Biomedicine & Pharmacotherapy 97 (2018) 1521–1537

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Review

Nanotherapeutics: An insight into healthcare and multi-dimensional applications in medical sector of the modern world

Minakshi Prasad[a,*], Upendra P. Lambe[a], Basanti Brar[a], Ikbal Shah[a], Manimegalai J[a], Koushlesh Ranjan[b], Rekha Rao[c], Sunil Kumar[c], Sheefali Mahant[d], Sandip Kumar Khurana[e], Hafiz M.N. Iqbal[f], Kuldeep Dhama[g], Jyoti Misri[h], Gaya Prasad[i]

[a] Department of Animal Biotechnology, LLR University of Veterinary and Animal Sciences, Hisar, Haryana, 125004, India
[b] Department of Veterinary Physiology and Biochemistry, Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut, Uttar Pradesh, 250110, India
[c] Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, Haryana, 125001, India
[d] Department of Pharmaceutical Sciences, Maharishi Dayanand University, Rohtak, Haryana, 124001, India
[e] Central Institute for Research on Buffaloes, Sirsa Road, Hisar, Haryana, 125001, India
[f] Tecnologico de Monterrey, School of Engineering and Sciences, Campus Monterrey, Ave. Eugenio Garza Sada 2501, Monterrey, N. L., CP 64849, Mexico
[g] Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, 243 122, India
[h] Division of Animal Health, Indian Council of Agriculture Research, New Delhi, India
[i] Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut, Uttar Pradesh, 250110, India,

ARTICLE INFO

Keywords:
Nanoparticles
Nanotherapeutics
Nanomedicines
Nanocarriers
Drug delivery
Cancer
Tissue engineering
Safety concerns
Regulatory issues
Health
Biomedical Applications

ABSTRACT

In recent years nanotechnology has revolutionized the healthcare strategies and envisioned to have a tremendous impact to offer better health facilities. In this context, medical nanotechnology involves design, fabrication, regulation, and application of therapeutic drugs and devices having a size in nano-range (1–100 nm). Owing to the revolutionary implications in drug delivery and gene therapy, nanotherapeutics has gained increasing research interest in the current medical sector of the modern world. The areas which anticipate benefits from nano-based drug delivery systems are cancer, diabetes, infectious diseases, neurodegenerative diseases, blood disorders and orthopedic problems. The development of nanotherapeutics with multi-functionalities has considerable potential to fill the lacunae existing in the present therapeutic domain. Nanomedicines in the field of cancer management have enhanced permeability and retention of drugs thereby effectively targeting the affected tissues. Polymeric conjugates of asparaginase, polymeric micelles of paclitaxel have been recmended for various types of cancer treatment .The advancement of nano therapeutics and diagnostics can provide the improved effectiveness of the drug with less or no toxicity concerns. Similarly, diagnostic imaging is having potential future applications with newer imaging elements at nano level. The newly emerging field of nanorobotics can provide new directions in the field of healthcare. In this article, an attempt has been made to highlight the novel nanotherapeutic potentialities of polymeric nanoparticles, nanoemulsion, solid lipid nanoparticle, nanostructured lipid carriers, dendrimers, nanocapsules and nanosponges based approaches. The useful applications of these nano-medicines in the field of cancer, nutrition, and health have been discussed in details. Regulatory and safety concerns along with the commercial status of nanosystems have also been presented. In summary, a successful translation of emerging nanotherapeutics into commercial products may lead to an expansion of biomedical science. Towards the end of the review, future perspectives of this important field have been introduced briefly.

1. Introduction

Nanotherapeutics is a recent application of nanotechnolgy that have wide ranging impact on medical field [1]. Nanomedicine has emerged from nanotechnology, is rather a nascent field of science, whose history dates back to 1959, as predicted by Richard P. Feynman [2]. A nanometer is one millionth part of a millimeter where the word nano means 'dwarf' [3]. Nanotechnology, deals with the investigation, modification, and control of atomic/molecular structures of object ranging, between 1–100 nm in size [4].

The branch of nanomedicine is exploiting a wide range of nanotechnological approaches, including numerous biological devices and

* Corresponding author.
E-mail address: minakshi.abt@gmail.com (M. Prasad).

https://doi.org/10.1016/j.biopha.2017.11.026
Received 26 August 2017; Received in revised form 28 October 2017; Accepted 3 November 2017

nano-biosensors. Quantum effects taking place at nano-level have an impact on biological, chemical, physical, optical and mechanical properties which permits scientists to exploit the benefits of such phenomena [5]. Nano medicine also includes newly emerging concepts and applications of molecular nanotechnology for designing of nano-machines called nano-robots. Biological macromolecules and structures or xenobiotic chemical drugs provide basic working power to nanostructures. The most revealing fact about nanomaterials is that their size is similar to many of the biological macromolecules which facilitate the use of nano-materials in *in-vivo* as well as *in-vitro*. Thus, by the unification of nanotechnology with biological material, several diagnostic kits, analytical tools, physiotherapy applications and drug delivery vehicles have been developed till date. Therefore, the nano-therapeutics as a branch of medicine has a vast scope of research and development. Unlike the conventional methods of medication, in this technique the drug attach on nanoparticles which enables it to act more efficiently, and accurately with few side effects. Nanotherapeutics provides new opportunities to improve the safety and efficacy of conventional therapeutics [6,7]. Due to this, different national and international agencies and pharmaceutical companies are investing to generate new drug delivery methods, gene therapies, and *in-vivo* imaging techniques. Nanomedicine sales reached up to $16 in, only in nanotechnology. According to a new report by Grand View Research, Inc. the nanomedicine market is anticipated to reach $ 350.8 billion by 2025 showing significant impact on global economy [8].

Nowadays, the healthcare industry is striving to achieve increased productivity, improved access and higher quality of treatment at lower costs. Chronic, serious neurological disorders such as cancer, diabetes, HIV/AIDS and heart disease have been a challenge for health care professionals. Another challenge includes infectious diseases, where conventional antimicrobial agents used for their treatment develop adverse side effects and multiple drug resistance. Target specificity is one of the major hurdles to get the therapeutic efficiency. Nanoparticles have proved as one of the logical and encouraging tools for delivery of medicine in controlled and targeted manner. Nanomedicine plays a significant role in overcoming these challenge because nanotechnology based formulations enhance pharmacokinetic properties, bioavailability and drug targeting in various disorders. Besides prevention and treatment of diseases, nano medicine possesses potential applications in diagnosis, monitoring therapy, drug discovery, surgery, and gene delivery using molecular knowledge of human system [9–11].

In the light of facts mentioned above, nanotechnology has profound applications in healthcare management (Fig. 1). In past two decades, several nano-therapeutics have been approved by FDA for the treatment of hepatitis, cancer, cardiovascular diseases, neurological diseases, autoimmune diseases, diabetes, high cholesterol, Parkinson's disease, and certain infectious diseases (Table 6) [12]. Moreover, hundreds of nanocarrier based products are currently available at various stages of the preclinical and clinical development [13].

This review highlights the contribution of nanotechnology with intent to aid the researchers in exploring nanocarriers such as polymeric nanoparticles, nanoemulsions, nanogels, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, nanocapsules, nanosponges in the field of drug delivery. An overview of applications of nanotechnology from different perspectives such as nutrition, diagnosis, biosensor systems, blood purification, tissue engineering and nanotechnology based medical devices including nanorobots are also included. A brief discussion on the significance influence of nanoparticles on the health consequences, regulatory status, safety concerns, and commercial potential has also been given. It is an attempt to provide a bird's eye view to the healthcare professionals about developments in this field.

2. Nanoparticles in drug delivery

Application of nanotechnology in drug delivery has the potential to revolutionize the treatment of various diseases like cancer, diabetes, infection, neurodegenerative diseases, blood disorders and orthopedic problems [14]. Ideally, these strategies are meant to improve the drug absorption, therapeutic concentration, and stability, resulting in effective drug targeting. Reproducibility and long-term release of the drug within the target tissue are other features of nano-based drug delivery systems [15]. Rational design of nanotherapeutics leads to the formulation of nano-platforms of a particular shape, size and surface properties that are indispensable for biological interactions and resultant therapeutic effects [16]. Nanotechnology based formulations possess unique physical and chemical characteristics responsible for a wide range of applications in various disorders [12] (Fig. 2). The nanoformulations reported recently play an important role in the healthcare sector (Table 1). Majority of nano-therapeutic products in the market are available for parenteral administration, while several being meant for oral administration [17]. A significant number of preclinical and clinical trials can be expected to result in the development of new nanotherapeutics intended for non-parenteral routes of delivery such as pulmonary, ocular, nasal, vaginal and dermal. The choice of the route of delivery and associated barriers to be crossed is of particular interest for drug delivery systems (European Commission/ETP) [18]. Over the time, several nanoparticles based formulations were developed to improve the drug delivery system.

2.1. Polymeric nanoparticles

The most commonly used polymeric nanoparticles are fabricated from synthetic polymers. Due to variation in purity and batch-to-batch consistency, natural polymers, resulting in poor reproducibility and controlled release behaviour for the entrapped drug (s). On the other hand, synthetic polymers are available with good to batch reproducibility and purity which facilitates the modification of drug release pattern from polymeric nanoparticles [39]. Nanoparticles prepared using synthetic polymers have been explored extensively for drug delivery (Table 2). Hydrophilic moieties can be encapsulated into synthetic polymer-based nanoparticles by double emulsion technique because it is difficult to maintain the activity of biological molecules in the presence of volatile organic solvents. Widely used synthetic polymers reported for drug delivery include biodegradable aliphatic polymers such as polylactide (PLA), poly lactide-co-glycolide, copolymers (PLGA) and poly (ε- carpolactone), as well as non-biodegradable polymers like polyacrylates and poly (methyl methacrylate) [40].

Polymeric nanoparticles can effectively protect unstable drug moieties from degradation, thereby preventing the side effects of toxic drugs. Natural polymeric nanoparticles are comprised of polymers such as alginate, chitosan, albumin and gelatin [40]. The application of polymeric nanoparticles with dexamethasone or α-tocopheryl succinate palliates cisplatin ototoxicity which resulted from chemotherapy treatment. The nanoparticles that entrap, transport and finally deliver dexamethasone or α-tocopheryl succinate are capable of partially preventing ototoxicity produced from high doses of CDDP [41]. Otherwise, these poorly soluble drugs show severe side effects when systemically administered for longer periods of time. The incorporation of these medicinal products in hydrophobic cavity of nanoparticles provides the desired *in vitro* and *in vivo* effects. Some of the popularly marketed formulations of the polymeric nanoparticles are Decapeptyl®, Gonapeptyl Depot®, Enantone Depot®, and Abraxane [42,43].

2.2. Nanogels

Nanogels, comprising of flexible hydrophilic polymers, can be prepared as plain gels [44]. The drug can be incorporated spontaneously in the nanogel upon swelling in water. As a result, gel collapses, leading to the formation of solid, dense nanoparticles with a decrease in solvent volume. Owing to biocompatibility, high moisture content and desirable mechanical features, nanogels propose unique applications for

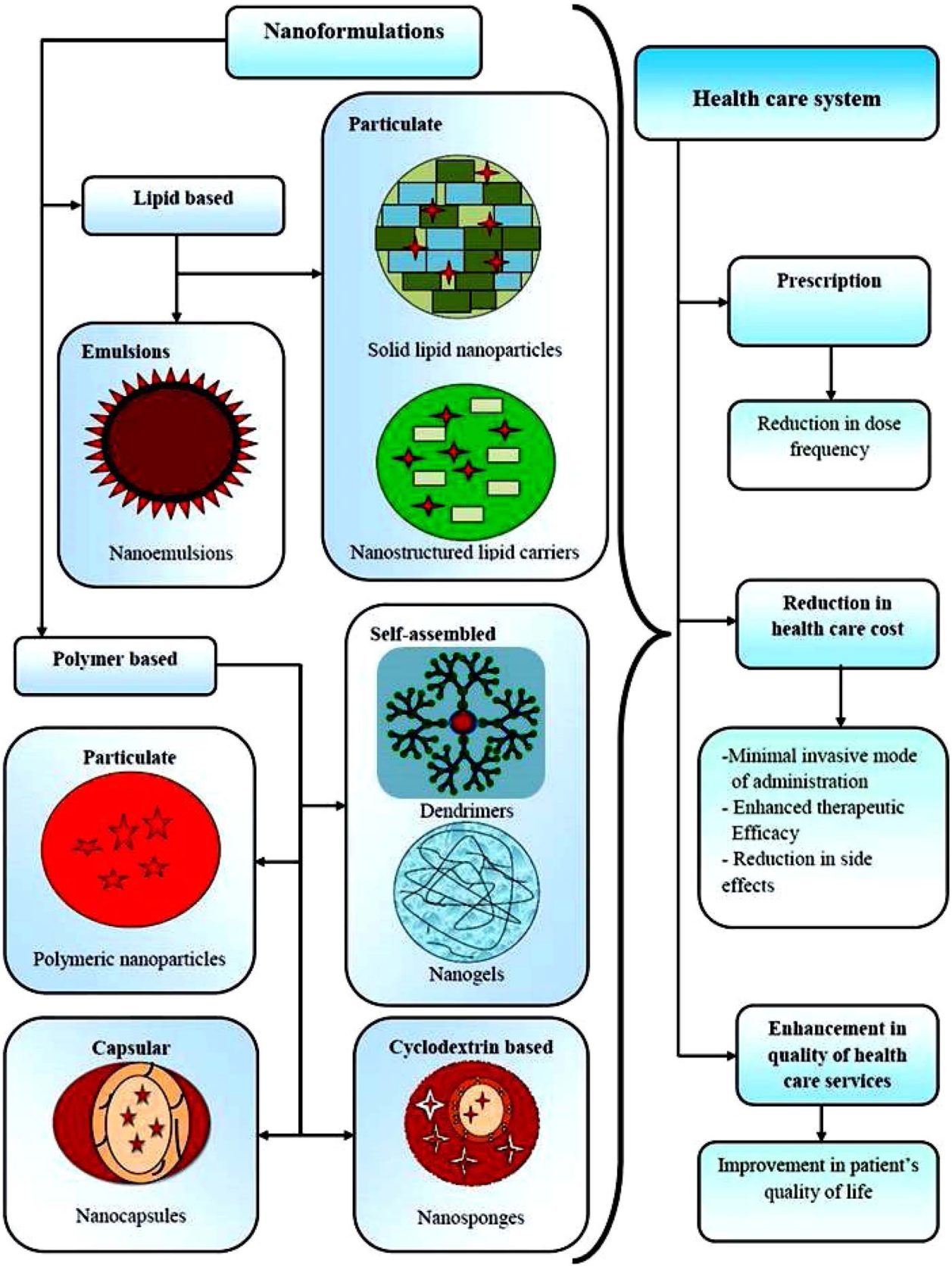

Fig. 1. Nanotherapeutics in Healthcare.

