Chapter

Introductory Chapter: Overview on Nanomedicine Market

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1. Introduction

Nanomedicine is an emerging field that has caught the interest of many medical scientists and chemists due to its unique characteristics that open the door wide for several unique applications that might lead to solving many problems that were found difficult to tackle in medicine. Nanomedicine has opened a new category of medicines called nanomedicines where the medicine is reduced to the nanoscale size, hoping to enhance its physicochemical properties. The chapter summarizes the nanomedicines that have been approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) and the nanomedicines whose clinical trials based on previously published review articles by Anselmo and Mitragotri are ongoing [1, 2].

To gain insight to current trends in nanomedicine research and the most successful types of nanomedicines in the market, the approved nanomedicines are presented in **Figure 1**. The number of approved nanomedicine products is 29 till 2019 [1]. Liposomes represented 44.8% (13 products). Inorganic nanoparticles ranked second with 41.4% (12 products). Other nanoparticles (polymeric and protein) have only 4 products (13.8%). These findings are very interesting as liposomes are one of the oldest nanomedicines. This opens an argument about the challenges in nanomedicine translation as a new platform requires further investigations to prove its activity and safety. On the other hand, cancer nanotherapeutics is ranked first with 10 products in the market, followed by iron-replacement therapies with 8 products. Also, it is worth to mention that imaging agents (six marketed products) are ranked in third place, especially the inorganic nanoparticles (three products).

Moreover, nanomedicines, currently undergoing clinical trials, are presented in **Figure 2**. The number of products under clinical trials is 47 till 2019 [1], where liposomes represented 61.7% (29 products) and micelles ranked second with 19.15% (9 products). Other nanoparticles have only nine products (19.15%). Also, these findings are similar to approved nanomedicine, where liposomes are the most used nanomedicine. On the other hand, 39 products are dedicated for cancer treatment. It is worth to mention that 10 products out of the 39 products are loaded with gene therapy and not chemotherapeutic agents.

Generally, the total number of nanomedicines in the market or in clinical trial are 76 products, where liposome formulations were the most used delivery system with 55.26% (42 products), followed by inorganic nanoparticles with 21% (16 products) as presented in **Figure 3**. According to the World Health Organization in 2015, the first leading cause of death in around 50% of countries is cancer [3]. According to the International Agency for Research on Cancer report that published in 2018 on the global burden of cancer, there are 18.1 million cancer cases and 9.6 million cancer deaths in 2018 [3]. These reports inspired the

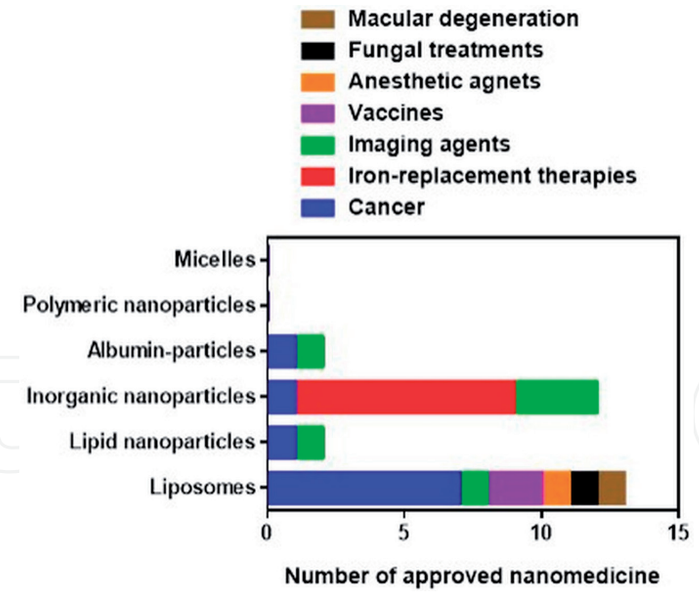

Figure 1.
Clinically approved nanomedicine for therapy and diagnostic.

