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The Importance of Nanopharmaceuticals and Nanomedicines Applications and Properties: A Current Review

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Abstract

Nanotechnology is recognized as a new and rapidly developing field in the pharmaceutical and medical fields. The breakthroughs in nanoscience are developing in almost every field of science, and at the same time, nanotechnologies make life easier in terms of science in the modern era. Nanoscience and nanotechnology are developing fields of study that involve structures, devices, and systems with innovative features and functionalities as a result of the arrangement of their atoms on the 1-100 nm scale. This area became the subject of increasing public awareness and debate in the early 2000s. Nanotechnology contributes to nearly every field of science, including physics, materials science, chemistry, biology, computer science, and engineering. Especially in recent years, nanotechnologies have been applied to human health with promising results, especially in the field of cancer therapy. Moreover, in recent years, nanotechnology has become a widely used technology in a wide range of medical and pharmaceutical applications. Drug-delivery systems based on nanoparticle technology have the potential to launch an industrial revolution that might serve as a watershed moment for future pharmaceutical industries. The main aims of developing nanoparticles as a delivery system are to improve bioavailability by increasing solubility and dissolution rate, to target the drug to specific organs, and to control the drug release rate. To fully understand the nature of nanotechnology, it is useful to review the history of discoveries that led to the current understanding of this science. This review summarizes the progress and key principles of nanomedicine, nanopharmaceuticals, nanoscience, and nanotechnology, and also highlights the pre-modern and modern historical ages of discoveries and historical milestones of nanotechnology and nanomedicines.

Keywords: Nanopharmaceuticals, nanomedicine, nanotechnology, pharmaceutical nanomedicines

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Introduction

The word 'nano' is a Greek prefix that means 'dwarf' or something very small and equals one billionth of a meter (10^{-9} m = 0.000000001). We should differentiate between nanoscience and nanotechnology, nanoscience is the study of structures and molecules on nanometer sizes ranging from 1 to 100 nm, and nanotechnology is the technology that utilizes it in practical applications such as devices (Mansoori *et al*., 2005). In comparison, a single human hair is 60,000 nm thick and the DNA double helix has a radius of 1 nm (Gnach *et al*., 2015; Figure 1). The development of nanoscience may be traced back to the 5th century B.C., to the Greeks and Democritus, when scientists debated whether the matter is continuous, and hence infinitely divisible into smaller pieces, or composed of small, indivisible, and indestructible particles which are now known as atoms. Pharmaceutical nanotechnology has resulted in significant advancements in human life and health care (Chang *et al.*, 2015). Biomaterials used in this field are primarily intended to improve drug delivery systems, imaging, and diagnostic technologies, while nanoscale materials are widely used in other industries such as electronics and optics (Pourmand *et a*l., 2012). The application of nanotechnology in treating some of the most critical metabolic and genetic diseases and cancers, delivery systems, genetic tests, as well as imaging and diagnostics, will consume significant amounts of funding for research and development in both academia and industry (Demetzos, 2016; Pourmand *et a*l., 2012; Weissig *et al.*, 2014).

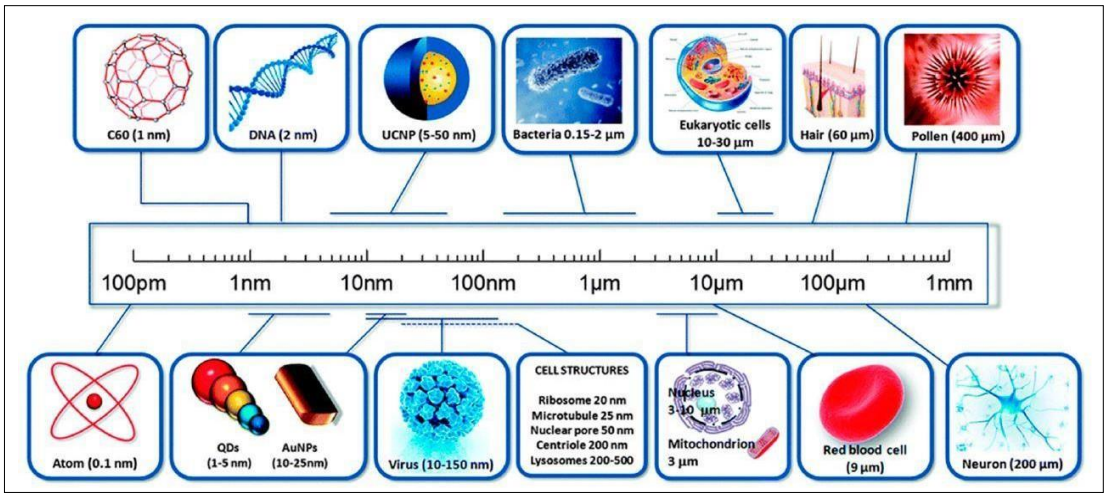

Figure 1. A comparison of nanomaterial sizes (Gnach *et al*., 2015)

One of the most promising technologies of the 21st century is nanotechnology. It is the ability to apply nanoscience theory by observing, measuring, manipulating, assembling, controlling, and creating materials on the nanoscale scale. Different techniques are discussed for each parameter researched, emphasizing their advantages and disadvantages and demonstrating which nanomaterials may be researched adequately with each technique. Thereafter, the terms nanosystems, nanomedicine, and colloidal nanomaterials are derived from the specific entity they represent (e.g., nanorods or nanoparticles), their composition (such as drug delivery systems or non-viral gene delivery systems), and their use (e.g., drug delivery systems or non-viral gene delivery systems) (Figure 2). Noteworthy, nanotechnology provides humankind with exceptional opportunities to improve its well-being, but it also has certain limitations that entail thorough investigation by regulatory and scientific authorities (Weissig *et al*., 2015; Bawa *et al*., 2016). The present research reviews the literature on nanopharmaceuticals and nanomedicines along with their importance, properties, and applications in humans.

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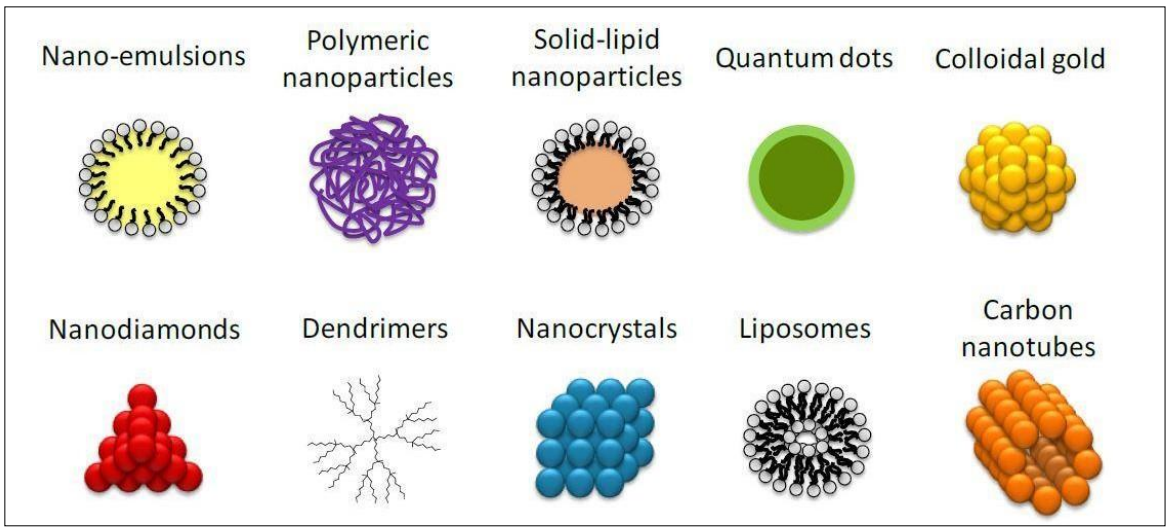

Figure 2. A schematic illustration of the most commonly used types of nanomedicine made up of various materials (Cristina *et al*., 2017)

History

Humans first employed nanoparticles and structures in the fourth century AD, when the Romans exhibited one of the most fascinating examples of nanotechnology in the ancient world. The Lycurgus cup in the collection of the British Museum is one of the most important achievements in the ancient glass industry. It is the oldest and most famous example of dichroic glass (Figure 3). Dichroic glass refers to two types of glass that change color depending on the lighting. This means that the Cup has two colors: green in direct light and red-purple when light shines through the glass (Harden *et al*., 1959).