polymer-based drug carrier systems. These gels have increased surface area for polyvalent bioconjugation and an internal network for entrapment of biomolecules. Physical encapsulation of bioactive compounds such as DNA, proteins, carbohydrates, and drugs in the polymeric mesh along with their *in-vitro* release pattern has been extensively explored as a targeted mode of drug delivery for biomedical

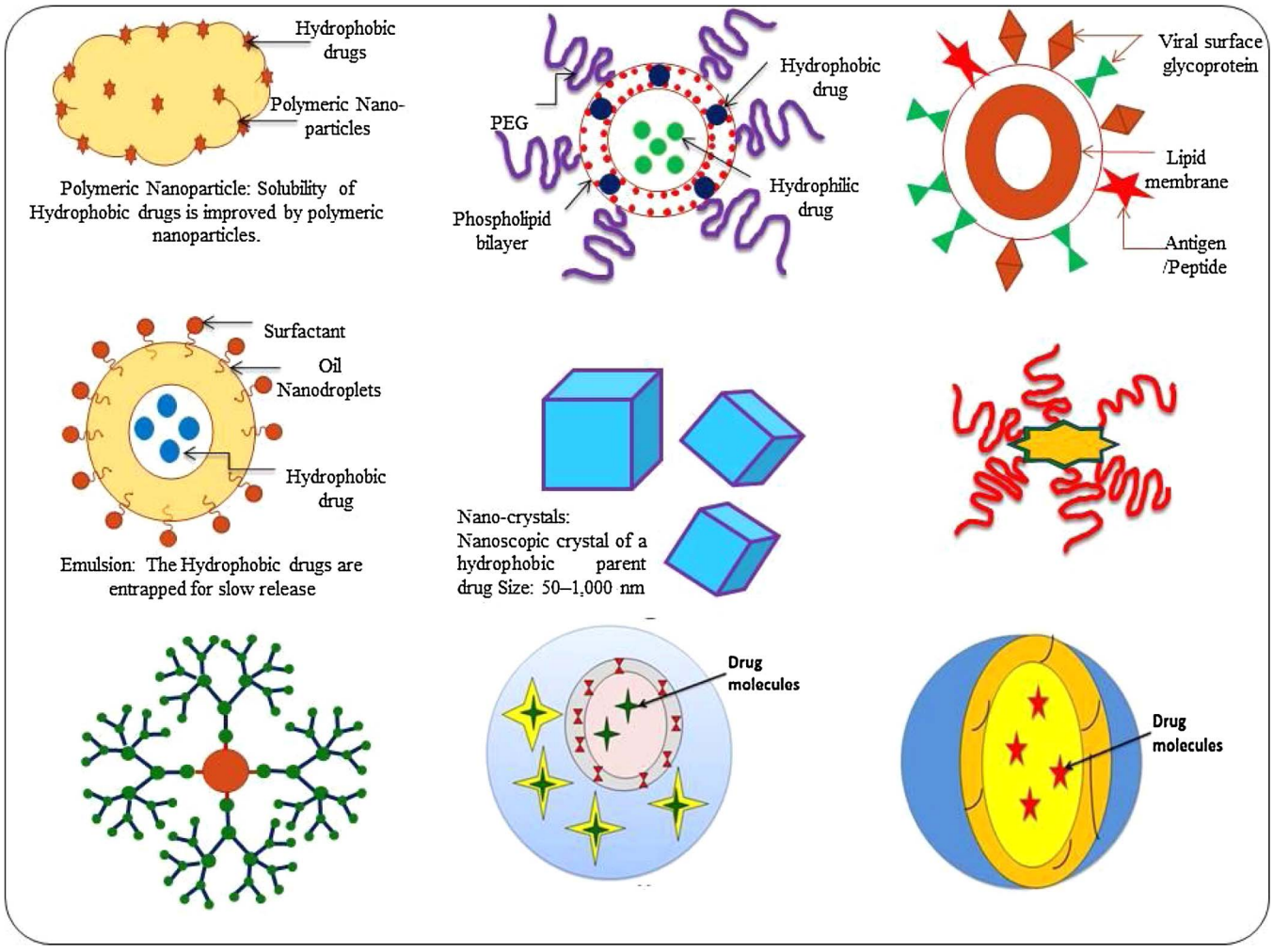

Fig. 2. Structure of various nanoformulations.

Table 1
: Applications of novel nano-carriers in healthcare.

Formulations	Active molecule	Action	References
Chitosan nanoparticles	Temozolomide	Enhanced the stability	[19]
Chitosan nanoparticles	Paclitaxel	Improved apoptotic and anticancer efficacy	[20]
Chitin nanogel	Clobetasol	Compared anti-psoriatic activity with marketed cream	[21]
Polymeric nanogels	Cisplatin/Doxorubicin	Synergistic effect through combination chemotherapy	[22]
Nanogels	Doxorubicin	Enhanced tumor growth inhibiting potential of doxorubicin in vivo	[23]
Nanoemulsions	Psoralen	Improved transdermal delivery	[24]
Nanoemulsions	Paclitaxel and baicalein	Minimize multidrug resistance through co-encapsulation of drug	[25]
Solid lipid nanoparticles	Efavirenz	Improved bioavailability and brain targeting	[20]
PEGylated solid lipid nanoparticles	Puerarin	Improved protective effect of drug in acute myocardial ischemia	[26]
Nano-polymers	Nanofillers	Produce solid dispersions of carbamazepine, a poorly water-soluble drug.	[27]
Conjugated nano-structured lipid carriers	Simvastatin	Drug targeting to lungs	[28]
Nano-structured lipid carriers	Aceclofenac	Imroved dermatokinetic profile of drug	[29]
Nano-structured lipid carriers	AMD3100 and IR780	Increased photo-thermal anticancer potency and anti-metastatic the potential *in vivo*	[30]
Titanium dioxide nanoparticles	Titanium	Drug-releasing nano-engineered titanium implants parathyroid hormone (PTH):	[31]
PEGylatedPAMAMG4dendrimers	Methotrexate	Enhanced drug loading capacity	[32]
Polymeric nanoparticle-encapsulated curcumin	Curcumin	Bioavailability of curcumin and curcumin glucuronide in the central nervous system of mice after oral delivery of nano-curcumin	[33,34]
Nanoparticles of Hydroxyapatite	Nano-hydroxyapatite	Study of enhanced solubility and intestinal absorption of cisplatin by coating with nano-hydroxyapatite	[35]
Ethyl cellulose nanoemulsion	Dexamethasone	Dexamethasone (DXM): A better drug delivery system	[36]
Cyclodextrin-nanosponges	Efavirenz	Twice increase in oral bioavailability	[37]
Cyclodextrin-nanosponges	L-dopamine	Controlled drug delivery in Parkinson's diseases	[38]

applications [45]. Various synthetic approaches for the preparation of nanogels include micro-molding and photolithographic methods, modification of biopolymers, continuous micro fluidics, and heterogeneous living/controlled radical and free radical polymerizations [46].

Several criteria are needed to design and fabricate effective nanogel

Table 2
: Various types of nanoparticles for drug delivery systems.

Types of nanoparticle	Example	Properties	Advantage	Limits
Polymeric nanoparticles: polylactide (PLA), poly lactide-co-glycolide, copolymers (PLGA) and poly (ε-carpolactone), alginate, chitosan, albumin and gelatine.	Decapeptyl®, Gonapeptyl Depot®, Enantone Depot®, Abraxane	Biodegradable aliphatic, fabricated from synthetic polymers.	Facilitates the modification of drugs (hydrophobic) release, protect unstable drug moieties from degradation, preventing the side effects of toxic drugs.	Poor reproducibility
Nanogels: Poly(lactic acid), poly(lactic)–poly(glycolic) copolymers, polyacrylates and polymethacrylates, poly(e-caprolactone)	Aerogel AA, C16–catCA nanogel, PGMA nanogels (PGED-NGs),	Biocompatible, high moisture content, increased surface area for polyvalent bioconjugation	Polymer-based drug carrier systems, provide stability for long lasting circulation in blood.	Less stability
Nanoemulsion: (a) water in oil nanoemulsions (b) oil in water nanoemulsions (c) bi-continuous nanoemulsion	Norvir, Restasis, Cyclosporin A, Etomidat, Diprivan, Flurbiprofenaxtil, Troypofol, Dexamethasone, Alprostadilpalmitate	Isotropic and sustained by suitable surfactant	Colloidal drug delivery system, overcome the unpleasant taste of oily liquids, provide prolonged activity to drugs, protection against hydrolysis and oxidation,	Less stability
Solid lipid nanoparticles: oil-in-water nanoemulsions by using a solid lipid,	Ciprofloxacin (CIP)-loaded SLNs	Controlled-release pattern with different lipids.	Cheap raw materials, high biocompatibility, improvement in bioavailability, protection of sensitive moieties from environmental hazards and controlled drug-release	Crystalline nature of solid lipids makes them less suitable for drug delivery system
Nonstructured lipid carriers: solid lipid incorporated into liquid lipids	Fluconazole-loaded NLCs	Immobilization of therapeutic drugs and prevent coalescence, high drug loading potential	Low toxicity, controlled release, drug protection, explored for delivery of hydrophobic and hydrophilic drugs.	Tendency to gelation, low incorporation rate
Dendrimers: poly-propylenemine, polyamidoamine, arginine terminated peptide dendrimers	PPI, AstromolR, DAB, PAMAM Starburstk, PAMAM dendrimers,	Water solubile, nano size, narrow polydispersity index	Explored for biodelivery through transdermal, oral, ocular and pulmonary routes, facilitate diverse cargo delivery, transdermal penetration	Low yield in synthesis
Nanocapsules: Resveratrol-loaded lipid-core-nanocapsules	SOLUDOTS-PTX	Chemically stable, biocompatible and high reproducibility	Protect the encapsulated material, agrochemicals, sanitizing products, cosmetics and sewage treatment, cancer treatment, self healing, contagion treatment	Delays the release of active moieties
Nanosponges	Glymasason, Prostavastin, Brexin, Mena-gargle		Capacity to load both hydrophilic and lipophilic moieties	Include only small molecules

based drug carrier system for *in vivo* therapeutic applications. One important criterion is the nanogel stability for long lasting circulation in blood. The unique novel functionality for bioconjugation of nanogel surfaces with specific ligands is another that can recognize receptors on infected cells. Lastly, the biodegradability of nanogels should not only modify the drug release for a desired period but also enable to remove the empty device after release of the drug [46]. In a recent study, topical delivery of chitin nanogel loaded with clobetasol (anti-psoriatic drug) having a size of 132 ± 14 nm is determined [21]. This nanogel exhibited remarkable toxicity towards THP-1 and HaCaT cell lines by MTT assay. Nanoformulation (0.35 mg ml^{-1}) showed significant anti-inflammatory potential with an average of 70% and 65% inhibition of LOX and COX activities depicted in THP-1 cells. Increased transdermal flux was obtained from *in vitro* skin permeation studies. *In vivo* anti-psoriatic activity performed on imiquimod model evidenced the significance of nanogel for topical application of clobetasol for psoriasis [21]. Sane Care Nanogel, ZyflexNanogel, Augen Nanogel Eye-care Gel, Skin Perfect Brightening Nanogel [47], and Oxalgin are some selected and marketed nanogel preparations.

2.3. Nanoemulsions

Nanoemulsions constitute an interesting colloidal drug delivery system, which is thermodynamically stable and can be sterilized by filtration [48]. These are heterogeneous mixtures of oil droplets in aqueous medium, resulting in nano droplets with small size distribution. The resultant nanoemulsions appraise as translucent or transparent, isotropic, and sustained by suitable surfactant [49]. Three types of nanoemulsions can be formulated: (a) water in oil nanoemulsion (water dispersed in oil medium, (b) oil in water nanoemulsion (oil dispersed in aqueous medium, (c) bi-continuous nanoemulsion [50]. The most extensive feature of nanoemulsions is conceal the unpleasant taste of oily liquids. These also provide a prolonged activity to drugs and protection against hydrolysis and oxidation. Hence, these nanoformulations may be found as efficient and impregnable delivery option with heigh bioavailability. Nowadays, nanoemulsions are being widely explored for targeting various photosensitizers, anticancer drugs, or therapeutic agents. These nanoformulations propose several applications such as delivery of drugs, diagnosis of biologicals and chemical agents [50].

Simion *et al.* in 2016 fabricated P-selectin targeted dexamethasone-loaded lipid nanoemulsions (132–143 nm) to reduce vascular inflammation [51]. The prepared formulations were characterized for physicochemical assays. In their study, nano-formulation was found functional in *in-vitro* and *in vivo* study. It decreases the endothelium activation selectively and consequently monocyte infiltration, resulting in significant reduction in the lungs inflammation in a model mouse. Norvir (Ritonavir), Restasis, Gengraf (Cyclosporin A), Etomidat-Lipuro (Etomidate), Ropion (Flurbiprofenaxtil), Diprivan, Troypofol (Propofol), Limethason (Dexamethasone) and Liple (Alprostadilpalmitate) are some examples of nanoemulsion formulations [52].

2.4. Solid lipid nanoparticles

Lipid nanoparticles prepared with a solid matrix are known as solid lipid nanoparticles (SLNs). They are made from oil-in-water nanoemulsions by using a solid lipid. At the beginning of 1990, the first generations of SLNs were evolved [53]. The advantages associated with SLNs include cheap raw materials, avoidance of organic solvents, use of physiological lipids, ease of scale-up, high biocompatibility, improvement in bioavailability, protection of sensitive moieties from environmental hazards and controlled drug-release [54]. The polymorphic transition, drug expulsion phenomena, an irregular gelation tendency and low drug incorporation, owing to crystalline nature of solid lipids makes them less suitable for drug delivery system [55].

Recently, ciprofloxacin (CIP)-loaded SLNs was prepared with superior antibacterial activity using an ultrasonic melt-emulsification [56]. These were well fabricated with nanoparticles size ranging from 165 to 320 nm and a polydispersity index falling between 0.18 and 0.33, along with high entrapment efficiency. CIP release exhibited a controlled-release pattern with different lipids. Ciprofloxacin SLNs are prepared with stearic acid (CIPSTE) displayed the maximum burst effect, resulting in rapid drug release. This CIPSTE composition was found stable at room temperature for 120 days. SLNs for various delivery routes such as oral [57], dermal [58], pulmonary [59], ocular [60] and rectal [61] have been explored thoroughly with *in vitro* and *in vivo* evaluation. Nano base and nano pearl are SLN formulations available in the market [62].

2.5. Nonstructured lipid carriers

Nonstructured lipid carriers constitute the second generation lipids nano-systems comprising of solid lipid incorporated into liquid lipids [63]. These nano carriers enable strong immobilization of therapeutic drugs and prevent coalescence of particles in comparison to emulsions [64,65]. Further, due to the liquid oil droplets in a solid matrix, their drug loading potential is increased in comparison to SLNs. The advantages of NLCs over the polymeric nanoparticles include biodegradability, low toxicity, controlled release, drug protection and avoidance of organic solvents during fabrication. In recent years, NLCs have been extensively explored for delivery of hydrophobic and hydrophilic drugs. The NLCs have been developed with an objective to meet industrial requirements regarding validation and qualification, simple technology, scale up and low cost [66].

