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REVIEW

Nanomedicine-based commercial formulations: current developments and future prospects

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Abstract

Background In recent decades, there has been a considerable increase in the number of nanomedicine-based formulations, and their advantages, including controlled/targeted drug delivery with increased efficacy and reduced toxicity, make them ideal candidates for therapeutic delivery in the treatment of complex and difficult-to-treat diseases, such as cancer.

Areas covered This review focuses on nanomedicine-based formulation development, approved and marketed nanomedicines, and the challenges faced in nanomedicine development as well as their future prospects.

Expert opinion To date, the Food and Drug Administration and the European Medicines Agency have approved several nanomedicines, which are now commercially available. However, several critical challenges, including reproducibility, proper characterization, and biological evaluation, e.g., via assays, are still associated with their use. Therefore, rigorous studies alongside stringent guidelines for effective and safe nanomedicine development and use are still warranted. In this study, we provide an overview of currently available nanomedicine-based formulations. Thus, the findings here reported may serve as a basis for further studies regarding the use of these formulations for therapeutic purposes in near future.

Keywords Commercial formulations · Clinical trials · Nanomedicines · Pharmacokinetics

Introduction

Nanotechnology, which is considered a "modern scientific breakthrough" and has been explored and heralded in several scientific studies over the past decades (Bayda et al. 2019), refers to the production and use of materials, systems, and equipment at the nanoscale (Jain 2008). It offers the possibility to provide solutions to persistent problems and unmet needs via the use of interconnected platforms in a plethora of areas, such as chemistry, physics, engineering, biotechnology, and medical sciences. Thus, it expands the possibilities of modern research, especially in the medical field (Mack 2005). Current nanotechnology-based developments in this area include enhanced and precise medicine, the minimization of adverse effects/toxicity, and meeting previously unmet medical needs of patients (Waheed et al. 2022). In recent decades, nanomedicines have been produced, engineered, and industrialized at the chemical, macromolecular, and cellular levels (Mitchell et al. 2021). For example, the use of nanopharmaceuticals, theranostics, and nanoimaging agents in nanomedicine has resulted in significant advancements in disease detection, tomography, prevention, and care (Farjadian et al. 2019).

Poor pharmacokinetic characteristics, such as poor solubility, permeability, and bioavailability limit the therapeutic utility of many potent drug. Thus, the development of formulations with improved pharmacokinetics profiles is necessary (Chenthamara et al. 2019). Nanomedicine-based formulations, either as therapeutic agents or as carriers, can thus be utilized to ensure that drugs target the desired sites and improve the pharmacokinetics and therapeutic profile of drugs (Yetisgin et al. 2020). Notably, the important characteristics of nanomedicines, including nanoscale size (1–100 nm) and large surface area, offer unique possibilities for precise interactions with cells and tissues based on the identification of the appropriate biological targets (Soares et al. 2018). Further, the advantages of nanomedicine-based

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formulations include decreased undesirable toxicity resulting from non-specific distribution, improved patient adherence, and favorable clinical outcomes (De Jong and Borm 2008).

The availability of funds and the utilization of multidisciplinary technologies in the industry and academia have resulted in the fabrication of some promising nanomedicine-based formulations, such as liposomes, polymer/lipid nanoparticles, and polymer-conjugates (Puri et al. 2009). Several strategies including: (a) the utilization of new materials, fabrication processes, and techniques for the enhancement of drug stability and targeting; (b) the development of nanosized formulation to provide access through some biological barriers resulting in potent drug targeting, and (c) the loading of desired amounts of drugs, their protection from hostile environments and delivery at a required concentration to the target site without affecting the co-existing healthy tissue, thereby reducing toxicity, have been developed (Zhang et al. 2013).

In this study, we reviewed nanomedicine-based formulations and their considerations as well as their commercialization. We also reviewed the challenges associated with their development, their limitations, and future prospects. Thus, we provide an overview of currently available nanomedicine-based formulations. This may serve as a basis for their use for therapeutic purposes in the near future.