Figure 3. The Lycurgus Cup (British Museum)

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In 1990, scientists used Transmission Electron Microscopy (TEM) to examine the cup in order to understand the phenomena of dichroism (Barber *et al*., 1990). The presence of nanoparticles 50-100 nm in diameter is responsible for the observed dichroism (two colors). X-ray analysis revealed that these nanoparticles are silver-gold (Ag-Au) alloys with an Ag: Au ratio of around 7:3 and about 10% copper (Cu) dispersed in a glass matrix (Freestone *et al*., 2007; Wagner *et al*., 2000). As a result of light absorption (520 nm), the Au nanoparticles turn red. The red-purple color is produced by absorption by larger particles, whereas the green color is caused by light scattering by colloidal dispersions of Ag nanoparticles larger than 40 nm. The Lycurgus cup is known as one of the oldest synthetic nanomaterials (Mansoori *et al.*, 2005). The earliest results linked to the development of nanomedicine were discovered at ETH Zurich in the late 1960s (NNI, 2019). Nanomedicine has seen considerable technological and industrial growth in the last few decades. It has been marked by certain significant initiatives that have prepared the path for its growth.

Nanotechnology in Medicine

The goal of nanomedicine can be broadly described as the complete monitoring, control, construction, repair, defense, and improvement of all human biological systems at the molecular level, ultimately to provide medicinal advantages. In this sense, nanoscale refers to active components or things with sizes ranging from one nanometer to hundreds of nanometers. These could be found in a micro-device (with a macro-interface) or in a biological environment. However, the emphasis is always on nano-interactions within the framework of a larger device or directly within a sub-cellular (or cellular) system. The size of nanoparticle systems ranges from a few nanometers for micelles to hundreds of nanometers for liposomes. For example, drug delivery systems can easily interact with biomolecules on both the cell surface and inside the cell. Thus, nano-drug delivery systems can not only transport small encapsulated or grafted chemotherapeutic drugs less than tens of nanometers in size but also deliver them inside cells once they have entered them. Such systems can also be decorated with antibody fragments on their surfaces to target specific tissues, increasing the specificity of drug delivery.

Nanomedicine

The word "nanotechnology" originally became widely known in a 1986 book titled "Engines of Creation: The Coming Era of Nanotechnology" by K. Eric Drexler. The theory was initially proposed by Nobel winner Richard Feynman in his 1959 presentation titled 'There's Plenty of Room at the Bottom' (Feynman, 1960). The early envisioned uses of nanotechnology concerned chemical synthesis using nanoscale devices and atomic-level information storage (Devreese, 2007). Nanotechnology has since been used in many fields, including wastewater treatment (Qu *et al*., 2013), the textile industry (Sawhney *et al*., 2008), high-performance batteries (Chan *et al*., 2008), biology (Briggs *et al*., 2012), and medicine Langer *et al*., 2015). In medical applications, nanotechnology has resulted in substantial advances in cancer therapy (Coccia *et al.*, 2015), disease diagnostic imaging Karimi *et al*., 2016), tissue engineering (Parpura, 2016), and most significantly, drug and gene delivery systems (Karimi *et al.*, 2016). Today, the use of nanotechnology in biomedical sciences and healthcare, in particular, is known as 'nanomedicine,' and it is regarded as a hot development field of nanotechnology

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(Farokhzad *et a*l., 2006; Sayes *et al*., 2017). The United States Food and Drug Administration (US FDA) has approved the commercialization of 100 nanomedicine applications and devices throughout the past few decades (Etheridge *et al*., 2013). This demonstrates how important nanotechnology is in today's biological science (Dilnawaz *et al*., 2018; Ragelle *et al.*, 2017). As a consequence, the US federal government has contributed more than $1.4 billion in funding for the National Nanotechnology Initiative, confirming the significance of nanotechnology Iyer *et al*., 2015). Nanotechnology plays an important role in the field of medicine and drug delivery, due to the significant limitations and difficulties that affect conventional pharmaceutical agents, as well as older formulations and delivery systems. One of the major issues with conventional Drug Delivery Systems (DDS) is the difficulty in removing the residual parts of such systems, which might leave non-biodegradable material within the patient's body and induce toxicity (Bhowmik *et al*., 2012). Similarly, most conventional DDSs have a high initial burst of drug release immediately after drug administration, and moreover, the drug solubility in conventional DDSs is low (Karimi *et al*., 2016). Here, nanopharmaceuticals can be promising solutions for the above-mentioned problems (Nikalje, 2015).

The Concept of Nanopharmacy

Nanotechnology is a multidisciplinary research area dealing with the physical and chemical properties of chemicals and materials at the scale of nano-sized particles (from 0.1 nm to 100 nm) (Bawa *et al*., 2009; Lin *et al*., 2008). It also studies the techniques that can be used to manipulate materials by utilizing these unique characteristics. The essence of nanotechnology is the ability to produce new products with specially designed target functions and special properties through artificial manipulation at the atomic and molecular levels. It is now widely accepted that the application of nanotechnology will alter pharmaceutical product design and manufacturing procedures (Bennett-Woods, 2008; Virdi, 2009). In addition to nanotechnology, nanopharmacy incorporates medicine, pharmacology, biology, and Information and Communication Technology (ICT). As a result, nanopharmacy must be considered as an example of a techno-scientific complex known as "converging technologies" (Houdy *et al*., 2011). Converging Technologies is a term that is now used to describe synergies between originally separate fields that result in revolutionary innovations and, consequently, new impacts. Although some nanopharmaceuticals has been introduced to the market, these are still early and basic applications. More revolutionary applications are yet to come (Graur, 2011). The materials used in nanopharmacy share specific properties that distinguish them from other technologies (Houdy *et al*., 2011), the most common of which is their nanoscale size. Aside from size, nanopharmacy is commonly associated with chemical and physical properties, surface charge, and shape (Bawa *et al*., 2009). On a process level, nanopharmacy is attributed to certain functions that have enormous potential in addressing traditional drug failures (Bawa *et al*., 2008). Nanoparticles are commonly referred to as agents for (targeted) drug delivery, quantitative drug release, imaging, and diagnosis. Nanopharmacy contains all practical fields related to nanopharmaceuticals Research and Development (R&D), nanopharmaceuticals manufacturing, nanopharmaceuticals application, and nanopharmaceuticals management. Nanopharmacy is an example of converging technologies that connect disciplines such as nanotechnology, biotechnology, and informatics.