The availability of many commercial products acknowledges the success story of this carrier. Further numerous NLC formulations are commercially available including NLC repair cream and NLC reconstruction cream. NLCs have been explored for treatment of various diseases, through various administration routes *viz.* oral, topical, ocular, pulmonary, and parenteral [67]. Fluconazole-loaded NLCs were fabricated using probe ultrasonication method and investigated for antifungal activity on a large number of *Candida* species. Using fluconazole NLCs, a significant decrease in MIC for all *Candida* groups was observed ($P \ll 0.05$). Furthermore, it was reported that *C. albicans* was found to be more susceptible to fluconazole-loaded NLCs than *C. parapsilosis* and *C. glabrata* ($P \ll 0.05$) [68].

2.6. Dendrimers

Dendrimers are unique three-dimensional, globular hyper branched nano polymeric architectures. Attractive features like water solubility, nano size, narrow polydispersity index, modifiable molecular structure, availability of cavities in the interior and multiple functional groups at the periphery distinguish them from other nano-systems. Terminal functionalities act as a platform for conjugation and drug targeting. Additionally, these peripheral functional groups provide them tailor-made properties, improving their versatility [69]. Polyamidoamine is the most widely explored dendrimer for drug delivery. Their synthesis starts from amine group that react with methyl acrylate and leads to the formation of two new branches having ester terminated dendrimer. 'Full-generation' amine-terminated dendrimer can be produced by subsequent amidation of methyl ester with ethylene diamine. PAMAM dendrimers are nonimmunogenic, biocompatible and water-soluble, have terminal amine functional groups which can be modified for drug targeting [69]. Besides solubility enhancement, dendrimers have been exhaustively explored for biodelivery through transdermal, oral, ocular and pulmonary routes. Some of the synthetic cationic polymers like acid-labile amidized facilitate diverse cargo delivery [70]. Modification of their structure may resolve toxicity-related issues [69].

In a recent study, it was revealed that arginine terminated peptide dendrimers, along with sonophoresis can potentially improve the transdermal penetration of ketoprofen [71]. The results showed that

Table 3
Application of peptide/protein in healthcare.

Peptide/Protein	Mechanism of action	Effect	Reference
Pituitary adenylate cyclase-activating peptide	Regulates peptide stimulating adenylate cyclase	Cognition improvised	[95,96]
Leptin	Anorexia generating satiety signaling factor	Reduced food indicate and weight	[97–99]
Insulin	Controls level of glucose uptake	Improves memory	[100–102]
Galactose permease	Feeding regulation	Reduce body weight	[103–105]
Exendin	GLP-1 receptor agonist: increased release of insulin	Reduce blood glucose level	[106–108]
Albumin	Molecule for targeted drug delivery	Changes the pattern of the delivery and improves the stability	[109–111]
Sinapultide	Surfactant: respiratory tract	Mechanical ventilation	[112]
Peginesatide	Erythropoetin analogue	Increases RBC number	[113]
Pasireotide	Affinity to somatostatin analog: receptor-5	Treatment of Cushings disease	[114]
Carfilzomib	Anticancer: Proteasome inhibitorTertapeptide: analogue of epoxomicin	Treatment of multiple myeloma	[115]
Linaclotide	Agonist of Guanylate cyclase 2C	Irritable bowel syndrome and Chronic idiopathic constipation	[116]
Teduglutide	Glucagone like peptide 2 (GLP-2) analogue	Short bowel syndrome	[117]

combination of peptide dendrimer and ultrasound application worked synergistically. *In vivo* studies also demonstrated that dendrimer and ultrasound-mediated permeation of drug led to higher plasma concentration of active drug in comparison to passive diffusion. Transdermal ketoprofen administrations with A8 dendrimer showed comparable drug absorption and plasma concentration with oral route [71]. The commercially available poly-propylenemine (PPI, AstromolR, DAB) [72] and polyamidoamine (PAMAM; Starburstk) dendrimers have been most widely studied for pharmceutical use [73].

2.7. Nanocapsules

Nanocapsule usually consists of either liquid or solid core in which drug is loaded in to the pocket which is encapsulated by exclusive membrane of synthetic or natural polymers. [74,75]. The nanocapsules with lipid core were prepared using precipitation method. The prepared nanoparticles were evaluated for physical, chemical and biological features. Most important features to be considered during their synthesis are particle size and their distribution. These can be measured by X-ray diffrection, X-ray photoelectron spectroscopy, Transmission electron microscopy (TEM), scanning electron microscopy (SEM) multi-angle laser light scattering superconducting quantum interference device [75]. Commercially available bioactive nanocapsules are chemically stable, biocompatible and highly reproducible. They have mesmerize the attention of research groups due to their coating which protect the encapsulated material against unenviable consequences, such as dissolution in liquid and delays the release of active moieties. Nanocapsule possesses wide range of biomedical applications in biomedical engineering, agrochemicals, sanitizing products, cosmetics as well as sewage treatment. Additionally their utility has also been investigated in drug delivery for cancer treatment [76], radiotherapy [77], self healing, contagion treatment [78] and applicable in food and agriculture. In future the novel improved nanocapsules will opens new avenues in research and development for delivery of bioactive compounds to the target tissues [75].

Resveratrol-loaded lipid-core-nanocapsules (RSV-LNC) fabricated and characterized for their potential to target the colon cancer cells. The RSV-LNC revealed a sustained and controlled release of drugs. RSV entrapped in a nanocapsule resulted in an improved anticancer effect in HT29 cancer cells, in comparison to free RSV. On the basis of *in-vitro* evaluation, RSV loaded nanocapsules hold a promising potential to enhance the therapeutic efficacy in colon cancer cells. However, further investigations on animal models are suggested to authenticate the improved behaviour of RSV nanoformulations [79]. SOLUDOTS-PTX (Paclitaxel lipid nanocapsules) is presently under clinical trials (adisinsight.springer.com).

2.8. Nanosponges

Nanosponges have been gaining the attention of pharmaceutical research scientists for drug delivery as they have the capacity to load both hydrophilic and lipophilic moieties [80,81]. These are tiny, non-toxic, porous scaffold colloidal structures having numerous cavities where drug molecules may be entrapped. β-cyclodextrins are the most widely employed in the fabrication of these nanocarriers. Various cross-linkers such as hexamethylene di-isocyanate, carbonyl di-imidazole, pyromellitic dianhydride, diphenyl carbonate can be explored in their manufacture. These structures are insoluble in water as well as organic solvents [82]. These are self- sterile [83–85], stable up to 300 °C and pH range from 2-11. Trotta and coworkers fabricated cyclodextrin nanosponges using ultrasound-assisted synthesis technique [86] and explored them for antitumor drugs [87]. Efavirenz is a non-nucleoside reverse transcriptase inhibitor (class II drug), which is commonly prescribed in HIV [20]. However, this drug shows less solubility and limited bioavailability. To enhance the solubility and dissolution of this drug, beta-cyclodextrin cross linking with carbonates in variable ratios was carried out [37]. Glymasason, Prostavastin, Brexin and Mena-gargle are some of the marketed nanosponge formulations [88].

3. Application of nano therapeutics

3.1. Proteins and peptides delivery

Proteins and peptides have several biological activities in almost every field of medicine and exhibited great promise for treatment of various diseases (Table 3 and 4). These are also involved in the diagnosis of various metabolic, cardiovascular and neurological disorders (Alzheimer's, Parkinson's) and diseases including diabetes and cancer [89,90] (Fig. 3). These macromolecules are called as biopharmaceuticals when they are directly used to treat a disease. Nanoparticles and dendrimers are used for controlled release and more efficient delivery of drugs [91]. Moreover, they are highly specific according to particular localization signal that is provided on peptides [92–94]. Another important system for drug delivery is micro-RNA. They are constructed by a combination of two mi-RNAs to stop expression of the dis-regulatory gene in cancer.

3.2. Nano-electromechanical system

Nano electromechanical system has critical structural elements below 100 nm. Their effect is being analyzed for the active release of drugs and maintaining its level in the body of the patient. The application of this system is potentially important in the treatment of cancer

Table 4
List of peptides with antimicrobial properties.

Peptide	Mechanism of Action	Antimicrobial activity	Reference
hLF1-11 (Human Lactoferrin 1-11)	Bacterial membrane lysis	Antimicrobial: Gram positive, negative and some fungi	[118–120]
CKPV2 peptide	Alpha MSH (Melanocyte stimulating hormone) derivative	Antimicrobial and anti-inflammatory activity: *C. albicans*	[121–123]
Dhvar-5 plus Chitosan	Cell wall disruption	Antimicrobial activity: MRSA	[124]
AP-114DPK-060LL-37 plus cubosomes	Unknown mechanism	Gram negative bacteria	[125]
Nisin-ZMelittin plus NLCs	Cell wall lipid-II pore formation	*Staphylococcus aureus, Staphylococcus epidermidis* and *Escherichia coli.*	[126]
β-naphthylalanine	Anti-LPS activity	Gram negative bacteria	[127]
*Sp*PR-AMP1 (*Portunus pelagicus)*	Unknown	Gram positive bacteria & Vibrio	[128]

with the help of iron nanoparticles and gold nanoshells. In case of patients having insulin dependent diabetes mellitus (IDDM), this has been proved to be very effective [129]. In Nano electromechanical system the toxicity or overdose drugs can be avoided, and level of drug can be maintained in the body [130].

3.3. Implants

In the last two decades, there is an ongoing demand of regenerative medicine and substitutes for damage organs. Nano-engineered implants introduced for the control release of bioactive therapeutics (*e.g.* hormones or drugs) and treatment of localized pathologies. Many recent advances in this field have been proven to be very useful. The drugs can be tailor-made designed from few nano-grams to several hundred micrograms. Recently, nano-engineered titanium implants are designed for controlled drug releasing [31]. The titanium tube used for the delivery of hormones and drugs in combination for the faster recovery of bones which also showed better osteoblast binding capacity [31]. The concept of nano-engineered implants not only limited to bones but could be applied for skin and cardiovascular engineering.

3.4. Non viral delivery systems for gene and protein delivery in cancer therapy

There are many potential nanoparticles, which are having applications in diagnosis of disease, study of pharmaceutical efficiency of drugs, apoptosis of cancer cells and gene therapies. [131–134]. The success of gene therapy depends on the development of efficient, non-toxic, easily controllable vehicle that encapsulate and deliver foreign genetic material into specific cell types [135]. Nanoparticles have high

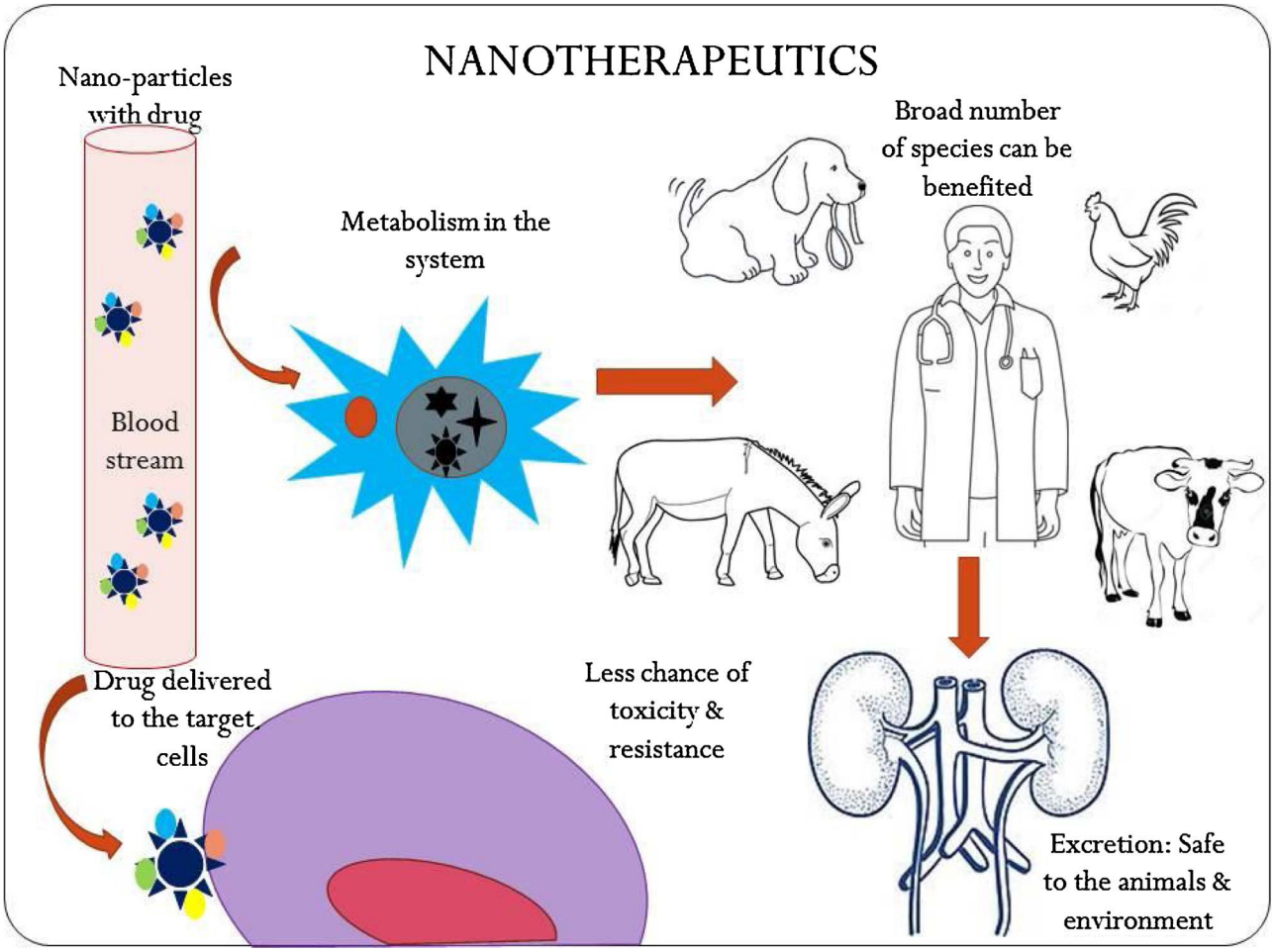

Fig. 3. Safe nanodrug delivery system in multispecies patient.