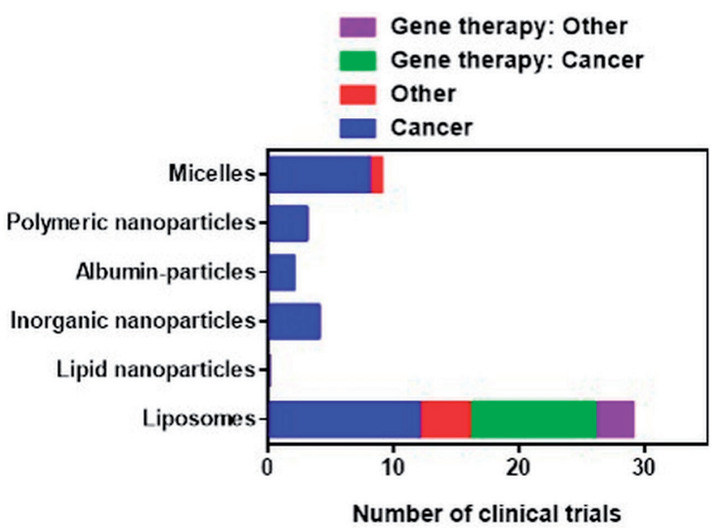

Figure 2.
Nanomedicine currently undergoing clinical trials for therapy and diagnostic.

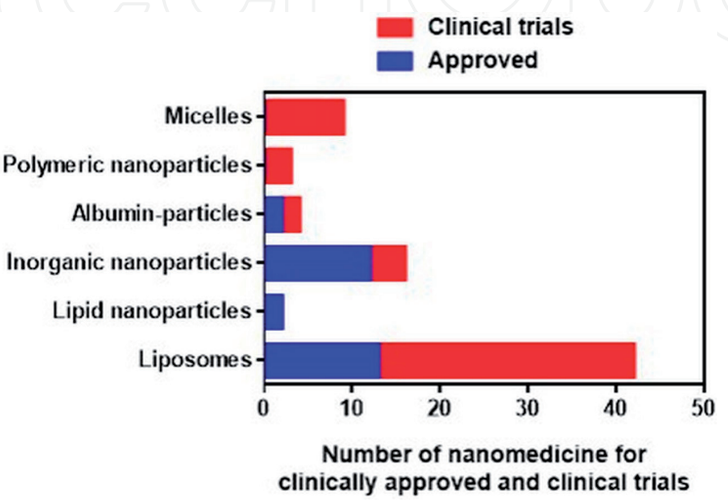

Figure 3.
Total number of nanomedicines approved and under clinical trials (therapeutic and diagnostic).

pharmaceutical industry to invest in this market. As mentioned previously, there are only 10 nanomedicine products out of 29 products available in the market to treat cancer, while there are 39 products out of 47 products for cancer treatment. This number of clinical trials for cancer is mainly derived by the 15 years of support by the US National Cancer Institute through the Centers of Cancer Nanotechnology Excellence (CCNEs) [4].

2. Types of nanomedicines

Nanomedicines are mainly classified into two classes, either inorganic nanoparticles such as gold, silica, and iron oxide or organic nanoparticles such as polymeric, liposomes, and micelles (**Figure 4**). These nanoparticles are mostly used for therapeutic and diagnostic nanoparticles. Inorganic nanoparticles have been used for a variety of applications including lymph node imaging, hyperthermia, and anemia treatment. Some of them have successfully gone through preclinical studies and clinic trials. Along with inorganic nanoparticles, organic-based nanoparticles have successfully reached the clinical phase and currently reached the market for different applications like vaccination, microbial infection, and cancer.

2.1 Liposome-based nanomedicines

Liposome-based nanomedicine is a type of drug formulation where a drug is encapsulated inside the phospholipid bilayer structure to enhance its bioavailability and therapeutic activity. Liposome formulations are one of the oldest nanomedicines with a well-established technique. Many research efforts were focused on using liposomes to encapsulate several cargos like small molecules such as doxorubicin, nucleic acid such as RNAs, and biological molecules such as vaccines for hepatitis A virus. Furthermore, administration of the liposomes without an encapsulated drug is also a possibility if the liposome subunits have a certain therapeutic effect such as sphingomyelin and cholesterol. PEGylation is an option to consider while using liposomes due to its importance in adding stealth to the delivery system. Most of the approved liposome-based nanomedicines are used for the treatment of cancer diseases. They take a large place in research as 10 out of the 29 approved nanomedicines are liposome-based.