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Development of Nanomedicine

Pharmaceutical nanomedicine is expected to play a significant role in the global pharmaceutical business and healthcare system. Since 1995, the FDA and the European Medicines Agency (EMA) have approved around 70 nanomedicine products for marketing (Farjadian *et al.*, 2019, Choi *et al*., 2018, Ventola, 2017, Bulbake *et al*., 2017, Prasad *et al*., 2018, Anselmo *et al*., 2019, Klein *et al*., 2019) (Table 1), with an additional twice this number now in clinical trials. According to several reports, the number of nanotechnology-based drugs is expanding on a yearly basis. Every year, novel nanomedicines of already approved pharmaceuticals enter clinical trials to investigate effectiveness improvements over traditional formulations (Caster *et al*., 2017). This is because of significant expansion in research and development activities and considerable market demand, emphasizing the significance of nanotechnology in the field of drug delivery. Moreover, the majority of nanomedicines approved to date have demonstrated decreased toxicity rather than increased effectiveness (Caster *et al*., 2017). Many nanoparticle-based medications have hit the market and are used on a daily basis by many patients (Table 1). These products are manufactured by a variety of companies throughout the world and demonstrate the effectiveness of nanomedicines as therapeutic agents. 78 nanomedicines have been approved and delivered to the market since 1989. The FDA has approved 66 of these nanomedicines, while the European Medicines Agency has approved 31. The FDA and the EMA have approved 20 nanomedicines internationally, whereas some nanomedicines have got approval from only one side (FDA: 43 nanomedicines; EMA: 12 nanomedicines). Since 2010, there has been a considerable increase in the number of marketed nanomedicines as a result of the advantages to the healthcare system. Nanocrystals, lipid-based nanoparticles, polymer-based nanoparticles, dendrimer-based nanoparticles, protein-based nanoparticles, and inorganic nanoparticles are the several types of nanomedicines that are currently on the market globally (Table 1).

Table 1: List of worldwide marketed nanomedicines approved by the FDA and the EMA

Type	Trade Name	Company	Date of Approval	Active Ingredients	Indication
Nanocrystals	Emend®	Merk & Co. Inc.	FDA (2003)	aprepitant	antiemetic drug [Andrews et al., 2001; Müller et al., 2008]
	Ivemend®	Merk & Co. Inc.	FDA, EMA (2008)	fosaprepitant dimeglumine (prodrug of aprepitant)	antiemetic drug [Garnock-Jones et al., 2016]
	Ostim®	Osartis GmbH & Co.	FDA (2004)	calcium hydroxyapatite	bone-grafting material [Huber et al., 2006]
	Rapamune®	Wyeth Pharmaceuticals Inc. (a subsidiary of Pfizer Inc.)	EMA (2001), FDA (2010)	sirolimus (rapamycin)	prevents rejection of kidney transplants [Narayan et al., 2017] (immunosuppressant)
	Rapamune®	Wyeth Pharmaceuticals Inc. (a subsidiary of Pfizer Inc.)	FDA (2015)	sirolimus (rapamycin)	a rare progressive lung disease [Narayan et al., 2017] (lymphangioleiomyomatosis)
	Vitoss®	Orthovita Inc.	FDA (2003)	β-tricalcium phosphate	bone-grafting material [Marya et al., 2017]
	Ritalin LX®	Novartis	FDA (2002)	methylphenidate	attention deficit hyperactivity disorder (ADHD) [Diller, 1996] in children
	Avinza®	Pfizer Pharmaceuticals	FDA (2002)	morphine sulfate	psychostimulant [Caldwell et al., 2002]
	Focalin XR®	Novartis	FDA (2008)	dexamethylphenidate HCl	ADHD in children [Chavez et al., 2009]
	Invega®	Janssen Pharmaceuticals	FDA (2009)	paliperidone	schizophrenia [Janssen, 2012]
	Invega Sustenna®	Janssen Pharmaceuticals	FDA (2009)	paliperidone Palmitate	schizophrenia [Janssen et al., 2009]
	Megace ES®	Par Pharmaceuticals	FDA (2005)	megestrol acetate	antianorexic [Musaji, 2009]
	NanOss®	RTI Surgical	FDA (2005)	hydroxyapatite	bone substitute [Epstein, 2015]
	EquivaBone®	Zimmer Biomet	FDA (2009)	hydroxyapatite	bone substitute [Langston et al., 2016]
	OsSatura®	Isotis Othobiologics Inc.	FDA (2003)	hydroxyapatite	bone substitute
	Epaxal®	Crucell Berna Biotech	EMA (1993)	inactivated hepatitis A virus vaccine	prevents hepatitis A infection [Clarke et al., 2006]
	Zanaflex®	Acorda	FDA (2002)	tizanidine HCl	muscle relaxant [Kaddar et al., 2011]
	Ryanodex®	Eagle pharm	FDA (2014)	dantrolene sodium	malignant hyperthermia [Wappler, 2018]
	TriCor®	Abbott Laboratories	FDA (2004)	fenofibrate	antihyperlipidemia [Alagona, 2010]
Lipid-based Nanoparticles	Doxil®	Johnson & Johnson	FDA (1995), EMA (1996)	doxorubicin (adriamycin)	metastatic ovarian cancer, HIV-associated Kaposi's sarcoma (KS) [Barenholz, 2012]
	Lipodox®	Sun Pharma Global FZE	FDA (2013)	doxorubicin hydrochloride	metastatic ovarian cancer, HIV-associated KS [Smith et al., 2016]
	DaunoXome®	Galen Ltd.	FDA, EMA (1996)	daunorubicin	cancers and HIV-associated KS [Petre et al., 2007]
	Onivyde®	Merrimack Pharmaceuticals	FDA (2015)	irinotecan	metastatic pancreatic cancer [Drummond et al., 2006]
	DepoCyt®	Pacira Pharmaceuticals	EMA (2002), FDA (2007)	cytarabine	lymphomatous meningitis [Glantz et al., 1999]
	Myocet®	Teva Pharmaceutical Industries Ltd.	EMA (2000)	doxorubicin hydrochloride	breast cancer [Balazsovits et al., 1989; Batist et al., 2001]
	Caelyx®	Janssen Pharmaceuticals	EMA (1996)	doxorubicin	breast cancer, ovarian cancer, HIV-associated KS [Tejada-Berges et al., 2002; Franco et al., 2018]
	Mepact®	Takeda France SAS	EMA (2009)	mifamurtide	osteogenic sarcoma [Frampton et al., 2010]
	Marqibo®	Talon Therapeutics	FDA (2012)	vincristine	Philadelphia chromosome-negative chronic myelogenous leukemia in adult patients [Johnston et al., 2006; Krishna et al., 2001]
	Onpattro®	Alnylam	FDA & EMA (2018)	patisiran	hereditary transthyretin (TTR) mediated amyloidosis [Weng et al., 2019; Huang, 2019]
	Lipusu®		FDA (2016)	paclitaxel	breast cancer, non-small-cell lung cancer (NSCLC) [Zhou et al., 2021]
	AmBisome®	NeXstar Pharmaceuticals	EMA (1990), FDA (1997)	amphotericin B	antifungal drug [Lister, 1996]
	Vyxeos®	Jazz Pharmaceutics	FDA (2017), EMA (2018)	daunorubicin and cytarabine	acute myeloid leukemia [Krauss et al., 2019]
	Abelcet®	Defiante Farmaceutica	FDA (1995)	amphotericin B	antifungal drug [Lister, 1996]
	DepoDur®	SkyePharma	FDA (2004), EMA (2006)	liposomal morphine sulphate	postoperative analgesia [Hartrick et al., 2004]
	Curosurf®	Chiesi	FDA (1999)	poractant alfa	respiratory distress syndrome (RDS) [Van Helden et al., 1998; Gharehbaghi et al., 2014]
	Zevalin®	Bayer Pharma	FDA (2002) Disc. * EMA (2004)	90Y-ibritumomab tiuxetan	lymphoma [Rizzieri, 2016]
	Inflexal®	Crucell Berna Biotech	EMA (1997)	inactivated influenza virus vaccine	prevents influenza infection [Glück et al., 1994; Conne et al., 1997]
	Pfizer-BioNTech Vaccine	Pfizer Pharmaceuticals	FDA (2020)	mRNA vaccine	prevents COVID-19 infection [Oliver et al., 2020; Meo et al., 2021]
	Moderna COVID-19 Vaccine	ModernaTX Inc.	FDA (2020)	mRNA vaccine	prevents COVID-19 infection [Meo et al., 2021; Hinton, 2020]
	Visudyne®	QLT Phototherapeutics	FDA & EMA (2000)	photosensitizer (PS), benzoporphyrin	choroidal neovascularization caused by wet age-related macular degeneration [Lister, 1996]