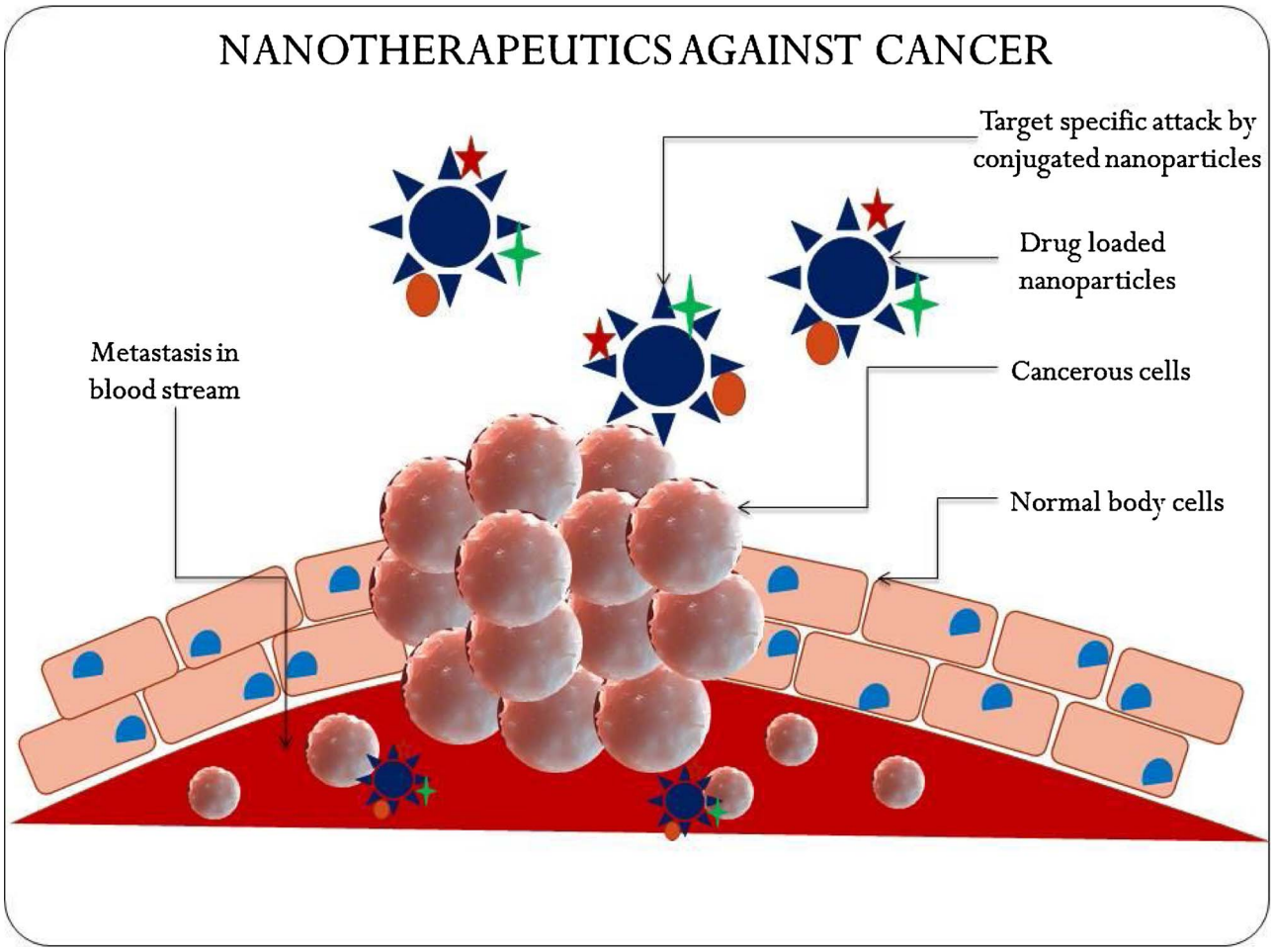

Fig. 4. Nanotherapeutics for cancer cell treatment.

surface area to volume ratio; therefore it is easy to incorporate various functional groups on their surfaces (Fig. 4). These functional groups can be used to search and bind some tumor cells. More importantly, the smaller size of nanoparticles hampers aggregation [136]. Choosing of suitable material is essential for drug delivery. The non-viral vectors are vital include polymers like liposomes-protamine-DNA complex [137], poly L-lysine [138], Ploy ethylenimine [139] and Liposomes [140] etc. These particles conjugate with genes/drugs and dispense to the target. For gene therapy nanoparticles are classified into three categories, lipid based, polymer based and metal based nanoparticles [141]. A delivery formulation should encapsulate and protect the nucleic acid for successful gene therapy. The nanoparticles extend the hope for triumph gene therapy. Since last decade, considerable research efforts apply for developing the non-viral delivery systems for gene therapy especially in cancer treatment [142]. The successful cancer gene therapy requires treatment of metastatic disease. The wild- type p53 act as tumor suppressor and play an important role in cancer biology. Virus mediated gene transfer approach has been reported in transduction of wt p53 into cancerous cell. But the effectiveness was limited by the low number of transduced cells and detection of infected cells [143]. Charge reversal polymers like PEI, PLL and nanogels are potentially applicable in cancer drug delivery. They also carry large molecules like DNA and bring directly into nucleus and significantly increase their cellular uptake. Zhang et al. in (2014) demonstrated the nuclear localization properties of such cationic polymers [144]. Recently several charge reversal carriers were developed for drug distribution and also provide strategies for efficient cancer therapy. To overwhelm the immunogenic problems nonviral (physical and chemical approaches) based gene delivery methods have been appraise [135]. Combinations of drugs can be used in the delivery system for better results and prognosis [145,146].

3.5. Photodynamic therapy

Nanoparticle based photosensitizing drug has been used in photodynamic therapy for the treatment of pre-skin cancer, acne and sun damage. Depending on the part of the body being treated, nanoparticles are placed either in the specific area of skin or blood stream through a vein and activated to express illumination from the light outside. With this exposure, nanoparticles absorb a certain wavelength of light and absorbed by the target tissue. The excited nanoparticles react with oxygen and produce high energy free oxygen radicals. These molecules can react and destroy the cancerous tissue which is targeted. PDT might also help to destroy the blood vessels that feed the cancer cells and improve the immune system to attack cancer. This therapy is becoming popular because it has no long-term side effects. It does not leave any trail of toxic effects in other vital parts of the body. Photodynamic therapy has better potential as a non-invasive than surgery. It is target specific, and often costs less than other cancer treatment. Kanzius RF therapy is one of the best examples of nanoparticle hyperthermia [147,148]. Gold nanoparticles have the potential to join various therapeutic functions by targeting specific organs, tissues, and tumors [149–151]. Recently various types of nanomaterial have been used for the treatment of cancer (Table 5).

3.6. Nanotechnology based nutritive agents

Nanoparticles could facilitate the supplementation of nutrients and its bioavailability to the uplift growth of livestock. The nanoparticles

Table 5
Application of nanaomaterials in treatment of cancer.

Nano material used	Cancer: Application	Reference
GNPs	Glioblastoma: Nano-structures mediated co-delivery of therapeutic agents for glioblastoma treatment	[145]
Nano-polymers	Glyco-nano-oncology: design of functionalized nanoparticles for pharmacological delivery of multimeric glycans, lectins or selective inhibitors of lectin-glycan interactions with antitumor activity.	[146]
Prodrug-based nano-drug delivery systems (P-N-DDSs)	Combination therapy with the combinations of prodrugs with different chemotherapeutic agents, other therapeutic agents, nucleic acid or the combination of various types of therapy	[142]
Mesoporous nano silica MCM-41	The release studies of methotrexate (MTX), an anti-cancer drug, were performed	[152]
Chitosan based nano particles	Chitosan nanoparticle and micropartice comparison for anti-cancer activity of Propilis	[153]
Nano-Fe3O4/CA	Breast cancer: Alkylating drug efficasy Nimustine≫ > Semustine .Chlormethin.	[154]
Nano-graphene oxide	In vivo targeting of metastatic breast cancer via tumor vasculature-specific nano-graphene oxide	[155]
Nano-magetic formulation	Cancer cell destruction for pancreatic cancer therapy using Hsp90 inhibitor17- N-allylamino- 17-demethoxygeldanamycin (17AAG) loaded polymeric nano magnetic formulation	[156]
Cyclodextrin-nanosponges	Enhanced delivery of the drug in the treatment of prostate cancers.	[157]
Lipid nanocapsules	Effective in lung cancer therapy	[158]
ConjugatedDendrimers	Enhanced efficacy of drug in pancreatic cancer	[159]
Polyamidoamine dendrimers	Improved hepatic cancer therapy in hepatic cancer cells	[160]
Hyaluronan solid nanoemulsions	Enhanced paclitaxel targeting on ovarian tumor	[158]
Modified solid lipid nanoparticles	Synergistic antitumor activity against cervical cancer	[161]
Nanocapsules	Improvement in the therapeutic efficiency of drug in colon cancer cells	[79]
Lipid nanocapsules	Enhanced anticancer potential of drug	[162]

can stabilize the bioactive compounds and increase their cellular absorption. Due to their small size, they move fast in the digestive tract and facilitate the delivery of the nutrients. Phenolic compounds are the important micronutrients in our aliment and prevent the development of degenerative and neuro-degenerative disease. They have low bioavailability and easily destroyed by environmental stresses. When these phenolics encapsulated with nanoparticles, they work as a fine delivery system. Therefore, the nano-carriers are most effective for protection and delivery of phenolics [163].

4. Role of nanotechnology in diagnostic imaging

The medical imaging technique is a valuable tool for rapid diagnosis and evaluation of a wide range of pathologies. It allows for tracking the specialized cells involved in a disease. For this purpose, earlier certain photosensitive organic dyes were used [164,165]. It's a herculean task because the types of cells, numbers of dyes and their respective wavelength of light source would be required. Recently there has been a significant development in the field of imaging technology to identify and monitor the disease *in vivo*. The use of radiolabeled nanoparticles

Table 6
List of FDA-approved nanomedicines categriosed on material used.

Drug	Material Description	Nanoparticle benefits	Effective against	Year of approval
Cimzia® or certolizumab pegol (BSA)	Antibody conjugate	Increased circulation time and enhanced stability in vivo	Crohn's disease Rheumatoid arthritis Psoriatic Arthritis Ankylosing Spondylitis	2008 2009 2013 2013
Mircera® or Methoxy PEG-epoetin	Chemically synthesized erythrocyte-inducing agent	Enhanced stability of aptamers as a result of PEGylation	Anemia associated with chronic kidney disease	2007
Krystexxa®	Polymer-protein conjugate (PEGylated porcine-like uricase)	Increased stability of protein by PEGylation as well as insertion of specific mammalian protein	Chronic gout	2010
Plegridy® (Biogene)	Polymer-protein conjugate(PEGylated IFN beta-1a)	Increased stability of protein by PEGylation	Multple Sclerosis	2014
Adynovate (Baxalta)	Polymer-protein conjugate	Increased stability of protein by PEGylation	Hemophilia	2015
Marqibo® (Onco TCS)	Liposomal Vincristine	Increased delivery to tumour site; lower systemic toxicity arising from side-effects	Acute Lymphoblastic Leukemia	2012
Onivyde® (Merrimack)	Liposomal Irinotecan	Increased delivery to tumor arising from side-effects	Pancreatic Cancer	2015
Doxil®/Caelyx™ (Janssen)	Liposomal doxorubicin	Increased delivery to tumour site; lower systemic toxicity arising from side-effects	multiple myeloma	2008
Estrasorb™ (Novavax)	Micellar Estradiol	Controlled delivery of therapeutic	Menopausal therapy	2003
Abraxane®/ABI-007(Celgene)	Albumin-bound paclitaxelnanoparticles	Improved solubility; improved delivery to tumor bioavailability; extended release	Breast cancer NSCLC Pancreatic cancer	2005 2012 2013
EquivaBone® (Zimmer Biomet)	Hydroxyapatite	Mimics bone structure	Bone substitute	2009
Invega® Sustenna®(Janssen harms)	Paliperidone Palmitate	Permits the slow release of injectable less soluble drugs	Schizophrenia Schizoaffective Disorder	2009 2014
Ryanodex® (Eagle Pharm)	Dantrolene sodium	Faster administration at higher doses	Malignant hypothermia	2014
Feraheme™ or ferumoxytol (AMAG pharmaceuti.)	SPION withpolyglucose sorbitolcarboxymethylether	Magnetite suspension allows for prolonged steady release, reducing number of doses	Deficiency anemia iron deficiency in chronic kidney disease (CKD)	2009 2009 2009
Venofer® (Luitpold Pharm)	Iron sucrose	Allows enhanced dose	Iron deficiency in chronic kidney disease	2000
Feridex®/Endorem® (AMAG Pharma)	SPION-dex	Superparamagnetic character	Imaging agent	2008
GastroMARK™; umirem®	SPION-silicone	Superparamagnetic character	Imaging agent	2009

offers many advantages over conventional imaging techniques. The specificity of nanoparticles to select tissue in diagnostic imaging and drug-based therapies is critical and prevent non-specific cell binding. The nanoparticles are being used in the imaging tools like MRI and ultrasound, able to give better contrast than conventional techniques [166]. The success of nanoparticles used in imaging technology is the inherent property, which is their smaller size. This makes them useful in the field of diagnostic imaging and radiology. Fluorescent dye loaded nanoparticles are promising to the intravenously administered imaging system. Quantum dots are the best nanoparticles which are endowed with the property of confinement of quantum or energy packet and which can be expressed in the form of emission of light. They are size tuneable and attached to proteins that can penetrate the cell membrane. They are very useful for precise tumor removal in surgery. When quantum dots used in the MRI, they can show an excellent image of tumor sites [167]. They can produce a better contrast picture than the other chemical compounds [168]. Another example is cadmium selenide, which glows when exposed to UV light. The toxicity is the only disadvantage of the chemical compound from which the quantum dots nanomaterial is synthesized [169–171]. Both groups can produce different fluorescence by same excitation frequency [172]. When these nanoparticles injected into the body, they exude into the cancerous growth. They have brighter and better illuminance than the regularly used organic dyes [173,174]. The interest in polymeric nanoparticles as an imaging system for biological application has increased in the last decade. Nanoparticles like poly lactic *co*-glycolic acid (PLGA) are ideal for this purpose because they are biocompatible as well as biodegradable. FDA has also approved this for the safe delivery of drugs. In a study, the EtNBS encapsulated within PLGA to reduce the side effects associated with its free delivery and also retained the efficacy of therapeutic agents [175].

5. Biosensors

Biosensors are analytical devices that are capable of providing selective, sensitive information for bio-recognition of elements. They facilitate the fast observation and pathogen identification in clinical application. Gold nanoparticles based biosensor or nucleic acid hybridization systems are proven to have very good sensitivity. Magnetic nanoparticles smaller in size (≪100nm) provide higher surface area and lower sedimentation rates that improve the tissue diffusion. Therefore, they remain in the circulation and capillary system of the tissues and organs avoiding vessels embolism after injection. Much lateral flow assay or immune chromatographic assays are being designed by using both gold nanoparticles and magnetic nanoparticles on Ebola virus [176]. The magnetic nanoparticles are more sensitive than gold nanoparticles. The enzymatic property of nanoparticles is being exploited in a very advanced biosensor to achieve an excellent level of sensitivity [177]. Multicolor optical coding is a novel technology in which quantum dots of different size are designed on micro-beads which can emit a different frequency of light which can be used in the microarray technology. Nanopore technology is designed for the analysis of nucleic acid which converts the length of nucleotides into an electronic signature which can be matched with the signature present in the database by quick identification [178,179]. Sensor chip test can detect disease related biomarkers in a pathological condition such as cancer using just a drop of blood [180].