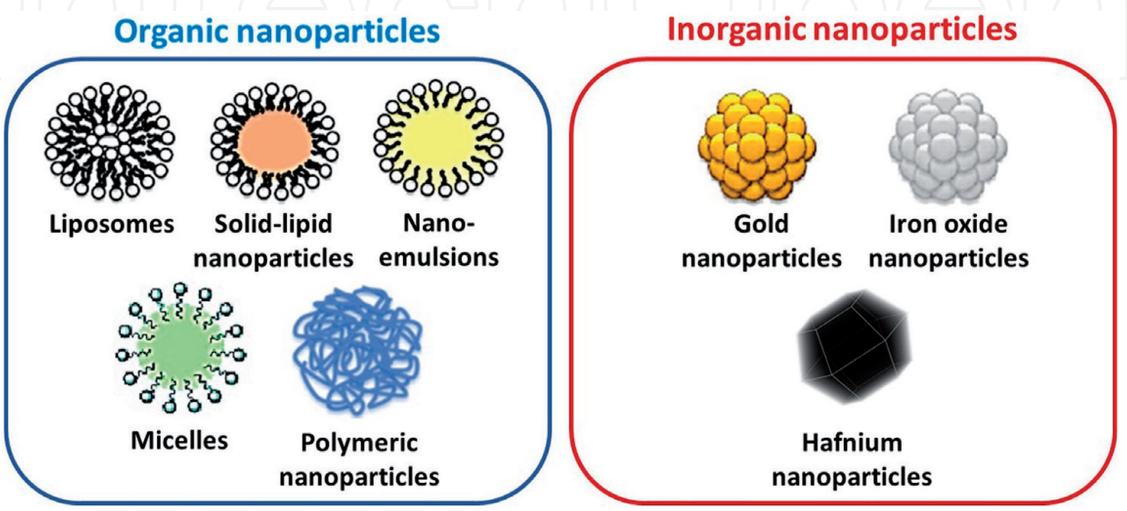

Figure 4.
Clinically approved and investigated nanomedicines including organic nanoparticles and inorganic nanoparticles.

2.2 Lipid-based nanomedicines

Lipid nanosystems including nanoemulsions and solid lipid-based nanoparticles are another form of nanomedicine, which are usually used to encapsulate hydrophobic cargos to improve permeation and control release profile. Usually, a surfactant is used to ensure a uniform dispersion. Lipid nanomedicine can also encapsulate some gene therapeutics such as siRNA or contrast agents used for imaging such as F-butane. Generally, lipid nanomedicine can improve the pharmacological effect by enhancing drug accumulation in targeted tissues beside its biocompatibility. However, there are several drawbacks like rapid clearance due to reticuloendothelial system (RES) uptake and some limitations for administration routes and challenges regarding system stability [5, 6]. Unlike liposomal-based nanomedicines, lipid-based nanomedicines are not limited for cancer diseases only. Some of the diseases that are treated by lipid-based nanomedicines are amyloidosis, hepatitis B, and hepatic fibrosis. Furthermore, several types of nanoemulsion were loaded with drugs like simvastatin, cinnarizine, coenzyme Q10, and cyclosporine, which used as antihyperlipidemia, antihistaminic, antioxidant, and immunosuppressants, respectively.

2.3 Albumin-based nanomedicines

Albumin-based nanomedicines are another form of nanosystems, where albumin, especially human serum albumin (protein), is used as a carrier. Albumin nanosystems can be loaded with different cargos via a simple self-assembly procedure of albumin in aqueous solution with simple crosslinking step. The main advantage of albumin is biocompatibility. Despite that, only 2 out of the 29 listed approved nanomedicines and 2 out of the 65 nanomedicines under clinical trials are albumin-based. It is currently used in imaging and delivering drugs that treat cancer diseases.