Type	Trade Name	Company	Date of Approval	Active Ingredients	Indication
Polymer-based Nanoparticles	Cimzia®	UCB	FDA (2008), EMA (2009)	IgG Fab' fragment that specifically recognizes and binds to TNF-α	rheumatoid arthritis [Connock et al., 2010], Crohn's disease [Schreiber, 2011], psoriatic arthritis [Mease et al., 2014], and ankylosing spondylitis [Landewé et al., 2014]
	Apealea®	Oasmia Pharmaceutical AB	EMA (2018)	paclitaxel	ovarian cancer, peritoneal cancer, fallopian tube cancer [Borgå et al., 2019]
	Adagen®	Enzon Pharmaceuticals Inc.	FDA (1990)	adenosine deaminase (ADA)	adenosine deaminase (ADA)-severe combined immunodeficiency disorder [Stephan et al., 1993]
	Neulasta®	Amgen, Inc.	FDA (2002)	filgrastim	febrile neutropenia, consequent infections arising due to lack of neutrophils [Sheridan et al., 1992]
	Oncaspar®	Enzon Pharmaceuticals Inc.	FDA (1994), EMA (2016)	L-asparaginase	acute lymphoblastic leukemia, chronic myelogenous leukemia [Harris et al., 2003]
	Genexol-PM®	Lupin Ltd.	FDA (2007)	paclitaxel	breast cancer [Kim et al., 2010]
	Pegasys®	Genentech USA, Inc	FDA, EMA (2002)	recombinant human alfa-2a interferon	hepatitis C [Fried et al., 2002], hepatitis B [Lau et al., 2005]
	Diprivan®	Fresenius Kabi	FDA (1989), EMA (2001)	propofol	(sedative-hypnotic agent) used in surgeryto induce relaxation before and during general anesthesia
	Somavert®	Pfizer Pharmaceuticals	EMA (2002), FDA (2003)	analog of human growth hormone (acts as an antagonist of GH receptors)	acromegaly [Leonart et al., 2018]
	Macugen®	Pfizer Pharmaceuticals	FDA (2004)	pegatinib sodium	choroidal neovascularization caused by wet age-related macular degeneration [Penman et al., 2020]
	Mircera®	Vifor	EMA (2007), FDA (2018)	epoetin β (EPO) (EPO is a genetically recombinant form of erythropoietin)	anemia [McGahan, 2008]
	PegIntron®	Merk & Co. Inc.	EMA (2000), FDA (2001)	alpha interferon (INF) molecule	hepatitis C [Jacobson et al., 2007]
	Krystexxa®	Savient Pharmaceuticals	FDA (2010)	pegloticase is a recombinant porcinelike uricase	refractory chronic gout [Nyborg et al., 2016]
	Plegridy®	Biogene	FDA (2014)	recombinant IFN-β	relapsing remitting multiple sclerosis (RRMS) in adult patients [Chaplin et al., 2015]
	Adynovate®	Baxalta US Inc.	FDA (2015)	coagulation factor VIII	hemophilia A [Turecek et al., 2016]
	Copaxone®/FOGA	Teva Pharmaceutical Industries Ltd.	FDA (1996), EMA (2016)	glatiramer acetate	multiple sclerosis (MS) [Grewal, 2009]
	Eligard®	Tolmar Pharmaceuticals Inc.	FDA (2002)	leuprolide acetate	prostate cancer [Berges, 2005]
	Renagel®	Sanofi	FDA (2000)	sevelamer carbonate	hyperphosphatemia caused by chronic kidney disease (CKD) [Slatopolsky et al., 1999]
	Renagel®/Renvela®	Genzyme	EMA (2007)	sevelamer HCL	hyperphosphatemia caused by CKD [Swanson et al., 2013]
	Restasis®	Allergan	FDA (2003)	cyclosporine	chronic dry eye [Hwang et al., 2016]
	Rebinyn®	NovoNordisk	FDA (2017)	recombinant DNA-derived coagulation FIX	hemophilia B [Ezban et al., 2019; Nielsen et al., 2020]
	Estrasorb™	Novavax, Inc.	FDA (2003)	estradiol (17β-estradiol) hemihydrate	moderate vasomotor symptoms due to menopause [Buster, 2010]
	Zilretta®	Flexion Therapeutics	FDA (2017)	triamcinolone acetonide	knee osteoarthritis [Rai et al., 2018]
Dendrimer-based Nanoparticles	VivaGel® BV	Starpharma	FDA (2015)	astodrimer sodium	anti-infective for prevention of recurrent bacterial vaginosis (BV)[Madan et al., 2015]
Protein-based Nanoparticles	Abraxane®	Celgene Pharmaceutical Co. Ltd.	FDA (2005, 2012, 2013), EMA (2008)	paclitaxel	approved by the FDA for treatment of metastatic breast cancer [Tornao, 2009] (2005), lung cancer [Yuan et al., 2012] (2012), and metastatic pancreatic adenocarcinoma [Choi et al., 2014] (2013)
	Ontak®	Eisai	FDA (1999)	diphtheria toxin	leukemia, T-cell lymphoma [Mann et al., 2007; Duvic et al., 2000]
Inorganic Nanoparticles	Feraheme™	AMAG Pharmaceuticals	FDA (2009)	ferumoxytol	anemia [Coyne, 2009; Schwenk et al., 2010]
	Venofer®	Luitpold Pharm	FDA (2000)	iron sucrose	iron deficiency in CKD [MacDougall et al., 2020]
	Dexferrum®	American Regent	FDA (1996)	iron dextran	iron deficiency in CKD [Hood et al., 2000]
	Ferinject®	Vifor	FDA, EMA (2013)	iron carboxymaltose colloid	iron deficient anemia [Lim et al., 2014]
	Ferrlecit®	Sanofi-Aventis	FDA (1999), EMA (2013)	sodium ferric gluconate	iron deficiency in CKD [Futterer et al., 2013]
	Hensify®	Nanobiotix	EMA (2019)	hafnium oxide nanoparticles	locally advanced squamous cell carcinoma [Germain et al., 2020]
	Infed®	Actavis Pharma	FDA (1992)	iron dextran	iron deficiency in CKD [Auerbach et al., 2011]
	Feridex®/Endorem®	AMAG Pharma	FDA (1996) Disc. * 2008	SPION-dex	imaging agent [Anselmo et al., 2015]
	GastroMARK™/Umi	Mallinckrodt Inc.	FDA (2009)Disc. * 2012	SPION-silicone	imaging agent [Wang et al., 2001; Gil et al., 2010]

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Development of Nanopharmaceuticals

Currently, it can take up to two decades for a drug to reach the market after its initial discovery/development (Bawa *et al*., 2008). Among other considerations, there should be enough skilled scientific and medical personnel willing to dedicate a decade or two of their lives to a single project, the fundamental scientific premise should be novel with appropriate intellectual property protection, and the economic business plan should persuade investors about future profits. Market needs should always be properly assessed, and profit/risk ratios have to be highly appropriate. Additionally, the distribution and shelf-life of therapeutic agents need to be clarified (Eaton, 2012). The following sections discuss some key steps along the way, including intellectual property, technical issues, general costs, and the ethics and regulatory affairs of the matter. In order to reduce the risk of failure, it is important to exploit expert market evaluation to assess the market needs and opportunities (Von Windheim *et al*., 2014; Figure 4).