Nanotechnology plays a great role in instrumentation. A pencil sized device arthroscope works based on nanotechnology which is used in minimally invasive surgeries [181]. Smaller the incision, faster and better the healing is the thumb rule of surgery. Nano electrochemical based biosensor is a major developing domain of nanodiagnostics. These sensors assure accurate and digital results and can be made into fancy devices. A multi-walled carbon nanotube is an ideal platform for such device; they require less amount of blood. An electrochemical sensor is the best routinely used an example for the detection of blood glucose level [182–184]. Nanowires can also be used in the diagnosis of cancers with just a drop of peripheral blood within five minutes [185]. Each nanowire is primed to detect a single type of targeted marker protein. Ten to thousands of different medical conditions can be diagnosed without adding to the cost of the test [185]. The sensitivity is thousand times better than other laboratory tests. Nanotechnology has augmented the personalization of oncology for tailored diagnostics and treatment of each according to the requirement. Different genomic tests has been systematically reviewed that could be used in screening, detection and diagnosis of target cancer affected part of the body in the individual [186].

6. Nanoparticles for blood purification

The cells and proteins can be separated from a complex mixture such as blood by using magnetically activated cell sorting or Dynabeads [187,188]. These have been successfully demonstrated to remove numerous harmful compounds from blood, such as toxins, pathogens and certain proteins with the help of a circuit similar to dialysis [189,190]. The dialysis works on the basic principle of diffusion or ultra-filtration of solutes across semipermeable membranes [191]. However, the nanoparticles based purification works on the specific targeting of compounds. For this purpose, fictionalized iron oxide or carbon coated metal nanoparticles are used. The presence of iron provides them with ferromagnetic or super magnetic properties [192]. These nanoparticles can be covalently conjugated to different proteins, antibodies, antibiotics [189] or any artificial compound on their surfaces [193]. These functionalized magnetic nanoparticles bind with the target compound in the blood or other complex body fluid. The fluid is then subjected to the external suitable magnetic field which allows all the magnetic nanoparticles to aggregate near the magnetic pole. In this way, particles can be easily separated along with the contaminants from the blood or other complex body fluids [194,195]. As compared to hemoperfusion (technique for blood purification) nanoparticles have High loading capacity, easily accessibility, improved selectivity and quick diffusion, very small numbers of nanoparticles are required in reduced dosage volume [196]. This is a novel pharmaceutical endeavor to tackle systemic infections by directly removing the cause or pathogens in the cases such as sepsis. It can direct the removal of pro-inflammatory endotoxins and cytokines [189] and helps in simplifying tedious traditional techniques such as dialysis. Despite having so many merits, this technology is still in the pipeline of development [197].

7. Application of nanotechnology in tissue engineering

Nanotechnology has been proved to be very useful in tissue engineering. It has potential to completely replace the conventional therapies like grafts, organ transplant, artificial implants etc. Nanoparticles (grapheme, carbon nanotubes, molybdenum disulfide and tungsten disulfide) are utilized as a base for fabrication of tissue engineering. It also, leads to efficient improvements in compression and flexion in polymeric nanocomposites which are imperative characteristic of bones [198]. Therefore, these types of nanocomposites can be successfully used as very light weight bone implants. The meat pieces can be fused together using a nanotechnology based approach called 'Flesh welder.' In this way, two pieces of chicken flesh could be fused together into one by applying a suspension of gold-coated nano-shells and infrared laser activities to this reaction [199]. This exquisite technique can be utilized to join the severed major veins during surgery and cauterize the tissue during cases of accident. In recent years, new terminology was introduced, that is nano-nephrology. In this, nanotechnology is subjected towards the diagnosis and therapeutic aspects of kidney diseases [200–203]. The nano-scale artificial kidney is the ultimate goal of this branch so that the problems during transplant rejection can be avoided.

Molecular mechanical assemblies based on nanotechnology can be

used to correct the pathological condition at the sub-microscopic level. These nano-scale mechanical devices are also called as nanorobots. When they introduced into the body, they can detect and repair the damage. Nanorobotics is the disciple of designing and constructing nanorobots with carbon nanotubes/silicon material ranging in between 0.1–10μm [204,205]. Future advancement in nanomedicine will be helpful in constructing such robots. K. Eric Drexler postulated a cell repair machine, which will prevent the cell from ageing. However, the first technical and scientific discussion of medical nanorobots was conducted by Freitas [1]. "The singularity is near" given by Kurzweil Raymond in 2005 [206]. The neuro-electronic interface clearance dealing with nano-devices empower the computers to connect with nervous system. A refutable energy provided by external sonic, chemical or magnetic source will allow the computers to connect and control the nervous system. Self-powered nano-devices have been developed that used glucose from biofluids. Overheating, leakage or electrical interference from the power source are the demarits of this technology. The structure of electrical circuit is utmost important because they placed in the nervous system.

8. Toxicity and safety concerns of nanotherapeutics

The most challenging aspect with the use of nanotherapeutic products is accumulation, analysis, classification, and characterization of the safety data about their clinical applications [207]. Nanomaterials, which often constitute the most important part of the nano-technological products, show considerable variation in their biological activity as well as toxicity based on surface chemistry [208]. In contrast, nanoparticles represent a huge health hazard since they are capable of penetrating the barriers present within the body and reaching the biological systems [209,210]. There are evidence of these particles causing serious harm to cellular membranes, organelles and DNA owing to generation of free radicals [211,212]. Hazardous materials thus adsorbed to the cell surface or present within cell micro structure may be delivered intracellularly or may stimulate an immune response by reacting with a receptor present on the cell surface [213,214].

In the last decade, cell experiments revealed DNA damaging effects of nano-particulate zinc oxide and titanium dioxide sunscreen formulations [215]. Nanotoxicity assessment of nanomaterial should be given due importance especially in the case of new nano-materials in the early stages of production [216,217]. The in-depth understanding of ADME nano-materials and the effect of critical product features on them would help to develop *in-silico* modeling techniques with the view to anticipating the biological and toxic effect of nano-therapeutic products [218]. The substrate stiffness and nanotopographical studies have been applied to find out the influence of nanomaterial on cell behaviour like spreading, adhesion, proliferation and differentiation [219]. The alteration of cellular surface may result in variation in pathological, developmental and physiological processes. Nanotechnology needs powerful tools and technology like Dippen nanolithography (DPN) to investigate the cell-substrate interactions at nanoscale level. Nanomaterials demand optimization by high throughput screening techniques before using in tissue engineering and regenerative medicine. This calls for collaborative research efforts to develop skills necessary for biological, clinical and toxicological investigations. The *in vitro* models are desirable to analyse the toxicity level of nanoparticles. The role of cell-nanotopography and interactions of human lung fibroblasts to nanomaterial (multi walled carbon nanotubes) has been described [220]. The physiologically relevant *in vitro* models were developed which provide rapid, inexpensive and reliable methods for nanotoxicological studies. The cell-nanotopographcal interaction and their effect on neural differentiation and ECM remodelling of hiPSCs was also reported [221]. They contributed to design the nanotopography configuration of pleuripotent stem cell neural lineage commitment. Although nanotopography has been a vigorous modulator of cell behaviour but it is unclear how the nanotopographal cue affect the nucleus, influencing cell morphology and functions. Wang and co-workers gave the comprehensive intuition into rational design of nanotopography for new nanomaterials and relate the cell-substrate interfaces of implants and medical devices [222]. Moreover, adequate regulatory mechanisms are imperative to circumvent the risk associated with the nano-therapeutics. Although several efforts have been made in this direction, the regulations regarding clinical use of nano-medicine need to be further strengthened [223–226].

The specifications for analysis of nanomedicine should be dictated by API (Active Pharmaceutical Ingredients) as well as the polymer used in its formulation [226]. The characteristic properties of nanomedicine pose a hurdle in their regulation. These properties may be altered either by introducing small changes in the raw materials or by modifying the production processes [224]. The regulatory framework must be designed from both the perspectives. The introduction and implementation of ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Humans) Q8, Q9 and Q10 (Quality Guidelines) haves not only favored the established therapeutic products but also facilitated the development of nanomedicines and production processes in future [6,227,228].

9. Commercialization of nanotherapeutics and their multi-dimensional applications

Nanotherapeutics systems present numerous advantages from the standpoint of health benefits, but their commercial viability and availability in the market have to meet some challenges. The possible risks and obstacles encompass scale up problems, low production rate, lack of quality control system, use of undesired materials, batch to batch variation in reproducibility, the high cost of production, difficulties in separating by-products, biocompatibility and toxicity issues, scrimpy knowledge regarding interaction between nanoparticles and drugs, reluctance of public and commercial companies, scarcity of venture funds and the media's negative focus about nano-materials. Nano-therapeutic commercialization faces a dearth of finances, reluctance on the part of a pharmaceutical industry about investment in nanotherapeutics, weak regulatory framework, and publicity of the toxicity associated with the use of nanomaterials without many scientific data [229]. Given these challenges, commercial availability of nano carrier based systems is highly complex and risky [229]. However, investment in nano-medicine is likely to increase particularly if the developed products are novel and cater to meet medical needs offering excellent cost-benefit ratio [229,230]. Additionally, nanotechnology can be utilized for reformulating off-patent proprietary drugs, creating avenues for patentability and revenue generation. The market success of nano-medicinal products such as Doxil and Abraxane has made the nanotherapeutics market more attractive [229,230]. Although, mass-marketing of nanotherapeutics is yet to be witnessed, nevertheless, this segment holds huge promise. The future of nanomedicine depends upon fixing the missing links between product development and commercialization of analytical techniques by accredited laboratories.

Nanotherapeutics, and nanoparticle-based nutraceuticals have shown promising avenues in both medical and veterinary fields and thus could strengthen the arena of biomedicine towards a new dimension [231–238]. Conducting more researches and exploration of the full potential of nanomaterials based therapeutics and designing of effective nanomedicines and advanced drug delivery regimens by exploiting the recent advances in inter- and multi-disciplinary fields of immunology, biotechnology, biochemistry, bioengineering and others is still required to bring out revolution in increasing the commercialization value and delivery of such products from bench to bed side. Silver nanoparticles have gained high attention for their antimicrobial potentialities [239–241]. The Metadichol, a nanoemulsion of policosanols, available as a nutritional supplement, has ability to displace viruses binding to the Vitamin D receptor and possess immune enhancing properties, thus could inhibit entry of viruses into host cells and has been recently

reported to posses anti-viral potential again Zika virus [242,243]. Such studies need to be supported with extensive researches towards bringing out useful pharmaceuticals, nutraceuticals, drugs, medicines, anti-microbial agents as commercialized products into the market for safeguarding the health of humans and their companion animals, livestock and poultry.

Translation of nanotechnology based medicines from pre-clinical stage to clinically useful products is a significant challenge. The pharmaceutical companies which have come up with products that have illustrated therapeutic utility are examples of the meticulous application of nanotechnology to the development of therapeutic systems. Citing examples of commercial anti-cancer nanomedicines, we hereby give an insight for facilitating the understanding of the reader about the revolutionizing impact of nanotechnology in the field of medicine. Based on this approach, doxorubicin loaded liposomal formulation (Doxil™/ Caelyx™) was the first anti-cancer nanomedicinal product approved by FDA [244–247]. The conventional formulation driven approach of product development has not yet been able to deliver the expected benefit to the patients.

10. Conclusion and future perspective

The application of nanotechnology in the field of medicine has already borne many breakthroughs and is continuing to grow towards becoming a vital component of the healthcare system. This fact is evident from the ever-increasing research publications and patents granted in the field of nanocarrier systems for drug delivery. Present review gives a brief account of various nano materials and their derivatives potential as a therapeutic agent and their merits over conventional therapeutic agents. Nanotherapeutics such as polymeric nanoparticles, nanoemulsions, nanogels, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, nanocapsules, nanosponges has been discussed in details. The applications of nano-medicines in the field of cancer, nutrition, and health have been emphasized. Also, future perspectives in the field of nano-robots have been briefly introduced. A multidisciplinary approach coupled with industry-academia partnership should drive further research pursuits in this area. The translation of scientific research into marketable products is still a challenge, and the future of emerging nanotherapeutics depends upon converting the potential research outcomes into fruitful commercial technology for stake holders. In coming future, nanotechnology can lead to major advances towards personalized medicine. The nano-diagnostics can be more exploited for further improved sensitivity and specificity of the diagnostic tests. Newer and more precise nanoparticles can be identified which can lead us to more precise disease diagnosis for its control.

Author contributions

All authors have equally contributed to the manuscript design, collection and analyzing literature, drafting, update, and revision. Minakshi and Gaya Prasad envisioned the idea, reviewed and edited the manuscript. Upendra Lambe, Basanti Brar, Ikbal, Manimegalai, Koushlesh Ranjan, Rekha Rao, Sunil Kumar, Sheefali Mahant collected the literature and analyzed for the compilation of the manuscript. Sandip Kumar Khurana further reviewed and edited the manuscript. Kuldeep Dhama and Hafiz MN Iqbal overviewed, analyzed and edited the manuscript.

Conflict of interest

Authorsp would hereby like to declare that there is no conflict of interests that could arise.

Acknowledgement

Authors are thankful to Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar India for providing facility to prepare the manuscript. All other authors acknowledge their respective institutes for providing literature facilities.

