

http://dx.doi.org/10.1016/j.nantod.2017.06.008
1748-0132/

Introduction

The fascinating world of nanomaterials and their various applications is not new. As early as 2500 BC, natural asbestos was used to increase the reinforcement of a ceramic mixture for decorative purposes [1]. The famous Lycurgus cup made by the Romans in the 4th century AD displayed different colors during the day and when illuminated from inside at night [2]. This gave the first definite evidence into the synthesis and application of gold colloids. Mesopotamians in the 9th century AD introduced silver and/or copper glazed ceramics [3]. It was not until the famous statement, "there is plenty of room at the bottom" from Feynman in 1959 [4] that brought nanotechnology back into focus of the modern scientific world and exactly a decade after, the term "nanotechnology" was coined [5]. Over the years, application of nanomaterials in biomedicine has vastly increased and the introduction of inorganic and polymeric materials further enhanced their role for drug delivery and sustained drug release. Fig. 1 outlines important dates in the evolution of nanomaterials from 2500 BC until today from their discovery/invention to different applications. Not all the listed nanomaterials in Fig. 1 have been approved for clinical use.

Although nanomaterials have found their applications in different fields of research for long, their role in medicine is new and emerging. Due to their small sizes, nanomaterials take a sweet spot that correlates with the sub-micron entities of the biological world, making them especially appropriate for interactions at that scale. Nanomaterials display many distinctive physicochemical properties that differ extensively from their corresponding bulk materials. It is mainly their size-related properties that dictate their physicochemical uniqueness and make them exceptional for various biological applications, *e.g.* drug delivery, tissue engineering, targeted drug delivery, bio-microelectromechanical systems (bioMEMS), biosensors, microfluidics, and diagnostics [6]. Due to the extraordinary opportunity it offers, nanomaterial-based drug delivery has emerged as the mainstream application of nanotechnology in medicine [7]. In addition to enhancing targeted delivery and controlled release of drugs, nanomaterials assist in improving their circulation time and biodistribution, solubility, intracellular delivery, and crossing biological membranes [8]. Nanomaterials in medicine have been traditionally used for drug delivery applications only; however, new nanoscale platforms have been developed that offer a diagnostic application in addition to their therapeutic ability [9]. Multifunctional nanomaterials have been developed that combine therapeutic, targeting, and imaging capabilities for advanced drug delivery systems and are gaining increasing attention from the research community [10].

In this review, we attempt to outline the evolution of nanomaterials for drug delivery applications over the last few decades. We maintain the focus on those materials that have the potential for clinical translation or have been approved for therapeutic purposes by the United States Food and Drug Administration (FDA). Carbon-based nanomaterials for biomedical and tissue engineering applications have been discussed elsewhere [11]. In the first section, nanomaterials of inorganic origin including gold, magnetic, and silica-based materials for drug delivery are discussed. The second section details the applications of polymer-based nanomaterials, where the development and role of dendrimers, polymeric micelles, nanogels, and polymeric nanoparticles are discussed. Lipid-based nanomaterials are explored in the next section, and the last section entails a summary of some of the nanomaterials that have been approved by the FDA for human use.

Inorganic nanomaterials

Over the last few decades, scientists have actively explored the synthesis of inorganic nanoparticles (INPs) for applications in various fields. In this section, we primarily focus on the synthesis of INPs for diagnostic and therapeutic applications, which require precision engineering of the nanoparticle properties. Fig. 2 outlines important applications of some INPs in diagnostics and drug delivery. The extensive research in the field has provided ample understanding to control the attributes at the nano-bio interface, which has led to numerous successful clinical trials and translations. INPs have also been exploited for their optical properties, which arise due to the quantum size effect, and have been shown to be modulated by control over size for application as effective imaging and contrast agents [12]. Similarly, various chemical modulations have been carried out on their surface, such as polyethylene glycol conjugation (PEGylation) [13], charge modulation, ligand conjugation, and inclusion of stimuli-responsive moieties and small-molecule probes for improved drug efficacy [14]. We further discuss the advances in the synthesis and surface modification of these INPs that have facilitated their successful drug delivery applications.

Gold nanoparticles (AuNPs)

First scientific insight into the property of AuNPs came from Michael Faraday in 1850 [15], where through synthesis he showed the ability to obtain a ruby red colloidal solution of AuNPs from yellow $HAuCl_4$ gold salt. However, medicinal application of gold salt was not proposed until 1890, as bacteriostatic against tuberculosis [16]. Subsequently, gold was also found to be effective in the treatment of Rheumatoid arthritis in 1927 [16]. This led to prominence of nanogold as therapeutic agent towards various Rheumatoid diseases.

AuNPs have been widely explored for applications in medicine due to (*i*) biocompatible nature, (*ii*) precise control over their