Importance of nanomedicine-based formulations and their ideal properties

Conventional drug delivery systems (CDDSs) are characterized by immediate and burst drug release; thus, their use often requires an increased frequency of administration (Singh et al. 2019). It has also been reported that drug toxicity resulting from the misuse of drugs owing to increased administration frequency, is probable with CDDSs (Wen et al. 2015). Additionally, the low solubility of drugs in CDDSs is a major challenge for pharmaceutical companies as this affects the overall therapeutic efficacy of the drug. Low drug stability is also another common disadvantage of CDDSs as the drug is prone to degradation by the biological fluids/microenvironments in the body (Wen et al. 2015). These formulation-related issues associated with CDDSs can be tactfully overcome via the use of nanomedicine-based formulations (Patra et al. 2018), which have as major advantages: (1) specific delivery of active pharmaceutical agents to the target site. This results in a decreased dosage and the attenuation of associated adverse effects (Choi and Han 2018), (2) enhancement of drug stability. This improves the pharmacokinetic profile and bioavailability of the drug (Onoue et al. 2014), (3) better drug safety and efficacy profiles (Farjadian et al. 2019), (4) the attainment of sustained and controlled drug release profiles (Patra et al. 2018), (5) passive drug targeting via enhanced permeation and retention (EPR) effects and active targeting of tumors and other pathological sites of the body (Golombek et al. 2018), and (6) potentially cheaper formulation (when produced at large scale) as compared with conventional dosage forms (Farjadian et al. 2019). Such advantages are beneficial for improving the quality of life of patients, while reducing the overall quality and cost of healthcare.

Additionally, therapeutic agents can be entrapped, adsorbed, or covalently attached to nanosystems for administration to the body (Yetisgin et al. 2020). A single therapeutic agent or a combination of drugs that provide synergistic therapeutic effects can be delivered using nanomedicine-based formulations (Zhang et al. 2016), which also offer the possibility to realize controlled drug delivery characteristics, resulting in a decrease in dosing frequency and providing huge potential opportunities for designing nanomedicine-based formulations for drugs that go off-patent (Patra et al. 2018). However, different factors (e.g., stability: physical and biological, manufacturing method, scale-up possibility, freeze-drying conditions, and sterilization requirements), which can influence the effectiveness of nanomedicine in drug delivery should be appropriately addressed (Desai 2012). Importantly, the biocompatibility, biodegradability, and non-immunogenicity of nanomedicine-based formulations are characteristics that play important roles in efficient therapeutic delivery, bringing about enhanced bioavailability and reduced adverse/side effects (Chenthamara et al. 2019). Lipids and polymers are the most commonly used materials for preparing biocompatible and biodegradable nanoparticles with higher stabilities, enhanced drug loading capacities, easy surface functionalization for targeting and improving pharmacokinetics profile, and low intrinsic toxicity (Bochicchio et al. 2021).

Considerations in nanomedicine development

Nanomedicine development is a complex process that requires the careful consideration of different aspects, including chemistry, manufacturing, and control aspects as well as economic and regulatory aspects.

The chemistry, manufacturing, and control considerations are a great challenge in the product development and manufacturing scale-up of nanomedicine-based formulations (Desai 2012). Therefore, determining the practicability of developing nanomedicine based on an understanding the composition and structure of the early formulation is necessary. This ensures reproducibility during confirmatory studies as well as safety and efficacy during human clinical trials (Soares et al. 2018). Additionally, for further development as

commercial formulations, it is also necessary to determine the physical, chemical, and functional properties of nanomedicines (Mazayen et al. 2022). The appropriate characterization of the chemical properties of each component of nanomedicines using different techniques, such as high-performance liquid chromatography or other chromatography techniques, nuclear magnetic resonance, and mass spectrometry is also necessary (Lin et al. 2014). Furthermore, Lin et al. (2014) reported that nanomedicine characterization should involve the establishment and an understanding of the particle size, zeta potential, purity, viscosity, and pH of the different components. More importantly, for further development, it is necessary to establish acceptable levels of confidence in the biological functions of nanomedicines (Fatehi et al. 2012).

Ensuring the reproducibility of potential commercial-scale manufacturing of nanomedicines, at a reasonable cost, is vital. Therefore, it is crucial to understand the early stages of nanomedicine preparation and determine the feasibility of their industrial-scale chemical handling and processing (Hua et al. 2018). At the laboratory scale, it is possible to process cytotoxic compounds and achieve complex processing. However, realizing such at an industrial scale may be expensive and challenging (Jacquemart et al. 2016). Furthermore, the complex nature of nanomedicine formulation and manufacturing requires close scrutiny to minimize batch-to-batch variations (Sharifi et al. 2022). Therefore, for successful development and commercialization, it is necessary to ensure the purity, potency, safety, and efficacy of the nanomedicines (Desai 2012). Hence, successful industrial-scale manufacturing requires a thorough understanding of the quality of the starting materials as well as the processes involved (Desai 2012).

Furthermore, it is also necessary to consider the investments associated with the development and scaling-up of nanomedicine production (Paliwal et al. 2014). In this regard, it is important to critically analyze proposed nanomedicine development strategies in comparison with other developmental portfolios. The cost of manufacturing equipment, instrumentation, and other facilities also need to be considered when developing investment strategies for nanomedicine development and their subsequent clinical application (Patra et al. 2018).