References

[1] R.A. Freitas, Nanomedicine: Basic Capabilities. Library of Congress Cataloging-in-Publication Data, (1999).
[2] R.P. Feynman, There's plenty of room at the bottom, Eng. Sci. 23 (1960) 22–36.
[3] D.J. Bharali, S.A. Mousa, Emerging nanomedicines for early cancer detection and improved treatment: current perspective and future promise, Pharm. Ther. 128 (2010) 324–335.
[4] C.L. Ventola, The Nanomedicine Revolution. Part 1, Emerging Concept 37 (2012), pp. 512–525 *P T.*.
[5] R. Seigneuric, L. Markey, D.S. Nuyten, From nanotechnology to nanomedicine: applications to cancer research, Curr. Mol. Med. 10 (2010) 640–652.
[6] V. Wagner, A. Dullaart, A.K. Bock, et al., The emerging nanomedicine landscape, Nat. Biotechnol. 24 (2006) 1211–1217.
[7] R.A. Freitas, What is nanomedicine? Nanomedicine, Nanotechnol. Biol. Med. 1 (2005) 2–9.
[8] Market research report, Nanomedicine Market Analysis by Products, (Therapeutics, Regenerative Medicine, Diagnostics), by Application, (Clinical Oncology, Infectious Diseases), by Nanomolecule (Gold, Silver, Iron Oxide, Alumina), & Segment Forecasts, (2017), pp. 2013–2025 Report ID: 978-1-68038-942-5.
[9] R.A. Freitas, The future of nanofabrication and molecular scale devices in nanomedicine, Stud. Health Technol. Inf. 80 (2002) 45–60.
[10] O.C. Farokhzad, R. Langer, Nanomedicine: developing smarter therapeutic and diagnostic modalities, Adv. Drug Deliv. Rev. 58 (2006) 1456–1459.
[11] B. Kim, J.T. Rutka, W.C. Chan, Nanomedicine, N. Engl. J. Med. 20 (2010) 2434–2443.
[12] S. Bhaskar, F. Tian, T. Stoeger, et al., Multifunctional nanocarriers for diagnostics, drug delivery and targeted treatment across blood-brain barrier: perspectives on tracking and neuroimaging, Part. Fibre Toxicol. 7 (2010) 3.
[13] T.J. Webster, Projections for nanomedicine into the next decade: but is it all about pharmaceuticals? Int. J. Nanomed. 3 (2008) 1.
[14] R.A. Petros, J.M. DeSimone, Strategies in the design of nanoparticles for therapeutic applications, Nat. Rev. Drug Discov. 9 (2010) 615–627.
[15] M. Shrestha, Nanotechnology to revolutionize medicine, J. Drug. Deliv. Ther. 2 (2012) 156–161.
[16] R. Duncan, R. Gaspar, Nanomedicine(s) under the microscope, Mol. Pharm. 8 (2011) 2101–2141.
[17] A. Hafner, J. Lovric, G.P. Lakos, et al., Nanotherapeutics in the EU: an overview on current state and future directions, Int. J. Nanomed. 9 (2014) 1005–1023.
[18] European Commission/ETP, Nanomedicine. Roadmaps in Nanomedicine Towards 2020, (2009) http://www.etpnanomedicine.eu/public/pressdocuments/publications/etpnpublications.
[19] A. Di Martino, P. Kucharczyk, Z. Capakova, et al., Enhancement of temozolomide stability by loading in chitosan-carboxylatedpolylactide-based nanoparticles, J. Nanopart. Res. 19 (2017) 71.
[20] S. Gupta, R. Kesarla, N. Chotai, et al., Systematic approach for the formulation and optimization of solid lipid nanoparticles of efavirenz by high pressure homogenization using design of experiments for brain targeting and enhanced bioavailability, Biomed. Res. Int. (2017) 5984014.
[21] R. Panonnummal, R. Jayakumar, M. Sabitha, Comparative anti-psoriatic efficacy studies of clobetasol loaded chitin nanogel and marketed cream, Eur. J. Pharm. Sci. 96 (2017) 193–206.
[22] H. Wu, H. Jin, C. Wang, et al., Synergistic cisplatin/doxorubicin combination chemotherapy for multidrug-resistant cancer via polymeric nanogels targeting delivery, ACS Appl. Mater. Interfaces 9 (2017) 9426–9436.
[23] D.Y. Yoon, J.C. Kim, *In vivo* lifetime and anti-cancer efficacy of doxorubicin-loaded nanogels composed of cinnamoyl poly (β-cyclodextrin) and cinnamoyl pluronic F127, J. Biomater. Sci. Polym. Ed. 28 (2017) 505–518.
[24] T.N. Barradas, J.P. Senna, S.A. Cardoso, et al., Hydrogel-thickened nanoemulsions based on essential oils for topical delivery of psoralen: permeation and stability studies, Eur. J. Pharm. BioPharm. pii (2016) S0939-6411: 30830-X.
[25] L. Meng, X. Xia, Y. Yang, et al., Co-encapsulation of paclitaxel and baicalein in nanoemulsions to overcome multidrug resistance via oxidative stress augmentation and *p*-glycoprotein inhibition, Int. J. Pharm. 513 (2016) 8–16.
[26] Z. Dong, J. Guo, X. Xing, et al., RGD modified and PEGylated lipid nanoparticles loaded with puerarin: formulation, characterization and protective effects on acute myocardial ischemia model, Biomed. Pharm. Ther. 89 (2017) 297–304.
[27] I. Duartea, L. Corvoa, P. Serodiob, et al., Production of nano-solid dispersions using a novel solvent-controlled precipitation process-benchmarking their *in vivo* performance with an amorphous micro-sized solid dispersion produced by spray drying, EurJ. Pharm. Sci. 93 (2016) 203–214.
[28] S.J. Li, X.J. Wang, J.B. Hu, et al., Targeting delivery of simvastatin using ICAM-1 antibody-conjugated nanostructured lipid carriers for acute lung injury therapy, Drug Deliv. 24 (2017) 402–413.
[29] N.K. Garg, G. Sharma, B. Singh, et al., Quality by design (QbD)-enabled development of aceclofenac loaded-nano structured lipid carriers (NLCs): an improved dermatokinetic profile for inflammatory disorder (s), Int. J. Pharm. 517 (2017) 413–431.
[30] H. Li, K. Wang, X. Yang, et al., Dual-function nanostructured lipid carriers to

deliver IR780 for breast cancer treatment: anti-metastatic and photothermal anti-tumor therapy, Acta Biomater. (2017) S1742-S7061(17)30079-X.
[31] K. Gulati, M. Kogawa, M. Prideaux, et al., Drug-releasing nano-engineered titanium implants: therapeutic efficacy in 3D cell culture model, controlled release and stability, Mater. Sci. Eng. 69 (2016) 831–840.
[32] L.F. Barraza, V.A. Jimenez, Alderete JB association of methotrexate with native and PEGylated PAMAM-G4 Dendrimers: effect of the PEGylation degree on the drug-loading capacity and preferential binding sites, J. Phys. Chem. B 121 (2016) 4–12.
[33] M. Szymusiaka, H. Xiaoyu, A. Paola, et al., Bioavailability of curcumin and curcumin glucuronide in the central nervous system of mice after oral delivery of nano-curcumin, Pharm. Nanotechnol. 511 (2016) 415–423.
[34] L. Jinglei, H.S. Gye, L. Woo, et al., Soluble starch formulated nanocomposite increases water solubility and stability of curcumin, Food Hydrocol. 56 (2016) 41–49.
[35] R. Miyasaka, S. Kikukawa, K. Sakuma, Enhanced solubility and intestinal absorption of cisplatin by coating with nano-hydroxyapatite, J. Drug Deliv. Sci. Technol. 35 (2016) 294–302.
[36] G. Calderoa, R. Montesa, M. Llinasa, et al., Studies on the formation of polymeric nano-emulsions obtained via low-energy emulsification and their use as templates for drug delivery nanoparticle dispersions colloids and surfaces B, Biointerfaces 145 (2016) 922–931.
[37] M.R. Rao, C. Shirsath, Enhancement of bioavailability of non-nucleoside reverses transciptase inhibitor using nanosponges, AAPS Pharm. Sci. Technol. (2016) 1–11.
[38] F. Trotta, F. Caldera, R. Cavalli, et al., Molecularly imprinted cyclodextrinnanosponges for the controlled delivery of L-DOPA: perspectives for the treatment of Parkinson's disease, Expert Opin. Drug Deliv. 13 (2016) 1671–1680.
[39] J. Panyam, V. Labhasetwar, Biodegradable nanoparticles for drug and gene delivery to cells and tissue, Adv. Drug Deliv. Rev. 55 (2003) 329–347.
[40] Z. Zhang, P.C. Tsai, T. Ramezanli, et al., Polymeric nanoparticles-based topical delivery systems for the treatment of dermatological diseases, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 5 (2013) 205–218.
[41] S. Martin-Saldana, R. Palao-Suay, M.R. Aguilar, et al., Polymeric nanoparticles loaded with dexamethasone or α-tocopheryl succinate to prevent cisplatin-induced ototoxicity, Acta Biomater. (2017) S1742–S7061 30123-X.
[42] C. Lherm, R.H. Muller, F. Puisieux, et al., Alkylcyanoacrylate drug carriers: II. Cytotoxicity of cyanoacrylate nanoparticles with different alkyl chain length, Int. J. Pharm. 84 (1992) 13–22.
[43] R. Cortesi, E. Esposito, G. Luca, et al., Production of lipospheres as carriers for bioactive compounds, Biomaterials 23 (2002) 2283–2294.
[44] G. Soni, K.S. Yadav, Nanogels as potential nanomedicine carrier for treatment of cancer: a mini review of the state of the art, Saudi Pharm. J. 24 (2016) 133–139.
[45] T. Jung, W. Kamm, A. Breitenbach, et al., Biodegradable nanoparticles for oral delivery of peptides: is there a role for polymers to affect mucosal uptake? Eur. J. Pharm. BioPharm. 50 (2000) 147–160.
[46] J.K. Oh, R. Drumright, D.J. Siegwart, et al., The development of microgels/nanogels for drug delivery applications, Prog. Polym. Sci. 33 (2008) 448–477.
[47] A. Sharma, T. Garg, A. Aman, et al., Nanogel-an advanced drug delivery tool: current and future, Artif. Cells Nanomed. Biotechnol. 44 (2016) 165–177.
[48] S. D'souza, V. Rosseels, O. Denis, et al., Improved tuberculosis DNA vaccines by formulation in cationic lipids, Infect. Immunol. 70 (2002) 3681–3688.
[49] F. Gao, Z. Zhang, H. Bu, et al., Nanoemulsion improves the oral absorption of candesartan cilexetil in rats: performance and mechanism, J. Control. Release 149 (2011) 168–174.
[50] M. Jaiswal, R. Dudhe, P.K. Sharma, Nanoemulsion: an advanced mode of drug delivery system, Biotech. 5 (2015) 123–127.
[51] V. Simion, C.A. Constantinescu, D. Stan, et al., *P*-Selectin targeted dexamethasone-loaded Lipid Nanoemulsions: a novel therapy to reduce vascular inflammation, Mediat. Inflamm. 2 (2016) 1–15.
[52] S. Setya, S. Talegaonkar, B.K. Razdan, Nanoemulsions: formulation methods and stability aspects, World J. Pharm. Sci. 3 (2014) 2214.
[53] R.H. Mueller, K. MaEder, S. Gohla, Solid lipid nanoparticles (SLN) for controlled drug delivery—a review of the state of the art, Eur. J. Pharm. BioPharm. 50 (2000) 161–177.
[54] K. Jores, W. Mehnert, K. Mader, Physicochemical investigations on solid lipid nanoparticles and on oil-loaded solid lipid nanoparticles: a nuclear magnetic resonance and electron spin resonance study, Pharm. Res. 20 (2003) 1274–1283.
[55] C.L. Fang, S.A. Al-Suwayeh, J.Y. Fang, Nanostructured lipid carriers (NLCs) for drug delivery and targeting, Recent. Pat. Nanotechnol. 7 (2013) 41–55.
[56] G.A. Shazly, Ciprofloxacin controlled-solid lipid nanoparticles: characterization, in vitro release, and antibacterial activity assessment, Biomed. Res. Int. (2017) 1–9.
[57] J.F. Pinto, R.H. Muller, Pellets as carriers of solid lipid nanoparticles (SLN) for oral administration of drugs, Pharmazie 54 (1999) 506–509.
[58] A. Dingler, R.P. Blum, H. Niehus, et al., Solid lipid nanoparticles (SLNTM/Lipopearls TM) a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products, J. Microencapsul. 16 (1999) 751–767.
[59] M.A. Videira, A.J. Almeida, M.F. Botelho, et al., Lymphatic uptake of radiolabelled solid lipid nanoparticles administered by the pulmonary route, Eur. J. Nucl. Med. 26 (1999) September, 1168–1168.
[60] R. Cavalli, M.R. Gasco, P. Chetoni, et al., Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin, Int. J. Pharm. 238 (2002) 241–245.
[61] M. Sznitowska, M. Gajewska, S. Janicki, et al., Bioavailability of diazepam from aqueous-organic solution, submicron emulsion and solid lipid nanoparticles after rectal administration in rabbits, Eur. J. Pharm. BioPharm. 52 (2001) 159–163.
[62] E.B. Souto, R.H. Müller, Cosmetic features and applications of lipid nanoparticles, Int. J. Cosmet. Sci. 30 (2008) 157–165.
[63] W. Zauner, N.A. Farrow, A.M. Haines, *In vitro* uptake of polystyrene microspheres: effect of particle size, cell line and cell density, J. Cont. Rel. 71 (2001) 39–51.
[64] E.B. Souto, R.H. Muller (Eds.), Nanoparticulate Drug Delivery Systems, 166 Informa Healthcare, New York, London, 2007, pp. 213–233.
[65] S.S. Shidhaye, R. Vaidya, S. Sutar, et al., Solid lipid nanoparticles and nanostructured lipid carriers-innovative generations of solid lipid carriers, Curr. Drug Deliv. 5 (2008) 324–331.
[66] H.R. Muller, R. Shegokar, C.M. Keck, Twenty years of lipid nanoparticles (SLN & NLC): present state of development and industrial applications, Curr. Drug Discov. Technol. 8 (2011) 207–227.
[67] M.A. Iqbal, S. Md, K. Sahni, et al., Nanostructured lipid carriers system: recent advances in drug delivery, J. Drug Target. 20 (2012) 813–830.
[68] H.R. Kelidari, M. Moazeni, R. Babaei, et al., Improved yeast delivery of fluconazole with a nanostructured lipid carrier system, Biomed. Pharmacother. 89 (2017) 83–88.
[69] A.K. Patri, I.J. Majoros, J.R. Baker, Dendritic polymer macromolecular carriers for drug delivery, Curr. Opin. Chem. Biol. 6 (2002) 466–471.
[70] B. Zhang, K. Wang, S. Jingxing, et al., Charge-reversal polymers for biodelivery, Bioins Biom Poly Syst Drug Gene Del. Wiley-VCH Verlag GmbH & Co. KGaA, 2014, pp. 223–242.
[71] J. Manikkath, A.R. Hegde, G. Kalthur, et al., Influence of peptide dendrimers and sonophoresis on the transdermal delivery of ketoprofen, Int. J. Pharm. 521 (2017) 110–119.
[72] R. Duncan, L. Izzo, Dendrimer biocompatibility and toxicity, Adv. Drug. Deliv. Rev. 57 (2005) 2215–2237.
[73] D. Tomalia, H. Baker, J. Dewald, et al., A new class of polymers: starburst-dendritic, Polym. J. 17 (1985) 117–132.
[74] D. Kim, E. Kim, J. Lee, et al., Direct synthesis of polymer nanocapsules: self-assembly of polymer hollow spheres through irreversible covalent bond formation, J. Am. Chem. Soc. 132 (2010) 9908–9919.
[75] P. Kothamasu, H. Kanumur, N. Ravur, et al., Nanocapsules: the weapons for novel drug delivery systems, Bioimp. 2 (2012) 71–81.
[76] C. Bouclier, L. Moine, H. Hillaireau, et al., Physicochemical characteristics and preliminary *in vivo* biological evaluation of nanocapsules loaded with siRNA targeting estrogen receptor alpha, Biomacromolecules 9 (2008) 2881–2890.
[77] E. Deutsch, K. Libson, J.L. Vanderheyden, et al., The chemistry of rhenium and technetium as related to the use of isotopes of these elements in therapeutic and diagnostic nuclear medicine, Int. J. Radiat. Appl. Instrum. B 13 (1986) 465–477.
[78] X.T. Dong, L.I. Zhang, W. Zhang, et al., Preparation and characterization of nanometer-sized CeO～2/polystyrene hybrid material, AC Phys. Sin. 17 (2001) 739–742.
[79] M. Feng, L.X. Zhong, Z.Y. Zhan, et al., Enhanced antitumor efficacy of resveratrol-loaded nanocapsules in colon cancer cells: physicochemical and biological characterization, Eur Rev. Med. Pharmacol. Sci. 21 (2017) 375–382.
[80] F. Trotta, R. Cavalli, Characterization and applications of new hyper-cross-linked cyclodextrins, Compos. Interface 16 (2009) 39–48.
[81] F. Trotta, M. Zanetti, R. Cavalli, Cyclodextrin-based nanosponges as drug carriers, Beilstein J. Org. Chem. 8 (2012) 2091–2099.
[82] F. David, Nanosponge Drug Delivery System More Effective than Direct Injection, (2011) www.phyorg.com.
[83] F. Trotta, P. Shende, M. Biasizzo, Method for preparing dextrin nanosponges, Beilstein J. Org. Chem. 8 (2012) 2091–2099.
[84] S. Selvamuthukumar, S. Anandam, K. Krishnamoorthy, et al., Nanosponges: A novel class of drug delivery system-review, Sci. J. Pharm. 15 (2012) 103–111.
[85] R.Z. Ahmed, G. Patil, Z. Zaheer, Nanosponges–a completely new nano-horizon: pharmaceutical applications and recent advances, Drug Dev. Ind. Pharm. 39 (2013) 1263–1272.
[86] Trotta, F, Cavalli, R, Tumiatti, W, et al. Ultrasound-assisted synthesis of cyclodextrin-based nanosponges.WO2006002814 A1 (2006).
[87] Trotta, F, Tumiatti, V, Cavalli, R, et al. Cyclodextrin-based nanosponges as a vehicle for antitumoraldrugs.WO, 3656, p.A1. (2009).
[88] M.E. Davis, M.E. Brewster, Cyclodextrin-based pharmaceutics: past, present and future, Nat. Rev. Drug Discov. 3 (2004) 1023–1035.
[89] A.A. Kaspar, J.M. Reichert, Future directions for peptide therapeutics development, Drug Discov. Today 18 (2013) 807–817.
[90] C. Hölscher, Drugs developed for treatment of diabetes show protective effects in Alzheimer's and Parkinson's diseases, Sheng Li Xue Bao. 66 (2014) 497–510.
[91] K. Chen, J. Guan, Bibliometric investigation of research performance in emerging nanobiopharmaceuticals, J. Informetr. 5 (2011) 233–247.
[92] K. Minamihata, Y. Maeda, S. Yamaguchi, et al., Photosensitizer and polycationic peptide-labeled streptavidin as a nano-carrier for light-controlled protein transduction, J. Biosci. Bioeng. 120 (2015) 630–636.
[93] S.S. Atharia, Z. Pourpakb, G. Folkertsd, et al., Conjugated alpha-alumina nanoparticle with vasoactive intestinal peptide as a nano-drug in treatment of allergic asthma in mice, J. Exp. Pharmacol. 791 (2016) 811–820.
[94] Y.A. Haggaga, B.K. Matchettc, E. Dakirc, et al., Nano-encapsulation of a novel anti-Ran-GTPase peptide for blockade of regulator of chromosome condensation 1 (RCC1) function in MDA-MB-231 breast cancer cells, Int. J. Pharm. 521 (2017) 40–53.
[95] D. Rat, U. Schmitt, F. Tippmann, et al., Neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) slows down Alzheimer's disease-like pathology in amyloid precursor protein-transgenic mice, FASEB J. 25 (2011) 3208–3218.
[96] N. Nonaka, W.A. Banks, H. Mizushima, et al., Regional differences in PACAP transport across the blood–brain barrier in mice: a possible influence of strain, amyloid β protein, and age, Peptides 23 (2002) 2197–2202.
[97] Z.M. Novakovic, M.C. Leinung, D.W. Lee, et al., Intranasal administration of