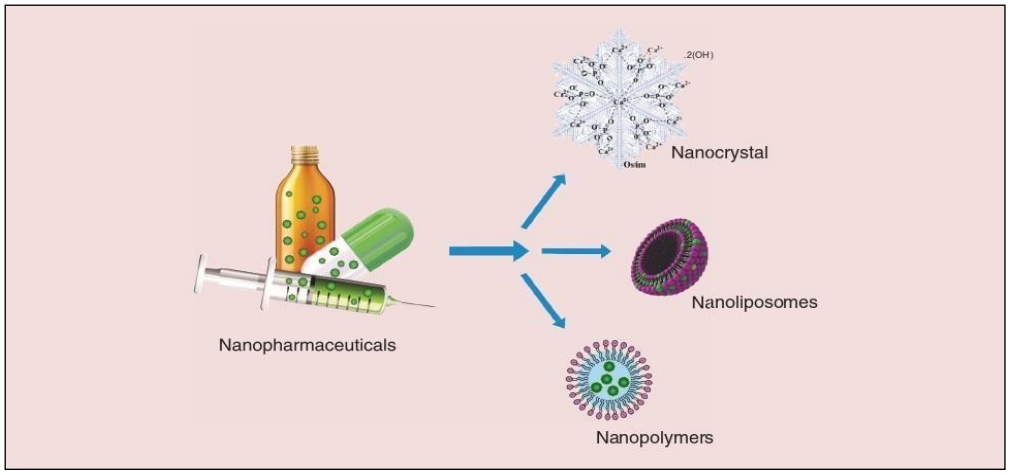

Figure 4. Three types of nanopharmaceuticals on the market are illustrated schematically

Advantages of Using Nanoparticles as Drug Delivery Systems

The advantages of using nanoparticles as drug carriers are due to two essential characteristics: their small size and, in most cases, the use of biodegradable materials (Amoabediny *et al*., 2018; Wilson *et al*., 2017). The effectiveness of most medication delivery strategies is found to be highly dependent on particle size. Due to their small particle size and large surface area, drug nanoparticles have improved solubility and bioavailability (Rizvi *et al*., 2018). Furthermore, their potential to cross the blood-brain barrier, enter the pulmonary system, and tumor endothelium, and absorb through tight junctions of skin endothelial cells add more value to them. In general, the nano-range size of these particles allows for efficient absorption by various cell types as well as selective drug accumulation in specific target locations (Kohane, 2007; Panyam *et al.*, 2003). Nanoparticles are also more suited for intravenous delivery than conventional microparticles. The smallest body capillaries are 5-6 m in diameter. To ensure that particles do not induce embolism, particles dispersed in the circulation should be considerably smaller than 5 m (Singh *et al*., 2009). Furthermore, typical oral or injectable

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medications that are presently available for usage are not always provided in the optimized formulations. As a result, products containing proteins or nucleic acids will necessitate more inventive carrier systems (nanoparticles) in order to improve efficacy and prevent instability (Vo *et al*., 2012).

Pharmaceutical Nanosystem Types

The types of pharmaceutical nanosystems are classified as, carbon nanotubes, quantum dots, nanoshells, nanobubbles, paramagnetic nanoparticles, liposomes, niosomes, dendrimers, polymeric micelles, polymeric nanoparticles, nanocapsules, solid lipid nanoparticles, nanoemulsions, fabrication of nanoparticles, dispersion of preformed polymers, coacervation or ionic gelation method, polymerization method, nano spray drying, and supercritical fluid technology.

Carbon Nanotubes

Carbon nanotubes were discovered for the first time in 1991 (Iijima, 1991). They are carbon-based tubular structures. These tubes are formed of graphite sheet cylinders that are sealed at one or both ends with buckyballs and range in length from 1 to 100 nm. Single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs) are two new popular designs (Reilly, 2007; Figure 5).

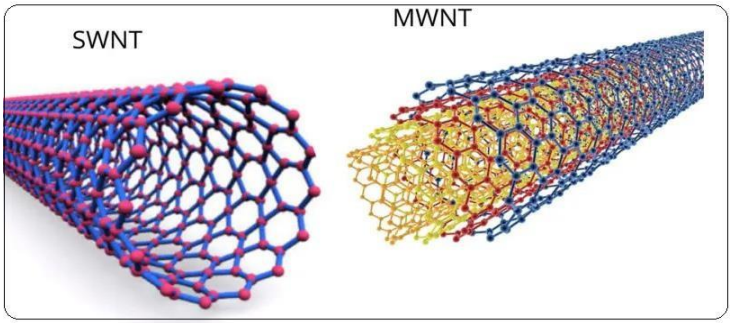

Figure 5. Carbon Nanotubes (Abazari *et al*., 2020)

Quantum Nanodots

Quantum dots (QDs) are semiconducting structures that range in size from 2 to 10 nm. They are nanocrystals with an inorganic semiconductor core CdSe and an organic shell covered with zinc sulfide to improve optical properties, and they are designed to glow when under the influence of light (Figure 6). The presence of a cap enhances QD solubility in aqueous buffers (Iga *et al*., 2008). Some of the diagnostic and therapeutic applications of QDs include cell labeling, biomolecule detection, and biological performance, DNA hybridization, immunoassays, and the advancement of non-viral vectors for gene therapy, carriers for cancer treatment, and transport vehicles for biological and non-biological agents (Bailey *et al.*, 2004).

Figure 6. Quantum Nanodots (Alexander *et al*., 2021)

Nanoshells

Nanoshells are modified drug-targeting models with a silica core and a metal outer layer (West *et al*., 2004). These nanoshells have recently received a lot of attention. The characteristics of these particles may be changed by changing the ratio between the core and shell. To achieve appropriate morphology, particles of specific shapes might be coated with a thin shell. Because precious materials may be added to low-cost cores, these shells offer the benefit of being affordable. As a result, precious materials are required in smaller quantities during synthesizing of nanoshells (Kalele *et al*., 2006). Immunological approaches may be used to produce nanoshell targeting; one example of this targeting strategy is gold nanoshells that were occupied with antibody moieties on their outer gold surface to improve targeting power toward cancer cells (Loo *et al*., 2005; Figure 7). Nanoshells provide a variety of functions, including chemically stabilizing colloids and improving luminescent characteristics and medicines (Kherlopian *et al*., 2008).