Regulatory considerations for nanomedicine are also vital. Particularly, consultations with the Food and Drug Administration (FDA) at the early stages of nanomedicine development will aid in clarifying the associated scientific and regulatory issues and in addressing concerns regarding the safety, efficacy, and regulatory status of the formulations (Đorđević et al. 2022). Consequently, an appropriate evaluation framework needs to be used to evaluate the pathways and processes involved in nanomedicine development that are similar to those used in the conventional drug development process. The European Medicines Agency (EMA) has an Expert Working Group that has released some reflection papers for particular nanomedicines to guide marketing authorization applications (Hertig et al. 2021). However, it is still unclear whether the existing regulatory frameworks will pose challenges in future innovative nanomedicine development (Halamoda-Kenzaoui et al. 2022). The uncertainties related to the regulatory processes involving nanomedicines are presented in Fig. 1.

Clinical trials of nanomedicine-based formulations

By 2015, a total of 13 nanomedicines had been approved by the US FDA for the treatment of different diseases (Malviya et al. 2021). However, of recent, there has been a rocketing surge in the number of nanomedicine clinical trials. Based on 2021 data, a total of 100 nanomedicines are already being marketed, with another 563 new nanomedicines under clinical trial or other stages (Shan et al. 2022). Further, the majority of nanomedicines under clinical trial are in Phase I (33%) and Phase II (21%), and the prime focus of these nanomedicines is the treatment of cancer (53%) and infections (14%), as well as other diseases, such as blood disorders, endocrine and metabolic diseases, nervous system diseases, immunological diseases, cardiovascular diseases, ocular diseases, and skin diseases (Fig. 2). Additionally, nanomedicines are used in vaccine development and imaging diagnosis. The most prevalent categories of nanomedicines available in the market or in different phases of clinical trials include liposomes or lipid-based nanoparticles (33%), antibody–drug conjugates (15%), polymer-drug/protein conjugates (10%), and polymeric nanoparticles (10%) (Shan et al. 2022).

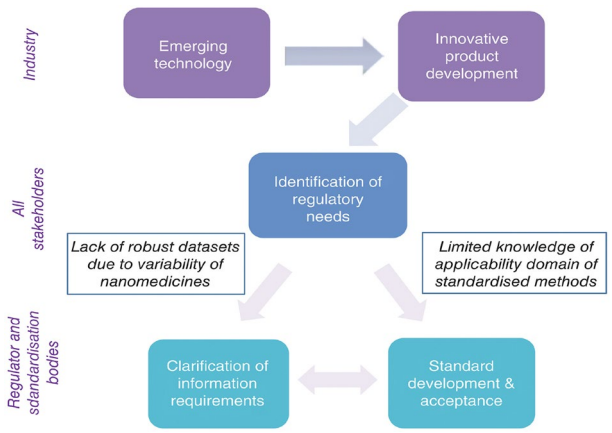

Fig. 1 Uncertainties related to the nanomedicine regulatory process [reprinted with permission from Blanka Halamoda-Kenzaoui et al. (2019)]