2.4 Micelle-based nanomedicines

Micelles are self-assembled nanosystem by amphiphilic molecules that have a hydrophilic part and a hydrophobic one. They have several advantages like high permeability and solubility, which improve drug bioavailability. However, they still have some drawbacks like insufficient control to drug release and cytotoxicity due to amphiphilic molecule use, which interact with cell membrane [5, 7]. Although several reports used block copolymeric micelles to reduce clearance and increase bioavailability of chemotherapeutic agents and other types of drugs, there are no approved micelle-based nanomedicines. However, there are currently nine micelle-based nanomedicines undergoing clinical trials. Majority of them are used for cancer treatment.

2.5 Polymeric-based nanomedicines

Polymeric nanoparticles are one of the most commonly used nanosystems for drug delivery. Several polymers have been used like ethyl cellulose, poly(lactic-co-glycolic acid), polylactic acid, cyclodextrin, alginate, and chitosan. Depending on the nature of the polymer, either hydrophilic or hydrophobic, there are several techniques that have been used to prepare polymeric nanoparticles. Several advantages like relative stability and prolonged duration of action make polymeric nanoparticles a promising platform for the market. However, there are no marketed products based on polymeric nanoparticles. Only three products are currently on clinical trials for cancer.

2.6 Inorganic-based nanomedicines

Inorganic-based nanomedicines have several subtypes. Due to degradability and biocompatibility issues, few types have been used for therapeutic purpose, while other types for diagnostic purpose like imaging agents. One of these subtypes are metal oxide nanoparticles such as hafnium oxide nanoparticles which enhance tumor cell death via electron production through their stimulation with external radiation. Another subtype is in the form of colloids such as iron dextran colloids, iron gluconate colloid, and other similar derivatives that are usually used for the treatment of iron-deficiency anemia. The last subtype mentioned is iron–/silica–/gold-based nanomedicines, either as nanoparticles with drugs arranged on the surface for the treatment of cancer or as nanoshells/nanoparticles used for thermal ablation of tumors. There are 12 products in the market that belong to this type. Eight products used iron-replacement therapies. On the other hand, four products are currently on clinical trials for treating cancer.

3. Nanomedicines pharmacokinetic and regulations

The pharmacokinetic parameters of nanomedicines are similar to free drugs with addition phase after drug administration, which is the liberation phase beside the standard absorption, distribution, metabolism, and excretion (ADME). This new phase is controlled by particle nature, size, shape, and surface properties. It is worth to mention that particle size is very important for absorption and elimination. Particles with particle size <5 nm is easily excreted from the kidney, while larger particle size could be eliminated by the liver or engulfed by mononuclear-phagocyte system. Moreover, particle size and shape can affect particle accumulation in targeted tissues like ellipsoidal shape that has better distribution and retention in tumor tissue than spherical one. Surface modification of nanoparticles can affect particle uptake and elimination. Many nanoparticles are coated for active and passive targeting. Passive targeting is a non-specific retention in target tissue like solid cancer tissue by enhanced permeability and retention mechanism. Active targeting is the selective uptake of nanomedicine by specific cells. Target moieties could be protein, antibody, or small molecule selective to specific tissues or cells. This mechanism is mainly controlled by homing to overexpressed cell surface receptors.

The Food and Drug Administration classified nanoscale materials to nanomaterials as "materials used in the manufacture of nanomedicine" or nanomedicine as "final products," The FDA approved 51 nanomedicines by the year 2016, 40% of which were in clinical trials between 2014 and 2016. According to the FDA evaluation of nanomedicines, it includes the physicochemical properties, followed by pharmacokinetics evaluation of nanomedicines. The pharmacokinetics evaluation includes (1) rate and amount of absorption, (2) retention in circulation, (3) half-life and complete elimination, (4) bioavailability differences, (5) distribution or accumulation to the body or specific tissue for active targeting, (6) decomposition or metabolism, (7) elimination, and (8) toxicity assessment of nanomedicines. On the other hand, the European Medicines Agency defined nanomedicines as "drugs composed of nanomaterials 1–100 nm in size, and these are classified into liposomes, nanoparticles, magnetic nanoparticles, gold NPs, quantum dots, dendrimers, polymeric micelles, viral and non-viral vectors, carbon nanotubes, and fullerenes." EMA has approved eight commercially available nanomedicines as first-generation nanomedicines. Currently, there are 48 nanomedicines in clinical trials (Phases 1–3) in the EU. EMA evaluates the pharmacokinetics and pharmacodynamics of nanomedicines through investigation of their chemical composition and physicochemical properties [8].