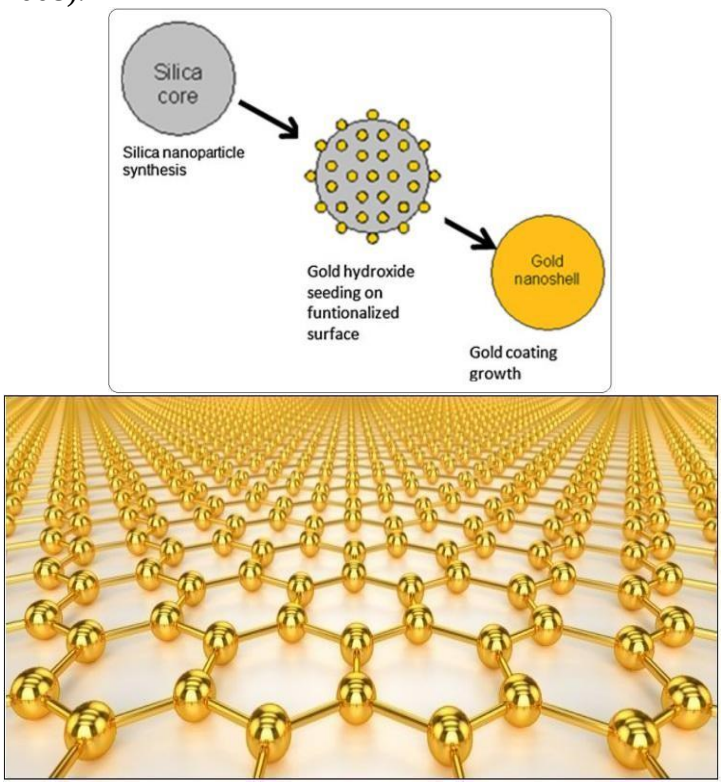

Figure 7. Nanoshells (Steen *et al*., 2012)

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Nanobubbles

Bubble-shaped particles are called nanobubbles which are formed in liquids at the nanoscale at the interface of lipophilic surfaces (Figure 8). They mix to form microbubbles, which are stable at room temperature when heated to body temperature. They arise in supersaturated solutions as a result of gas nucleation at the hydrophobic surface, resulting in air gas trapping. Plasmonic, bulk, oscillating, and interfacial nanobubbles are 4 types of these nanoparticles. Drugs for cancer treatment were successfully loaded into these particles, and they were able to target tumor tissues and boost tumor cell uptake with the addition of ultrasonic exposure (Gao *et al*., 2008; Klibanov, 2006).

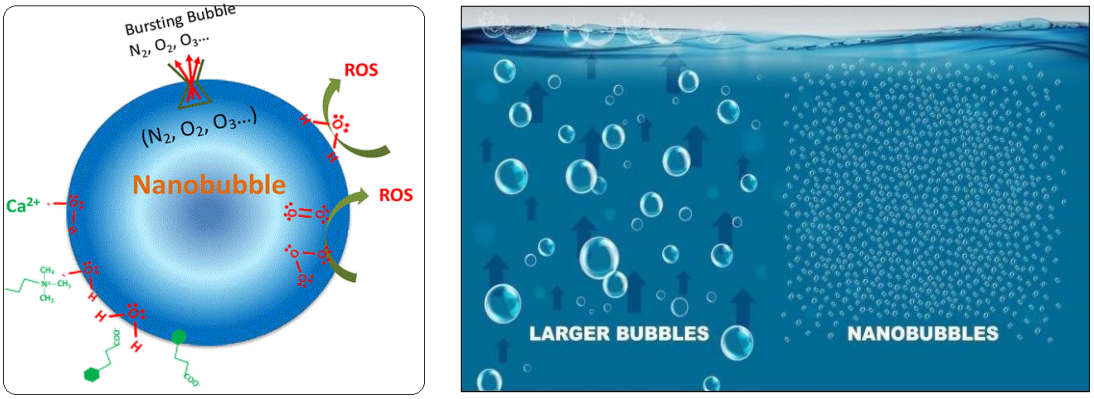

Figure 8. Nanobubbles (Atkinson *et al.*, 2019)

Paramagnetic nanoparticles

Magnetic nanoparticles are microscopic particles with a diameter of less than 100 nm that can be manipulated by a magnetic field (Figure 9). Magnetic elements are used to produce these particle materials. These nanoparticles are classified based on their magnetic sensitivity. Paramagnetic nanoparticles have a greater magnetic susceptibility than typical contrast forms. These nanoparticles are used in diagnostic and treatment strategies. The use of paramagnetic nanoparticle targeting is highly effective for the identification of specific organs (Cuenca *et al*., 2006).

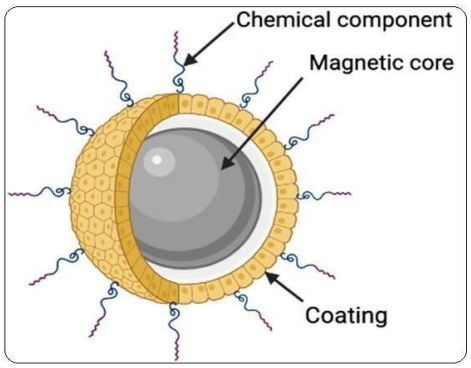

Figure 9. Paramagnetic nanoparticles (Dasari *et al*., 2022)

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The Direction of Cancer Nanomedicine

Cancer applications are the focus of 65% of currently ongoing clinical trials. Nanomedicine can make significant contributions to cancer treatment and early diagnosis. It is critical to emphasize that, while the primary goal remains to reduce or eradicate cancer, it is also essential to enhance patients' quality of life during treatment, thereby reducing the often-devastating side effects. This is another area where nanomedicine can make a significant contribution. The ability of nanomaterials to deliver drugs locally, ensuring therapeutic outcomes while reducing side effects, is thus important in cancer applications (The two directions of cancer nanomedicine, 2019). In this regard, nucleic acid-based technologies encapsulated in nanoparticle drug delivery systems can be used to develop anti-cancer vaccines and personalized immunotherapy (nucleic acid-based technologies). Several clinical trials on lipid-based nanoparticles and lipoplexes are currently ongoing. Radio-enhancers, such as NBTXR3, could be a revolutionary concept in the treatment of solid tumors by locally increasing the delivered dose of radiation. Another novel concept being investigated in clinical trials for the same purpose is stimuli-responsive nano-carriers with hyperthermia. In the OPTIMA Phase III study for primary liver cancer, for example, Thermodox, a doxorubicin-loaded heat-sensitive liposome (Swenson *et al*., 2015), is being examined in combination with hyperthermia. Nanomedicine can also improve the early diagnosis of cancer by providing ultrasensitive contrast agents. Several nano-sized diagnostic systems are currently being investigated in clinical trials, including iron oxide nanoparticles for Positron Emission Tomography–Magnetic Resonance Imaging (PET/MRI) and liposome/nanoparticle (Douek *et al*., 2014) mediated delivery of contrast agents (for example, 99Tc or 111In) for scintigraphy, SPECT, or PET analysis.

Nanomedicine is Not Only Focusing on Cancer

Among the trials discovered, 35% are investigating the use of nanomedicine for clinical applications other than cancer, indicating that nanomedicine has the potential to make a difference in other therapeutic areas for example the Central Nervous System (CNS). Nanomedicines can operate on / pass through the Blood-Brain Barrier (BBB) and administer therapy more efficiently within the CNS due to their unique physicochemical features (e.g., size, targeted agent coupling). Customized nanomedicines can cross the BBB via transcytosis or endocytosis. Relevant preclinical results were achieved in a variety of animal models of brain diseases, including gliomas (Jena *et al*., 2020), Huntington's disease (Valenza *et al*., 2015), Alzheimer's disease (Tiwari *et al*., 2019; Vilella *et al*., 2018; Metcalfe *et al*., 2017), and neurometabolic diseases (Salvalaio *et al*., 2016; Duskey *et al*., 2017; Rigon *et al*., 2019). Transcytosis-based strategies will typically allow for CNS delivery of small molecules, as well as nucleic acids or proteins, via systemic and non-invasive administration (Mizrahy *et al*., 2019). There is also ongoing research into employing gold nanoparticles in conjunction with laser activation to control nerve electrical activity or induce neural development (Paviolo *et al*., 2017). Such approaches pave the way for the treatment of neurodegenerative disorders including Parkinson's and Alzheimer's. Furthermore, nanomedicine has the potential to become a crucial player in cross-sectoral and cross-technological healthcare solutions. When integrated with other healthcare technologies, the unique features of nanoparticles (electrical, mechanical,

acoustic, and optical) bring up new possibilities. Furthermore, sensors should be included since nanomedicine has the potential to increase their sensitivity, speed, and miniaturization. Such nanosensors will be beneficial for detecting more sensitive biomarkers in a wide range of diseases (e. g. cancer, CNS, and infectious diseases). Research by Munawar and his colleagues (Munawar *et al*., 2019) provides an excellent summary of the possibilities of nanoparticles for nanosensors. Nanosensors are commonly used to monitor and control pandemics and plagues. There are currently diagnostic tools approved for diseases like Ebola and the Zika virus, which had the potential to become worldwide pandemics without nanotechnology-based products.