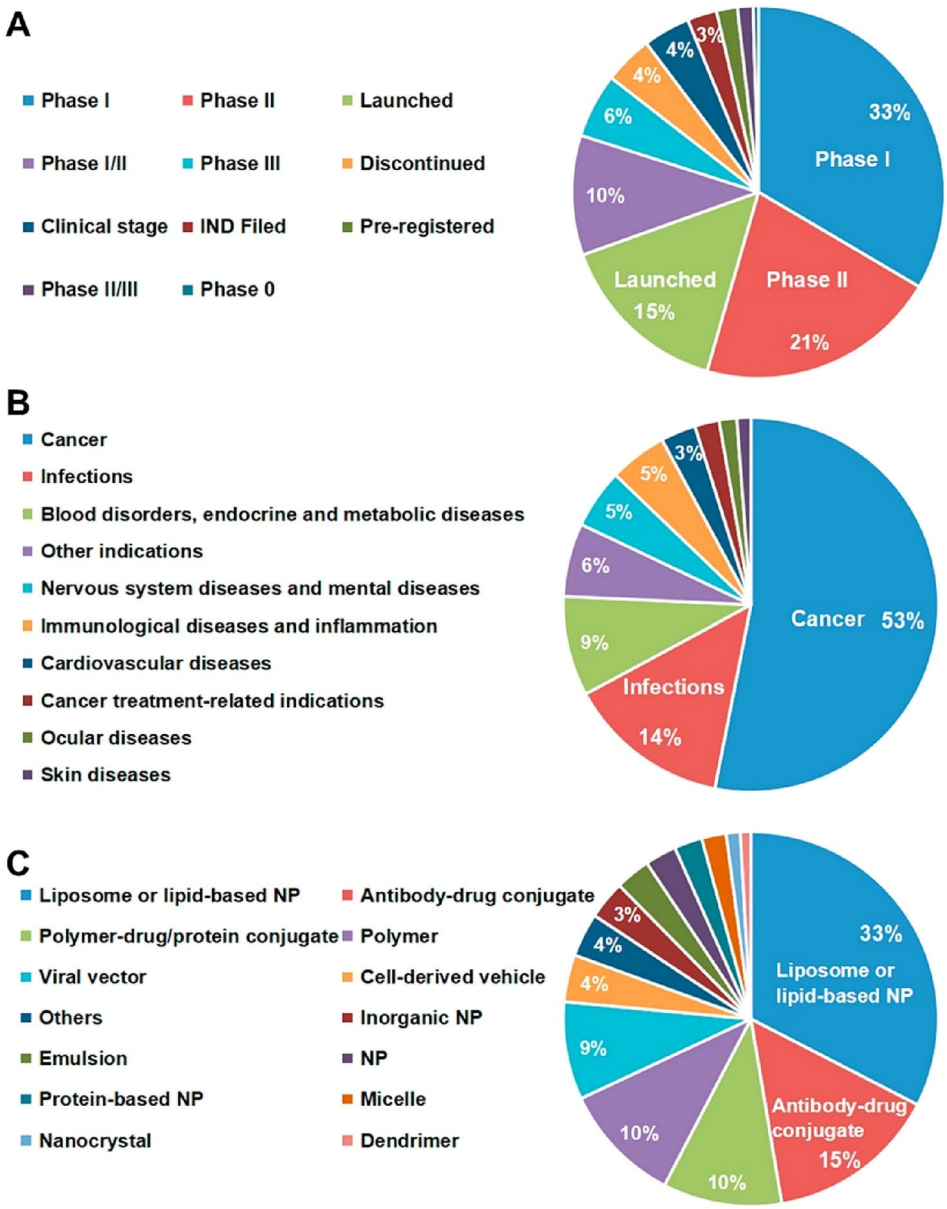

Fig. 2 Overview of nanomedicines that are available commercially or in clinical trial. **(A)** Development status, **(B)** Indications, and **(C)** Formulations. NP, nanoparticle [reprinted with permission from Shan et al. (2022)]

Commercial nanomedicine-based formulations

Presently, it has been suggested that nanomedicine-based formulations play a vital role in the global pharmaceutical market and healthcare system. To date, a total of approximately 100 nanomedicine-based formulations have been approved by the FDA and EMA (Shan et al. 2022). Further, several reports have suggested a significant annual increase in the number of nanomedicine-based formulations. Each year, several nanomedicine-based formulations of previously approved drugs enter clinical trial for the investigation of their efficacy relative to conventional dosage forms (Caster et al. 2017). Such nanomedicine-based advancements are attributed to the rapid growth in research and development (R&D) and high market demand. A representative list of FDA/EMA-approved and globally-marketed nanomedicine-based formulations is presented in Table 1.

Presently, approved and commercially available nanomedicine-based formulations include lipid-based nanomedicines, polymer-based nanomedicines, nanocrystals, inorganic nanoparticles, and protein-based nanoparticles. Among the lipid-based nanomedicines, liposomes are most commonly used for drug delivery. Specifically, liposomes are spherical vesicles (< 200 nm) composed of a lipid bilayer membrane surrounding a hydrophilic core. Hence, they are capable of delivering both hydrophilic and hydrophobic drugs, monoclonal antibodies, siRNA, and other biomolecules (Nakhaei et al. 2021). Further, they can circulate in the bloodstream for extended time periods, providing a

Table 1 Representative list of FDA/EMA-approved and globally-marketed nanomedicine-based formulations