mouse [D-Leu-4] OB3, a synthetic peptide amide with leptin-like activity, enhances total uptake and bioavailability in Swiss Webster mice when compared to intraperitoneal, subcutaneous, and intramuscular delivery systems, Regul. Pept. 154 (2009) 107–111.
[98] C. Schulz, K. Paulus, H. Lehnert, Central nervous and metabolic effects of intranasally applied leptin, Endocrin. 145 (2004) 2696–2701.
[99] S. Fliedner, C. Schulz, H. Lehnert, Brain uptake of intranasally applied radioiodinated leptin in Wistar rats, Endocrine 147 (2006) 2088–2094.
[100] C. Benedict, M. Hallschmid, A. Hatke, et al., B. Intranasal insulin improves memory in humans, Psychoneuroendocrine 29 (2004) 1326–1334.
[101] M.A. Reger, G.S. Watson, W.H. Frey, et al., Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype, Neurobiol. Aging 27 (2006) 451–458.
[102] S. Craft, L.D. Baker, T.J. Montine, Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial, Arch Neurol. 69 (2012) 29–38.
[103] N. Nonaka, S.A. Farr, H. Kageyama, et al., Delivery of galanin-like peptide to the brain: targeting with intranasal delivery and cyclodextrins, J. Pharmacol. Exp. Ther. 325 (2008) 513–519.
[104] K. Shiba, H. Kageyama, F. Takenoya, et al., Galanin-like peptide and the regulation of feeding behavior and energy metabolism, FEBS J. 277 (2010) 5006–5013.
[105] S. Shioda, H. Kageyama, F. Takenoya, K. Shiba, Galanin-like peptide: a key player in the homeostatic regulation of feeding and energy metabolism? Int. J. Obes. (Lond.) 35 (2011) 619–628.
[106] W.A. Banks, M.J. During, M.L. Niehoff, Brain uptake of the glucagon-like peptide-1 antagonist exendin (9-39) after intranasal administration, J. Pharmacol. Exp. Ther. 309 (2004) 469–475.
[107] T.H. Kim, C.W. Park, H.Y. Kim, et al., Low molecular weight (1kDa) polyethylene glycol conjugation markedly enhances the hypoglycemic effects of intranasally administered exendin-4 in type 2 diabetic db/db mice, Biol. Pharm. Bull. 35 (2012) 1076–1083.
[108] M.J. During, L. Cao, D.S. Zuzga, et al., Glucagon-like peptide-1 receptor is involved in learning and neuroprotection, Nat. Med. 9 (2003) 1173–1179.
[109] J.A. Falcone, T.S. Salameh, X. Yi, et al., Intranasal administration as a route for drug delivery to the brain: evidence for a unique pathway for albumin, J. Pharmacol. Exp. Ther. 351 (2014) 54–60.
[110] M.M. Migliore, T.K. Vyas, R.B. Campbell, et al., Brain delivery of proteins by the intranasal route of administration: a comparison of cationic liposomes *versus* aqueous solution formulations, J. Pharm. Sci. 99 (2010) 1745–1761.
[111] J. Morales, Defining the role of insulin detemir in basal insulin therapy, Drugs. 67 (2007) 2557–2584.
[112] FDA. FDA Approves Kyprolis for Some Patients with Multiple Myeloma. (2012) -07-20.
[113] Affymax and Takeda Omontys (Peginesatide), (2012) Retrieved April 29.
[114] Novartis Drug Signifor®. Approved in the EU as the First Medication to Treat Patients With Cushing's Disease, (2012) Retrieved-07-08.
[115] FDA, FDA Approves Surfaxin to Prevent Breathing Disorder in Premature Infants, 2012-03-06. Retrieved 2012-10-20. Fda.gov. (2012).
[116] FDA Press Announcements. Approves Linzess to treat certain cases of irritable bowel syndrome and constipation. Retrieved 11 February. fda.gov. (2017).
[117] P.B. Jeppesen, Teduglutide, a novel glucagon-like peptide 2 analog, in the treatment of patients with short bowel syndrome, Ther. Adv. Gastroenterol. 5 (2012) 159–171.
[118] C.P. Brouwer, M. Rahman, M.M. Welling, Discovery and development of a synthetic peptide derived from lactoferrin for clinical use, Peptides. 32 (2011) 1953–1963.
[119] A. Lupetti, A. Paulusma-Annema, M.M. Welling, et al., Candidacidal activities of human lactoferrin peptides derived from the N terminus, Antimicrob. Agents Chemother. 44 (2000) 3257–3263.
[120] A. Lupetti, A. Paulusma-Annema, M.M. Welling, et al., Synergistic activity of the *N*-terminal peptide of human lactoferrin and fluconazole against Candida species, Antimicrob. Agents Chemother. 47 (2003) 262–267.
[121] N. Rajora, G. Ceriani, A. Catania, et al., Alpha-MSH production, Receptors, and influence on neopterin in a human monocyte/macrophage cell line, J. Leuk Biol. 59 (1996) 248–253.
[122] A. Catania, S. Gatti, G. Colombo, et al., Targeting melanocortin receptors as a novel strategy to control inflammation, Pharmacol. Rev. 56 (2004) 1–29.
[123] A. Catania, G. Colombo, C. Rossi, et al., Antimicrobial properties of alpha-MSH and related synthetic melanocortins, Sci. World J. 6 (2006) 1241–1246.
[124] H. Xiaofei, B. Xiaojiong, L. Yalan, et al., Catechol-functional chitosan/silver nanoparticle composite as a highly effective antibacterial agent with species-specific mechanisms, Sci. Rep. 7 (2017) 1860.
[125] B. Lukas, U. Anita, M. Nada, et al., Cubosomes post-loaded with antimicrobial peptides: characterization, bactericidal effect and proteolytic stability, Int. J. Pharm. 16648 (2017), http://dx.doi.org/10.1016/j.ijpharm.
[126] A. Lewies, J.F. Wentzel, A. Jordaan, et al., Interactions of the antimicrobial peptide nisin Z with conventional antibiotics and the use of nanostructured lipid carriers to enhance antimicrobial activity, Int. J. Pharm. 29 (526) (2017) 244–253, http://dx.doi.org/10.1016/j.ijpharm.
[127] Y.Y. Hui, C. Yi-An, Y. Bak-Sau, et al., Role of β-naphthylalanine end-tags in the enhancement of antiendotoxin activities: solution structure of the antimicrobial peptide S1-Nal-Nal in complex with lipopolysaccharide, Biochem. Biophys. Acta Biomembr. 1859 (2017) 1114–1123.
[128] I. Chanprapa, A. Pawanrat, C. Walaiporn, et al., Characterization and antimicrobial evaluation of SpPR-AMP1, a proline-rich antimicrobial peptide from the mud crab Scylla paramamosain, Dev. Comp. Immunol. 74 (2017) 209–216.
[129] Roorda, WK, Advanced Cardiovascular Systems, Inc. Patent No. US 6283949 B1 (2001).
[130] V. Cimalla, F. Niebelschütz, K. Tonisch, et al., Nano electromechanical devices for sensing applications, functional materials for micro and nanosystems- EMRS, Sens. Actuators B Chem. 126 (2007) 24–34.
[131] A.Z. Wang, R. Langer, O.C. Farokhzad, Nanoparticle delivery of cancer drugs, Annu. Rev. Med. 63 (2012) 185–198.
[132] P.E. Herrero, A.F. Medarde, Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy, Eur J. Pharm. BioPharm. 93 (2015) 52–79.
[133] N.T. Ngoc, E. Raymond, Reinvention of chemotherapy: drug conjugates and nanoparticles, Curr. Opin. Oncol. 27 (2015) 232–242.
[134] M.A. Jahanian, A.F. Aghdam, N. Anarjan, et al., Application of chitosan-based nanocarriers in tumor-targeted drug delivery, Mol. Biotechnol. 57 (2015) 201–218.
[135] K. Wang, Q. Huang, F. Qiu, et al., Non-viral delivery systems for the application in p53 cancer gene therapy, Curr. Med. Chem. 22 (2015) 4118–4136.
[136] S.Y. Nie, G.J. Xing, J.W. Kim, et al., Nanotechnology applications in cancer, Ann. Rev. Biomed. Eng. 9 (2007) 257–288.
[137] S. Li, M.A. Rizzo, S. Bhattacharya, et al., Characterization of cationic lipid-protamine-DNA (LPD) complexes for intravenous gene delivery, Gene Ther. 5 (1998) 930–937.
[138] W.J. Kollen, A.E. Mulberg, X. Wei, et al., High-efficiency transfer of cystic fibrosis trans-membrane conductance regulator cDNA into cystic fibrosis airway cells in culture using lactosylated polylysine as a vector, Hum. Gene Ther. 10 (1999) 615–622.
[139] A. Bragonzi, G. Dina, A. Villa, et al., Biodistribution and transgene expression with nonviral cationic vector/DNA complexes in the lungs, Gene Ther. 7 (2000) 1753–1760.
[140] A. El-Aneed, An overview of current delivery systems in cancer gene therapy, J. Control. Release 94 (2004) 1–14.
[141] W. Yuhong, R. Ammaji, V.S. Raju, et al., Lipid nanoparticles for ocular gene delivery, J. Funct. Biomater. 6 (2015) 379–394.
[142] G. Yanxiu, M. Yakun, L. Lingbing, The application of prodrug-based nano-drug delivery strategy in cancer combination therapy, Colloid. Surf. Biointerfaces 146 (2016) 482–489.
[143] K.M. Santosh, N. Sarwat, K. Paturu, et al., A cationic cholesterol based nanocarrier for the delivery of p53-EGFP-C3 plasmid to cancer cells, Biomaterials 35 (2014) 1334–1346.
[144] B. Zhang, K. Wang, S. Jingxing, et al., Charge-Reversal Polymers for Biodelivery, Bioins Biom Poly Syst Drug Gene Del Wiley-VCH Verlag GmbH & Co. KGaA, 2014, pp. 223–242.
[145] B. Mujokoro, M. Adabi, E. Sadroddiny, et al., Nano-structures mediated co-delivery of therapeutic agents for glioblastoma treatment: a review, Mater. Sci. Eng. 69 (2016) 1092–1102.
[146] P.F. Hockle, A. Wolosiuk, J.M. Perez-saez, et al., Glyco-nano-oncology: novel therapeutic opportunities by combining small and sweet, Pharmacol. Res. 109 (2016) 45–54.
[147] N.S. Rejinolda, R. Jayakumarb, Y. Kima, Radio frequency responsive nano-biomaterials for cancer therapy, J. Control. Release 204 (2015) 85–97.
[148] A. Cicchettia, T. Rancatia, M. Ebertb, Modelling late stool frequency and rectal pain after radical radiotherapy in prostate cancer patients: Results from a large pooled population, Phys. Med. 32 (2016) 1690–169.
[149] C. Loo, A. Lin, L. Hirsch, et al., Nanoshell-enabled photonics-based imaging and therapy of cancer, Technol. Cancer Res. Treat. 3 (2004) 33–40.
[150] M. Chidambaram, R. Manavalan, K. Kathiresan, Nanotherapeutics to overcome conventional cancer chemotherapy limitations, J. Pharm. Pharm. Sci.: Publ. Canad. Soc. Pharm. Sci. Societecanadienne des sciences pharmaceutiques 14 (2011) 67–77.
[151] J. Conde, J.M. Fuente, P.V. Baptista, Nanomaterials for reversion of multidrug resistance in cancer: a new hope for an old idea? Front. Pharmacol. 4 (2013) 134.
[152] A.A. Rafi, M. Mahkam, S. Davaran, et al., A Smart pH-responsive nano-carrier as a drug delivery system: a hybrid system comprised of mesoporous nanosilica MCM-41 (as a nano-container) & a pH-sensitive polymer (as smart reversible gate-keepers): preparation, characterization and in vitro release studies of an anti-cancer drug, Eur. J. Pharm. Sci. 93 (2016) 64–73.
[153] N.M. Elbaz, I.A. Khalil, A.A. Abd-Rabou, et al., Chitosan-based nano-in-micro-particle carriers for enhanced oral delivery and anticancer activity of propolis, Int. J. Biol. Macromol. 92 (7) (2016) 254–269.
[154] H. Kui, K.Y. Ma, B. Yang, et al., The efficacy assessments of alkylating drugs induced by nano-Fe3O4/CA for curing breast and hepatic cancer, Spectrochim. Acta A Mol. Biomol. Spectrosc. 173 (2017) 82–86.
[155] D. Yang, L. Feng, C.A. Dougherty, et al., *In vivo* targeting of metastatic breast cancer via tumor vasculature-specific nano-graphene oxide, Biomaterials 104 (2016) 361–371.
[156] A.K. Rochani, S. Balasubramanian, G. Ravindran, et al., Dual mode of cancer cell destruction for pancreatic cancer therapy using Hsp90 inhibitor loaded polymeric nano magnetic formulation, Int. J. Pharm. 10 (2016) 648–658.
[157] C.L. Gigliotti, R. Minelli, R. Cavalli, et al., *In vitro and in vivo* therapeutic evaluation of camptothecin-encapsulated β-cyclodextrinnanosponges in prostate cancer, J. Biomed. Nanotechnol. 12 (2016) 114–127.
[158] J.E. Kim, Y.J. Park, Paclitaxel-loaded hyaluronan solid nanoemulsions for enhanced treatment efficacy in ovarian cancer, Int J. Nanomed. 12 (2017) 645–658.
[159] K. Ozturk, G. Esendagl, M.U. Gürbüz, M. Tulu, S. Çalış, Effective targeting of gemcitabine to pancreatic cancer through PEG-cored Flt-1 antibody-conjugated dendrimers, Int J Pharm. 517 (2017) 157–167.
[160] S.P. Kuruvilla, G. Tiruchinapally, M. ElAzzouny, et al., *N*-