4. Approved application and indication of nanomedicine

4.1 Cancer nanoparticle medicines

Most pharmaceutical industries are focusing on developing new products for cancer as it is the first cause of death in 50% of the countries. Nanomedicine products have a good share in this market with many approved products to treat several types of cancer at various stages. Abraxane® is a famous albumin-particle bound paclitaxel nanomedicine loaded for advanced non-small cell lung cancer, metastatic breast cancer, and metastatic pancreatic cancer. Doxil®, the first approved nanomedicine by the FDA in 1995, is a PEGylated liposome loaded with doxorubicin for ovarian cancer, HIV-associated Kaposi's sarcoma, and multiple myeloma. Marqibo® is a liposomal vincristine for Philadelphia chromosome-negative acute lymphoblastic leukemia. Hensify® is the recently approved nanomedicine for cancer in 2019 by the FDA. It is the hafnium oxide nanoparticles stimulated with external radiation to enhance tumor cell death via electron production for locally advanced squamous cell carcinoma. Most of the approved nanomedicines are non-PEGylated except Doxil and Onivyde, which is interesting as most reports have proven the importance of nanomedicine coating with PEG. Furthermore, all nanomedicine products do not have active target moiety. So, all of these products follow passive targeting approach without even stealth characteristics.

4.2 Iron-replacement nanoparticle therapies

Iron-replacement therapy to treat anemia is surprisingly another area for nanomedicine due to the significance of nanoscale iron-oxide colloid system in improving iron absorption to the body. The main advantage of iron-oxide nanomedicine is replacing the injection of free iron with its associated toxicity. Most of these nanosystems are coated with either polysaccharide or polymer to reduce iron toxicity. CosmoFer® is the first approved iron dextran colloid by the FDA in 1996. Injectafer® is the most recent one in 2013 by the FDA, which is iron carboxymaltose colloid.

4.3 Nanoparticle/microparticle imaging agents

Another area for nanomedicine, especially the inorganic ones, is diagnostics, mainly imaging agents. Iron-oxide nanomedicines are also approved as contrasting agents for magnetic resonance imaging, which is used to generate contrasted images for different types of cancers. The magnetic property and small particle size allow the distribution of iron-oxide nanomedicine in tumor tissue, which provide a precise imaging of cancer borders. Additionally, perflutren is also used as ultrasound contrast agent in either lipid- or albumin-based nanomedicines. Phospholipid-stabilized microbubble is another form of nanomedicine as ultrasound contrast agent, which is approved in 2001 by the EMA. Its main mechanism is encapsulating air bubbles, which act as reflectors for ultrasound.

4.4 Nanoparticles for vaccines, anesthetics, fungal treatments, and macular degeneration

Several clinical applications have been studied using nanomedicine. Diprivan® is the first FDA-approved nanomedicine in 1989 for anesthesia. Another field for nanomachine is vaccination with two products, which are Epaxal® for hepatitis A and Inflexal V® for influenza. Both vaccines are liposome-based nanomedicine due

to the similarity of liposome structure to cell structure. Another famous liposome product is AmBisome®, which is a liposome loaded with amphotericin B for treating systemic fungal infections with reduced toxicity. Abelcet® is another approved lipid-based nanomedicine loaded with amphotericin B. Finally, Visudyne® is a liposomal verteporfin for treatment of subfoveal choroidal neovascularization from age-related macular degeneration, pathologic, or ocular histoplasmosis.

5. Conclusion

Nanomedicines are currently in the middle of the road with great potentials but require many development considerations regarding assessment of physicochemical properties, pharmacokinetic properties, and pharmacodynamic applications. Based on the recent trends with 47 products in clinical trial phases, it is expected that within the next few years, more products will be available for several applications, especially cancer.

Conflict of interest

The authors declare no conflict of interest.

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