Type of formulation	Nanosystem type	Product name	Active ingredient(s)	Company	Approving organization and approval date	Indication(s)	References
Lipid-based nanomedicine	Liposome	Doxil®	Doxorubicin hydrochloride	Johnson and Johnson	FDA (1995) EMA (1996)	Metastatic ovarian cancer, HIV-associated Kaposi's sarcoma, multiple myeloma	James (1995); Barenholz (2012)
	Lipid complex	Abelcet®	Amphotericin B	Liposome Co	FDA (1995)	Aspergillosis in patients refractory to or intolerant of conventional amphotericin B and for invasive fungal infections	Rust and Jameson (1998)
	Liposome	DaunoXome®	Daunorubicin citrate	Galen Ltd	FDA (1996) EMA (1996)	HIV-associated Kaposi's sarcoma	Kaposi's sarcoma: DaunoXome approved (1996)
	PEGylated liposome	Caelyx®	Doxorubicin hydrochloride	Janssen Pharmaceutica NV	EMA (1996)	Metastatic breast cancer, ovarian cancer, AIDS-related Kaposi's sarcoma	Ranson et al. (2001)
	Unilamellar liposome	AmBiosome®	Amphotericin B	NeXstar Pharmaceuticals	FDA (1997) EMA (2006)	Fungal infections in febrile neutropenic patients; Aspergillosis, candidiasis, and cryptococcosis infections refractory to amphotericin B	Boswell et al. (1998)
	Liposome	Inflexal® V	Inactivated influenza virus vaccine	Crucell (former Berna Biotech Ltd.)	EMA (1997)	Prevents influenza infection	Herzog et al. (2009)
	Lipid surfactant	Curosurf®	Pulmonary surfactant	Chiesi Farmaceutici	FDA (1999)	Respiratory Distress Syndrome (RDS)	Ramanathan et al. (2004)
	Liposome	Myocet®	Doxorubicin hydrochloride and an anthracycline cytotoxic agent	Teva Pharmaceutical Industries Ltd	EMA (2000)	Metastatic breast cancer	Brucker et al. (2016)
	Liposome	Visudyne®	Verteporfin	QLT PhotoTherapeutics	FDA and EMA (2000)	Severe eye conditions like macular degeneration, decreased vision, ocular histoplasmosis, pathologic myopia	Bressler and Bressler (2000)

Table 1 (continued)

Type of formulation	Nanosystem type	Product name	Active ingredient(s)	Company	Approving organization and approval date	Indication(s)	References
	Liposome	Depocyt®	Cytarabine	Pacira Pharmaceuticals	FDA (1999) EMA (2001	Intrathecal treatment of lymphomatous meningitis	Rizzieri (2016); Glantz et al. (1999)
	Liposome	DepoDur®	Morphine sulfate	Endo Pharmaceuticals	FDA (2004) Disc.* EMA (2006)	Postoperative analgesia	Pasero and McCaffery (2005)
	Liposome	Mepact®	Mifamurtide	Takeda France SAS	FDA (2001) EMA (2009)	High grade non-metastatic osteosarcoma and myosarcoma	Frampton (2010)
	Liposome	Marqibo®	Vincristine	Talon Therapeutics	FDA (2012) Disc.* EMA (2012)	Philadelphia chromosome-negative acute lymphoblastic leukemia in adult patients	Silverman and Deitcher (2013)
	Liposome	Lipodox®	Doxorubicin hydrochloride	Sun Pharmaceutical Industries Ltd. (SPIL)	FDA (2013)	Kaposi's sarcoma, ovarian cancer, multiple myeloma	Chou et al. (2015)
	Liposome	Onivyde®	Irinotecan	Merrimack Pharmaceuticals	FDA (2015)	Metastatic pancreatic cancer	Milano et al., (2022)
	Liposome	Lipusu®	Paclitaxel	Luye Pgarna	FDA (2016)	Lung squamous cell carcinoma	Zhang et al. (2022)
	Liposome	Onpattro®	Patisiran sodium	Alnylam Pharmaceuticals, Inc	FDA and EMA (2018)	Polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults	Akinc et al. (2019)
	Liposome	Pfizer-BioNTech vaccine	mRNA vaccine	Pfizer Pharmaceuticals	FDA (2020)	Prevention of COVID-19 infection	Attia et al. (2021)
	Liposome	Moderna Vaccine	mRNA vaccine	ModernaTx Inc	FDA (2020)	Prevention of COVID-19 infection	Attia et al. (2021)
Polymer-based nanomedicine	Nanoemulsion	Diprivan®	Propofol	AstraZeneca LP	FDA (1989) EMA (2001)	Anesthetic agent for induction and maintenance of anesthesia. For sedation of patient under critical care and those requiring mechanical ventilator	Terblanche and Coetzee (2008)

Table 1 (continued)