Routes of Nanomedicine Delivery

Nanomedicine is the use of nanoscale materials engineered at nanoscale dimensions (1-1000 nanometres) in the diagnosis and treatment of human diseases (Flühmann *et al*., 2019). Pharmaceutical nanoformulations, in the example, can be designed to improve drug solubility and the delivery of cytotoxic medicines to cancer cells while reducing side effects (Alshawwa *et al*., 2022; Ulldemolins *et al*., 2021). Nanomedicines have the capacity to enter target cells I by crossing across the molecules that comprise the outer membrane, ii) by interacting with oppositely charged molecules on the cell membrane, or iii) by utilizing selective uptake processes involving particular cell receptors (Wei *et al*., 2021; Kumar *et al*., 2021; Yang *et al*., 2021). Significantly, nanomedicines may be designed to cross biological barriers via non-invasive, needle-free routes such as oral, inhalation, nasal, and dermal delivery (Wei *et al*., 2021; Figure 10).

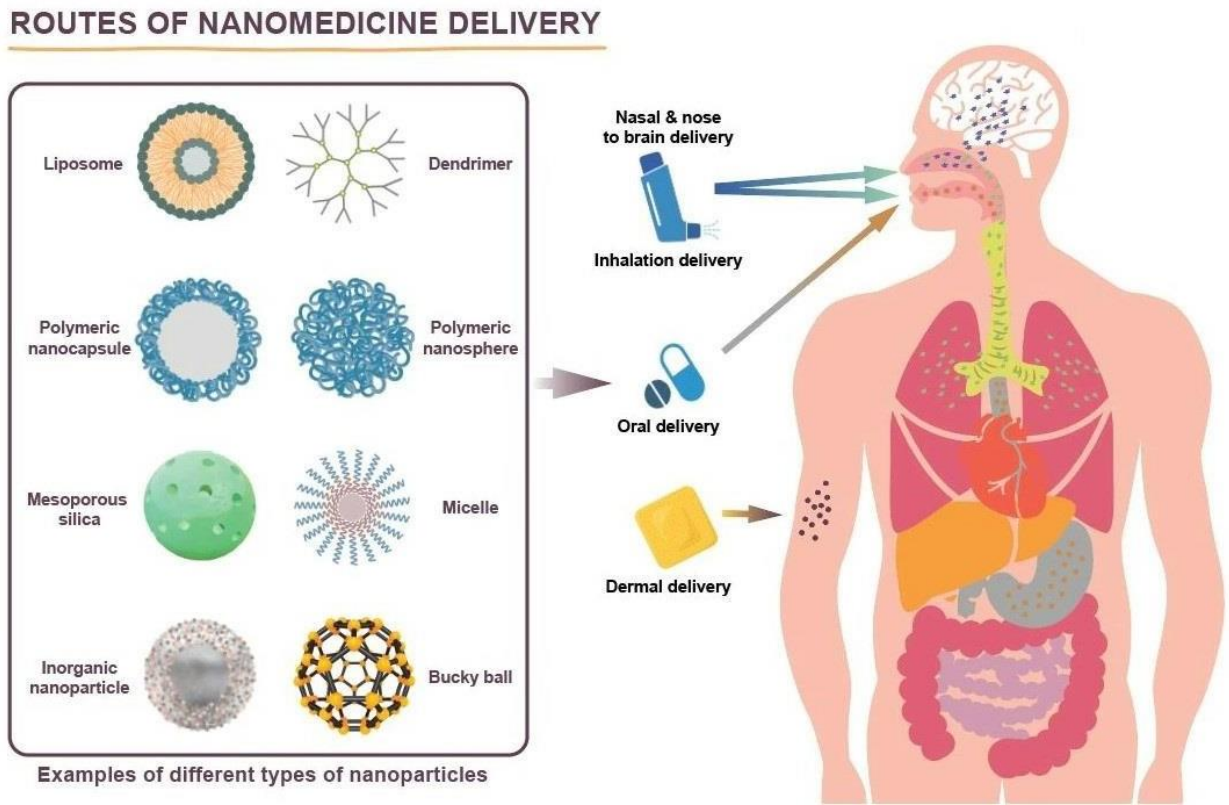

Figure 10. Routes of Nanomedicine Administration in the Human Body (Wei *et al*., 2021)

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Challenges in the Development of Pharmaceutical Nanomedicines

Over the last 20 years, the field of pharmaceutical nanotechnology has seen enormous expansion and progress. Particular attention has been paid to the field of nanomedicine because it promises to revolutionize medical care through more efficient, less toxic, and intelligent therapies that can be targeted at disease sites (Desai, 2012). Many nanomedicines have been successfully developed and authorized for clinical use, with considerable effort from both academia and the biopharmaceutical industry (Farjadian *et al*., 2019; Ventola, 2017). However, nanomedicine is still in its early stages with few success stories, since many kinds of challenges are experienced during the development of pharmaceutical nanomedicines. The challenges are categorized as challenges in drug delivery across different biological barriers, and challenges in the formulation, characterization, and manufacturing of nanomedicines.

Challenges in Nanomedicine Development Regulation

Most pharmaceutical nanoparticles are complex in nature, with multiple components and heterogeneous structures, where multiple components can affect the pharmacological behavior of the active ingredient, as compared to conventional pharmaceutical products, which typically use a single active ingredient. Because of this complexity, the regulation of nanomedicines may face several challenges (Desai, 2012; Mühlebach, 2018). Currently, newly developed medicines based on nanoparticles are evaluated by the FDA, EMA and other agencies on a case-by-case basis under the conventional framework of benefit/risk analysis (Desai, 2012; Paradise, 2019; Soares *et al*., 2018). Overall, there is a lack of standards for the evaluation of nanomedicine as they are a unique category of therapeutic agents (Desai, 2012). The FDA regulates pharmaceutical products in general under two main laws, the Federal Food, Drug, and Cosmetic Act (FDCA), which applies to all chemically synthesized medications and devices, and the Public Health Service Act (PHSA), which applies to biologically derived therapeutic products (Mühlebach, 2018; Paradise, 2019). These laws' definitions and policies differ depending on whether the product has a chemical action mode (drug), mechanical action mode (device), or biological source (Paradise, 2019). The FDA classifies nanomedicine as a combination product identified by the traditional regulatory pathway and supported by specific requirements to ensure safety and efficacy. For example, the FDA has approved paclitaxel and doxorubicin nanoformulations as new cancer drugs classified as combination products. Wider concerns have been raised about the inherent risks of nanotechnology and products containing nanoparticles as a result of the debate over the adequacy of current regulatory frameworks and procedures, including nanoparticle toxicity, the unintended consequences of nanoparticles' ability to cross the BBB, and the long-term effects of nanoparticles (Paradise, 2019; Resnik *et al*., 2007; Bawa *et al*., 2007). As we have recently entered the generic nanopharmaceuticals era, both generic manufacturers and drug regulators face significant challenges in defining a framework for evaluating generic nanopharmaceuticals to demonstrate that they are bioequivalent to branded ones, have the same physicochemical properties, and are safe and effective (Desai, 2012; Soares *et al*., 2018; Tinkle *et al*., 2014). The relationships between nanoparticle physicochemical characteristics and clinical Pharmacokinetics (PK) and safety are poorly known, and classic animal models may not be appropriate for effective extrapolation and prediction of nanoparticle biodistribution and toxicity in humans. This is especially

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significant when comparing a new drug based on nanoparticles to conventional formulations, as well as when comparing a generic approved nanomedicine to an innovative product. Similar results in conventional pharmacokinetics and toxicity studies, or a simple comparison of drug product composition, cannot be used to presume bioequivalence of generic and innovator nanomedicines.