Type of formulation	Nanosystem type	Product name	Active ingredient(s)	Company	Approving organization and approval date	Indication(s)	References
	Polymer-protein conjugate	Adagen®	Adenosine deaminase	Enzon Pharmaceuticals Inc	FDA (1990)	Adenosine deaminase-severe combined immunodeficiency disorder	Booth and Gaspar (2009)
	Polymer-based	Oncaspar®	L-asparaginase	Enzon Pharmaceuticals Inc	FDA (1994) EMA (2016)	Acute lymphoblastic leukemia	Ettinger (1995)
	Micelle	PegIntron®	PEGylated interferon alpha-2B	Merck & Co. Inc	EMA (2000) FDA (2001) Disc.*	Hepatitis	Tseng et al. (2014)
	Polymer-protein conjugate	Neulasta®	Filgrastim	Amgen, Inc	FDA (2002)	Neutropenia	Duncan (2005)
	Polymer-protein conjugate	Pegasys®	PEGylated interferon alpha-2A	Genentech, Inc	FDA and EMA (2002)	Hepatitis B and Hepatitis C	Hui and Lau (2005)
	Polymer-protein conjugate	Somavert®	Recombinant human growth hormone receptor antagonist	Pfizer, Inc	EMA (2002) FDA (2003)	Acromegaly	Parkinson et al. (2003)
	Nanoemulsion	Restasis®	Cyclosporine	Allergan	FDA (2003)	Chronic dry eye	Lallemand et al. (2017)
	Nanoemulsion	Estrasorb®	Estradiol	Novavax, Inc	FDA (2003)	Treatment of moderate to severe vasomotor symptoms in postmenopausal women	Simon (2006)
	Polymer-protein conjugate	Macugen®	Pegaptanib sodium	Pfizer, Inc	FDA (2004)	Wet age-related macular degeneration	Tobin (2006)
	Micelle	Genexol-PM®	Paclitaxel	Lupin Ltd	FDA (2007)	Breast cancer	Oerlemans et al. (2010)
	Polymer-protein conjugate	Mircera®	Epoetin beta	Vifor pharma	EMA and FDA (2007)	Renal anemia	Bartnicki et al. (2013)
	Polymer-peptide conjugate	Cimzia®	Certolizumab pegol	UCB	FDA (2008) EMA (2009)	Rheumatoid arthritis, Crohn's disease, psoriatric arthirits, ankylosing spondylitis	Curtis et al. (2019)
	Polymer-protein conjugate	Krystexxa®	Pegloticase	Savient Pharmaceuticals	FDA (2010)	Severe and treatment-refractory chronic gout	Padda et al. (2022)
	Polymer-protein conjugate	Plegridy®	Peginterferon beta-1a	Biogene	FDA (2014)	Relapsing remitting multiple sclerosis in adults	Gohil (2014)
	Polymer-protein conjugate	Adynovate®	Recombinant antihemophilic factor	Baxalta US Inc	FDA (2015)	Hemophilia A	Dunn et al. (2018)

Table 1 (continued)

Type of formulation	Nanosystem type	Product name	Active ingredient(s)	Company	Approving organization and approval date	Indication(s)	References
	Polymer-protein conjugate	Rebinyn®	Recombinant coagulation factor IX	Novo Nordisk Inc	FDA (2017)	Hemophilia B	Ezban et al. (2019)
	Polymer steroid mixture	Zilretta®	Triamcinolone acetonide	Flexion Therapeutics	FDA (2017)	Knee osteoarthritis	Paik et al. (2019)
	Micelle	Apealea®	Paclitaxel	Oasmia Pharmaceutical AB	FDA (2018)	Ovarian cancer, peritoneal cancer, fallopian tube cancer	Borgå et al. (2019)
Nanocrystals	Nanocrystal	Avinza®	Morphine	King Pharma	FDA (2002)	Chronic pain	Semenchuk (2002)
	Nanocrystal	Ritalin LA®	Methylphenidate hydrochloride	Novartis	FDA (2002)	Attention deficit hyperactivity disorder in children	Driessche et al. (2017)
	Nanocrystal	Zanaflex®	Tizanidine hydrochloride	Acorda	FDA (2002)	Muscle relaxant	Kaddar et al. (2012)
	Nanocrystal	Emend®	Aprepitant	Merck & Co. Inc	FDA (2003)	Antiemetic	Prommer (2005)
	Nanocrystal	Tricor®	Fenofibric aid	Abott Laboratories	FDA (2004)	Antihyperlipidemia	Saurav et al. (2012)
	Nanocrystal	NanOss®	Hydroxyapatite	RTI Surgical	FDA (2005)	Bone substitute	Epstein (2015)
	Nanocrystal	Megace® ES	Megestrol acetate	Par Pharmaceuticals	FDA (2005)	Anorexia, cachexia and AIDS-related weight loss	Tuca et al. (2013)
	Nanocrystal	IVEmend®	Fosaprepitant dimeglumine	Merck & Co. Inc	FDA and EMA (2008)	Antiemetic	Garnock-Jones (2016)
	Nanocrystal	Focalin® XR	Dexmethylphenidate hydrochloride	Novartis	FDA (2008)	Attention deficit hyperactivity disorder in children	Moen and Keam (2009)
	Nanocrystal	Invega®	Paliperidone palmitate	Janssen Pharmaceuticals	FDA (2009)	Schizophrenia	Nagino et al. (2011)
Inorganic nanoparticles	Iron nanoparticles	Dexferrum®	Iron dextran	American Regent	FDA (1996)	Iron deficiency in chronic kidney disease	Hood et al. (2000)
	Iron nanoparticles	Venofer®	Iron sucrose	Lutipold Pharmaceuticals, Inc	FDA (2000)	Iron deficiency in chronic kidney disease	Bhandari et al. (2015)
	Hafnium oxide nanoparticles	Hensify®	Hafnium oxide	Nanobiotix	EMA (2019)	Locally advanced squamous cell carcinoma	Bonvalot et al. (2019)

Table 1 (continued)

Type of formulation	Nanosystem type	Product name	Active ingredient(s)	Company	Approving organization and approval date	Indication(s)	References
Protein based nanoparticles	Engineered fusion protein nanoparticle	Ontak®	Denileukin diftitox	Eisai Co., Ltd	FDA (1999)	Leukemia, T cell lymphoma	Duvic and Talpur (2008)
	Albumin nanoparticle	Abraxane®	Paclitaxel	Eli Lilly	FDA (2005) EMA (2008)	Metastatic breast cancer	Yuan et al. (2020)

*Disc.** Discontinued

longer treatment effect (Sercombe et al. 2015). More importantly, they can accumulate at tumor or infection sites; thus, they naturally locate and deliver drugs to their target sites (Allahou et al. 2021). Additionally, stimuli responsive (temperature- and pH-sensitive) liposomes can be prepared to allow for controlled drug release (Lee and Thompson 2017). Further, polymer-based nanomedicines include polymer-protein conjugates and micelles. The conjugates provide protein drugs with targeting ability and enhanced circulation times (Kiran et al. 2021). It has also been observed that such polymeric nanoparticles facilitate drug release for an extended time period (Kamaly et al. 2016). Moreover, nanocrystals are versatile nanoparticles that can be used for improving the pharmacokinetic-pharmacodynamic properties of poorly soluble drugs (Gigliobianco et al. 2018). Specifically, they enhance the bioavailability and solubility of drugs by increasing surface area at the nanoscale to enhance dissolution (Joshi et al. 2019). Alternatively, inorganic nanoparticles can be used for drug delivery and can also be useful in imaging applications (Luther et al. 2020). In particular, metal oxides, metals, or silica are used as inorganic nanoparticles. In this regard, one of the most widely used inorganic nanomedicines are iron oxide nanodrugs, which have been approved for use in iron replacement therapies (Yadavalli and Shukla 2017; Dadfar et al. 2019). Protein-based nanoparticles include drug-conjugated protein carriers, with the protein itself functioning as the active therapeutic agent, or as a part of a combined complex for targeted delivery (Hong et al. 2020). Albumin protein nanoparticles have gained wider interest in the research community owing to their longer circulation times, ability to accumulate at tumors site via enhanced permeation and retention effects, and their ability to undergo cellular uptake via albumin-receptors (Hassanin and Elzoghby 2020).

Challenges in the development of nanomedicine-based formulations

Based on recent advances in nanomedicine-based formulations, several challenges that need to be considered for nanomedicine development have been identified. For example, the lack of proper methods for the characterization of the safety and efficacy of nanomedicines, is one of the major challenges in nanomedicine development (Desai 2012). In general, a large amount of data has been gathered for nanomedicines like liposomes, polymeric nanomedicines, and micelles. However, varied possibilities for formulation and application require toxicity data for each modification (Patra et al. 2018). Furthermore, to avoid the development of unpredictable side effects, there is a glaring need for an enhanced understanding of nanomedicines prior to them becoming commercially available. However, rigorous research is yet to be conducted to clarify and predict the effect of nanomedicines on biological systems, including the development of new assays that are not affected by nanomedicines (Đorđević et al. 2022).

Another challenge in the development of nanomedicine-based formulations is the lack of specific regulatory guidelines (Desai 2012). The FDA approval process for nanomedicines (including preclinical and human clinical studies) are same as those for any other drug or biologic agent (Đorđević et al. 2022). FDA has issued some guidelines for industries regarding the use of nanotechnology. These guidelines encourage manufacturers to consult with the FDA regarding the specific regulatory and scientific issues of relevance for nanomedicines early enough (Mühlebach 2018). Such consultation is also encouraged as it can help in addressing concerns regarding the safety, efficacy, public impact, and regulatory status of the product (Havel et al. 2016). However, separate regulatory guidelines are yet to be established for the development of effective and safe nanomedicine-based formulations. The different challenges associated with the development and commercialization of nanomedicines are presented in Fig. 3.