The Future Perspectives of Nanomedicine

Nanotechnology is already having an impact on the healthcare system. As many nanotechnology ideas have been developed and several nanotechnology-based drugs are already on the market, the impact of nanotechnology on healthcare is already visible and further developing. The previous two decades have seen a significant increase in progress and interest in nanotechnology, which bodes well for future advances in nanomedicine. Thus, there are likely to be different paths that nanomedicines will go in the future. One path has already been established, in which nanomedicines are mostly and are still being developed for cancer treatments since the majority of nanomedicines now on the market are anticancer. Another path is to design and develop nanomedicines to treat and target diseases other than cancer, as demonstrated by the recent FDA approvals of Patisiran (ONPATTRO®) (the first FDA-approved RNAi therapeutic) and VYXEOS® (a nanoparticle capable of delivering synergistic ratios of two drugs). More advancement along the second path may be necessary to expand the applicability of nanomedicines to diseases that Conventional Drug Delivery Systems (CDDSs) cannot effectively treat. For example, utilizing specific devices, and nanomedicine in medical diagnostics would enable more detailed detection and inspection of tissues at the cellular, subcellular, and molecular levels (Kruit *et al*., 2013). This type of diagnosis, known as "Personalized Medicine", would lead to the appropriate treatment. Furthermore, to receive the greatest benefits from the nanoparticle-based drug delivery strategy, in vitro, and in vivo studies should be conducted to better understand the behaviors of nanoparticles in order to accelerate nanomedicines through clinical development and then subsequently supply them to the patients in need. Nanotechnology is attracting growing investment from both governmental and commercial sectors across the world (Thassu *et al*., 2007). The global market for nanomedicine reached 138.8 billion dollars in 2016, and it is expected to reach 350.8 billion dollars by 2025. This demonstrates the significance of nanotechnology in the science of drug delivery. The main advantages of using nanotechnology to deliver therapeutic medicines include reducing unwanted toxicity from nonspecific distribution and improving patient adherence, with an indirect decrease in the load on the healthcare system. In recent years, the growing expense of healthcare has been a source of concern for most industrialized, developed, and developing countries. To enhance cost efficiency, governments should first obtain a better understanding of the cost-effectiveness of nanopharmaceuticals (Weissig *et al*., 2014; Weissig *et al*., 2015). It should be emphasized that the first stage in expanding this market is a standardized cost-effectiveness assessment to determine whether the additional health advantages of nanopharmaceuticals above regular formulations could be worth the extra expense. Thereby, governments will be allowed to set detailed and clear guidelines and evaluate the financial advantages of developing this market (Liang, 2013). The researchers predict that the market for nanopharmaceuticals and nanomedicines will expand further over the next 5 to 10 years, owing primarily to advances in bionanotechnology and nanoengineering, the implementation of clear rules on new nanotechnology-based drugs, additional funding from

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government organizations (Borges *et al*., 2018), greater agreement on environmental issues, and the formation of partnerships between nanomedicine entrepreneurs or R&D departments and leading medical and pharmaceutical companies.

Conclusion

In conclusion, nanopharmaceuticals may open the way for novel medicines for unmet medical needs as well as optimization of existing medications due to their promising properties. However, their limitations should be considered in the meanwhile, since adverse effects may occur during their usage in populations with metabolic variations as well as health status. The nanomedicine-modified biokinetics demands a well-established toxicology profile through in vitro and especially in vivo tests since the lab tests mostly cover their toxicity in cell lines with different physiological properties rather than in healthy people and patients. Nanomedicines have enabled improved drug delivery via non-invasive or needle-free ways. Furthermore, nanomedicines are incredibly adaptable, allowing for combination therapy and being developed for multiple target tissues. The nanotechnological research fields include Scanning Electron Microscope (SEM), nanoparticle research, supramolecular chemistry, molecular modeling, quantum computation, Microelectronic Mechanical Systems (MEMS), light-emitted diodes, targeted drug delivery, molecular biotechnology, tissue engineering, and others. This technology has been used by many scientific disciplines because the human body operates on a molecular scale with complex physiochemical properties. Nanotechnology entered and made significant changes that skyrocketed the possibilities for wielding the power and control of diseases, extending our understanding of pathogenesis, and identifying the most microscopic and decisive step in the process and targeting it for the cure and drug delivery, all of which will be accomplished through the use of nanotechnology. Nanomedicine was invented through the application of nanotechnology in medicine. A field that manipulates nano-scale particles for medicinal applications. The medical field was able to bend this technology to its will and utilize it to investigate any prospective applications of this technology to overcome present diagnostic and treatment limitations. It has been used in the diagnosis and treatment of cancer, diabetes, cardiovascular disease, and pain management by employing nanoparticles that sense changes in cell DNA and blood biochemistry for screening as well as targeted drug delivery systems to the particular desired site with a decrease in induced tissue damage and adverse effects. Nanotechnology is an emerging field that opens doors for unprecedented new approaches and novel innovations for future breakthroughs and potential applications in various fields. Once again, nanomedicine allows us to prevent diseases, make early diagnoses, and treat pathologies at the molecular level. Therefore, nanomedicine has the potential to alter present methods of diagnosis and treatments and it also inspires innovative research techniques and solutions.

Discussion

Additional efforts are necessary to expand the number of FDA-approved nanomedicines, and more research is needed to understand the evolution of these miracle particles. Pharmaceutical nanotechnology is not limited to translational research, but after many years of trial and error, we have to acknowledge that reliable pharmacological and toxicological effects are key elements of industrial formulation development. Understanding the intertwined processes involved in the biodistribution of nanocarrier delivery aggregation will eventually lead to wider

acceptance. We believe that multifunctional nanomedicines in the near future will be able to enhance drug delivery systems. To improve the effectiveness characteristics of nanomedicines and accurately evaluate them in clinical trials, further challenges must be overcome.

Abbreviations

AD	Anno Domini
BBB	Blood-Brain Barrier
CDDS	Conventional Drug Delivery Systems
CdSe	Cadmium Selenide
CNS	Central Nervous System
CU	Copper
DDS	Drug Delivery System
DNA	Deoxyribonucleic Acid
EMA	European Medicines Agency
FDCA	Federal Food, Drug, and Cosmetic Act
ICT	Information and Communications Technology
MEMS	Microelectronic Mechanical System
MWNT	Multi-walled Nanotubes
PET	Positron Emission Tomography
PET-MRI	Positron Emission Tomography–Magnetic Resonance Imaging
PK	Pharmacokinetics
QD	Quantum Dots
R&D	Research and Development
SEM	Scanning Electron Microscope
SPECT	Single-Photon Emission Computed Tomography
SWNT	Single-walled Nanotubes
TEM	Transmission Electron Microscopy
US FDA	United States Food and Drug Administration

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