Failure of some nanomedicine-based formulations

Pharmaceutical companies developing nanomedicines acquire funding from capital markets, venture capital, and partnerships with other companies; however, the clinical failure of the product often results in the termination of their development and business liquidation (He et al. 2019). One of the most common reasons for the clinical failure of nanomedicines is the nanomedicine showing toxicity in Phase I clinical trials (Fogel 2018). Furthermore, the choice of the drug carrier of the nanomedicine affects its physicochemical properties and the resulting payload, leading to failure (Patra et al. 2018). Moreover, the right selection of patients is a critical factor for ensuring successful clinical trials (Sacristán et al. 2016). High-quality production processes and reproducibility are also critical factors that could bring about the failure of nanomedicines (Soares et al. 2018). Therefore, all the factors that could be responsible for the failure of nanomedicines should be critically considered and addressed to ensure their successful development and subsequent approval for clinical use.

Future prospects of nanomedicine-based formulations

Significant progress has been made in the field of nanomedicine-based formulations in the past decades, with several FDA and EMA approvals. Notably, nanomedicines provide a wide range of avenues for the treatment

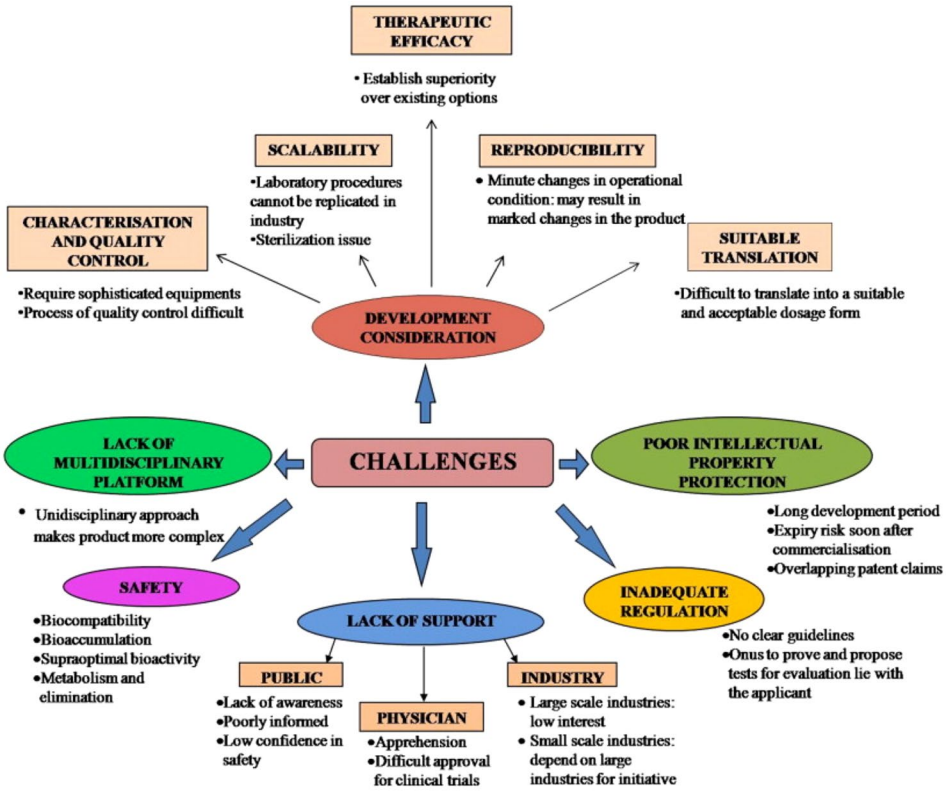

Fig. 3 Challenges in the development and commercialization of nanomedicines [reprinted with permission from Kaur et al. (2014)]

of complex and difficult-to-treat diseases, such as cancer, lung diseases, and ophthalmic diseases. The most common types of commercially available nanomedicine-based formulations include lipid-based nanomedicines, polymer-based nanomedicines, nanocrystals, inorganic nanoparticles, and protein-based nanomedicines. Such formulations are revolutionizing the treatment of different diseases and have significant impact on the healthcare system. However, the incorporation of a broad range of nanomedicine types is making the formulations more complex. Therefore, it is necessary to adequately address concerns regarding safety and efficacy, while following the guidelines established by agencies such as the FDA and EMA. Further, rigorous studies related to the detailed characterization of nanomedicines, their preclinical and clinical testing, and cost–benefit analyses are urgently needed. Hence, based on the findings reported in previous studies, future rigorous studies, and stringent guidelines to promote safe and effective treatment will make nanomedicines a unique solution for unmet clinical needs.

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Data availability Not applicable.

Declarations

Conflict of interest All authors (R.K. Thapa and J.O. Kim) declare that they have no conflict of interest.

Research involving human and animal rights This article does not contain any studies with human and animal subjects performed by the author.

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