Acetylgalactosamine-targeted delivery of dendrimer-doxorubicin conjugates influences doxorubicin cytotoxicity and metabolic profile in hepatic cancer cells, Adv. Healthcare Mater. (2017), http://dx.doi.org/10.1002/adhm.201601046.
[161] B. Liu, L. Han, J. Liu, et al., Co-delivery of paclitaxel and TOS-cisplatin via TAT-targeted solid lipid nanoparticles with synergistic antitumor activity against cervical cancer, Int. J. Nanomed. 12 (2017) 955–968.
[162] P. Resnier, N. Galopin, Y. Sibiril, et al., Efficient ferrocifen anticancer drug and Bcl-2 gene therapy using lipid nanocapsules on human melanoma xenograft in mouse, Pharmacol. Res. (2017) S1043-S6618: 31130-31136.
[163] A.F. Esfanjani, S.M. Jafari, Biopolymer nano-particles and natural nano-carriers for nano-encapsulation of phenolic compounds, Colloids Surf. B 146 (2016) 532–543.
[164] L. Han, X. Zhou, Synthesis and characterization of liposomes nano-composite-particles with hydrophobic magnetite as a MRI probe, Appl. Surf. Sci. 376 (2016) 252–260.
[165] J. Leea, A.C. Gordonb, H. Kimc, Targeted multimodal nano-reporters for pre-procedural MRI and intra-operative image-guidance, Biomaterials 109 (2016) 69–77.
[166] J. Lenga, J. Lia, J. Rena, et al., Star–block copolymer micellar nanocomposites with Mn, Zn-doped nano-ferrite as superparamagnetic MRI contrast agent for tumor imaging, Mater. Lett. 152 (2015) 185–188.
[167] S. Xiaoqian, C. Chana, J. Shia, et al., A graphene quantum dot-Fe3O4-SiO2 based nanoprobe for drug delivery sensing and dual-modal fluorescence and MRI imaging in cancer cells, Biosens. Bioelectron. 92 (2017) 489–495.
[168] Coffey, Rebecca, Twenty things you didn't know about nanotechnology, Discovery 31 (2010) 96.
[169] X. Zhua, G. Wua, N. Lua, et al., A miniaturized electrochemical toxicity biosensor based on graphene oxide quantum dots/carboxylated carbon nanotubes for assessment of priority pollutants, J. Hazard. 324 (2017) 272–280.
[170] M. Kominkovaa, V. Milosavljevica, P. Vitekc, et al., Comparative study on toxicity of extracellularly biosynthesized and laboratory synthesized CdTe quantum dots, J. Biotechnol. 24 (2017) 193–200.
[171] B.B. Manshiana, J. Jiménezb, U. Himmelreicha, et al., Personalized medicine and follow-up of therapeutic delivery through exploitation of quantum dot toxicity, Biomaterials 127 (2017) 1–12.
[172] Y.L. Hewakuruppu, Plasmonic pump–probe method to study semi-transparent nanofluids, Appl. Opt. 52 (2013) 6041–6050.
[173] Y. Parka, T. Wooa, H. Choa, et al., Detection analysis of phase-contrast X-ray imaging (PCXI) with single grid for nano-scopic applications, Optik 127 (2017) 562–566.
[174] M. Adrian, N. Gerspacha, T. Mojaradb, et al., Glass-based geometry-induced electrostatic trapping devices for improved scattering contrast imaging of nano-objects, Microelectron. Eng. 145 (2015) 43–48.
[175] H. Hung, O.J. Klein, S.W. Peterson, et al., PLGA nanoparticle encapsulation reduces toxicity while retaining the therapeutic efficacy of EtNBS-PDT in vitro, Sci Rep. 6 (2016) 332–334.
[176] D. Duana, K. Fana, D. Zhanga, et al., Nanozyme-strip for rapid local diagnosis of ebola, Biosen.s Bioelectron. 74 (2015) 134–141.
[177] P. Lambe, P. Minakshi, B. Brar, M. Guray, Ikbal, Nanodiagnostics: a new frontier for veterinary and medical sciences, JEBAS 4 (2016) 307–320.
[178] S. Sahaa, J. Gangulyb, S. Palc, et al., Influence of anisotropy and position-dependent effective mass on electro-optic effect of impurity doped quantum dots in presence of Gaussian white noise, Chem. Phys. Lett. 658 (2016) 254–258.
[179] J. Gangulya, S. Sahab, A. Berac, et al., Exploring electro-optic effect and third-order nonlinear optical susceptibility of impurity doped quantum dots: Interplay between hydrostatic pressure, temperature and noise, Opt. Commun. 387 (2017) 166–173.
[180] G. Zheng, F. Patolsky, Y. Cui, et al., Multiplexed electrical detection of cancer markers with nanowire sensor arrays, Nat. Biotechnol. 23 (2005) 1294–1301.
[181] J. Storrs Hall, Nanofuture: What's Next for Nanotechnology? Prometheus Books, Amherst, NY, 2005 ISBN 978-1591022879.
[182] M. Amatatongchaia, W. Sroyseea, S. Chairama, et al., Amperometric flow injection analysis of glucose using immobilized glucose oxidase on nano-composite carbon nanotubes-platinum nanoparticles carbon paste electrode, Talanta 166 (2017) 420–427.
[183] T. Kangkamanoa, A. Numnuama, W. Limbuta, et al., Chitosan cryogel with embedded gold nanoparticles decorated multiwalled carbon nanotubes modified electrode for highly sensitive flow based non-enzymatic glucose sensor, Sens. Actuators Chem. 246 (2017) 854–863.
[184] Y. Zhang, L. Wang, J. Yu, et al., Three-dimensional macroporous carbon supported hierarchical ZnO-NiOnanosheets for electrochemical glucose sensing, J. Alloys Compd. 698 (2017) 800–806.
[185] Technology Review. Drug Store Cancer Tests. Retrieved 2009-10-08. (2005).
[186] Q. Christine, R. Chang, K. Sharna, et al., An overview of recommendations and translational milestones for genomic tests in cancer, Genet. Med. 17 (2015) 431–440, http://dx.doi.org/10.1038/gim.2014.133.
[187] H. Penga, S. Brimijoinb, A. Hrabovskac, et al., Comparison of 5 monoclonal antibodies for immunopurification of human butyrylcholinesterase on Dynabeads: KD values, binding pairs, and amino acid sequences, Chem. Biol. Int. 240 (2015) 336–345.
[188] T. Wang, Y. Zhou, C. Lei, et al., Development of an ingenious method for determination of dynabeads protein A based on a giant magnetoimpedance sensor, Sens. Actuators Chem. 186 (2013) 727–733.
[189] I.K. Herrmann, Nanomagnet-based removal of lead and digoxin from living rats, Nanoscale 5 (2013) 8718–8723.
[190] J.H. Kang, An extracorporeal blood-cleansing device for sepsis therapy, Nat. Med. 20 (2014) 1211–1216.
[191] G. Lunardi, A. Armirotti, M. Nicodemo, et al., Comparison of temsirolimus pharmacokinetics in patients with renal cell carcinoma not receiving dialysis and those receiving hemodialysis: a case series, Clin. Ther. (2009) 1812–1819.
[192] C.C. Berry, A.S.G. Curtis, Functionalisation of magnetic nanoparticles for applications in biomedicine, J. Phys. Appl. Phys. 36 (2003) R198.
[193] J.J. Lee, Synthetic ligand-coated magnetic nanoparticles for microfluidic bacterial separation from blood, Nano Lett. 14 (2014) 1–5.
[194] C.M. Schumacher, Quantitative recovery of magnetic nanoparticles from flowing blood: trace analysis and the Role of Magnetization, Adv. Funct. Mater. 23 (2013) 4888–4896.
[195] C.W. Yung, J. Fiering, A.J. Mueller, et al., Micromagnetic–microfluidic blood cleansing device, Lab Chip 9 (2009) 1171–1177.
[196] I.K. Herrmann, R.N. Grass, W.J. Stark, High-strength metal nanomagnets for diagnostics and medicine: carbon shells allow long-term stability and reliable linker chemistry, Nanomedicine 4 (2009) 787–798.
[197] S. Shepherd, Harvard engineers invented an artificial spleen to treat sepsis, Boston Mag. (2015).
[198] L. Gaurav, A.M. Henslee, F. Behzad, et al., Two-dimensional nanostructure-reinforced biodegradable polymeric nanocomposites for bone tissue engineering, Biomacromolecules 14 (2013) 900–909.
[199] A.M. Gobin, D.P. O'Neal, D.M. Watkins, et al., Near infrared laser-tissue welding using nanoshells as an exogenous absorber, Lasers Surg. Med. 37 (2005) 123–129.
[200] R. Wagner, D.V. Loo, F. Hossler, et al., High-resolution imaging of kidney vascular corrosion casts with nano-CT, Micro Micoana 17 (2010) 215–219.
[201] Nanomedicine; Studies from university of Utah further understanding of nanotechnology, Sci. Lett. (2010).
[202] Y. Lin, Kevin, A. Kwong, et al., Nanoparticles that sense thrombin activity as synthetic urinary biomarkers of thrombosis, ACS Nano. 7 (2013) 9001–9009.
[203] K. Namekawa, S.M. Tokoro, A. Takao, et al., Fabrication of zeolite–polymer composite nanofibers for removal of uremic toxins from kidney failure patients, (2015) 10.1039/C3BM60263J pubs.rsc.org.
[204] M.B. Ignatyev, Necessary and sufficient conditions of nanorobot synthesis, Doklady Math. 82 (2010) 671–675.
[205] Freitas AR. Nanomedicine, Volume IIA: Biocompatibility. (2003). 1-57059-700-6.
[206] R. Kurzweil, The Singularity Is Near, Viking Press, New York City, 2005 I 978-0-670-03384-3.
[207] T.A. Faunce, Nanotherapeutics: new challenges for safety and cost-effectiveness regulation in Australia, Med. J. Aust. 186 (2007) 189–191.
[208] A. Seaton, K. Donaldson, Nanoscience, nanotoxicology, and the need to think small, Lancet 365 (2005) 923–924.
[209] J.P. Ryman-Rasmussen, J.E. Riviere, N.A. Monteiro-Riviere, Penetration of intact skin by quantum dots with diverse physicochemical properties, Toxicol. Sci. 91 (2006) 159–165.
[210] A.D. Maynard, Nanotechnology: assessing the risks, Nano Today 1 (2006) 22–33.
[211] Australian Safety, Compensation Council, A Review of the Potential Occupational Health and Safety Implications of Nanotechnology. Report for the Department of Employment and Workplace Relations. Adelaide: Flinders Consulting, (2006) http://www.ascc.gov.au.
[212] T. Xia, M. Kovochich, J. Brant, et al., Comparison of the abilities of ambient and manufactured nanoparticles to induce cellular toxicity according to an oxidative stress paradigm, Nano Lett. 6 (2006) 1794–1807.
[213] A. Penn, G. Murphy, S. Barker, et al., Combustion-derived ultrafine particles transport organic toxicants to target respiratory cells, Environ. Health Perspect. 113 (2005) 956–963.
[214] H. Vallhov, J. Qin, S.M. Johansson, et al., The importance of an endotoxin-free environment during the production of nanoparticles used in medical applications, Nano Lett. 6 (2006) 1682–1686.
[215] J. Lademann, H. Weigmann, C. Rickmeyer, et al., A Review of the Scientific Literature on the Safety of Nanoparticulate Titanium Dioxide or Zinc Oxide in Sunscreens, Australian Government, 2006.
[216] P. Takhar, S. Mahant, *In vitro* methods for nanotoxicity assessment: advantages and applications, Arch. Appl. Sci. Res. 3 (2011) 389–403.
[217] B.J. Crielaard, T. Lammers, R.M. Schiffelers, et al., Drug targeting systems for inflammatory disease: one for all, all for one, J. Control. Release 161 (2012) 225–234.
[218] A.M. Nystrom, B. Fadeel, Safety assessment of nanomaterials: implications for nanomedicine, J. Control. Release 161 (2012) 403–408.
[219] Y. Yang, K. Wang, G. Xiaosong, et al., Biophysical regulation of cell behaviour-cross talk between substrate stiffness and nanotopography, Engineering 3 (2017) 36–54.
[220] K. Wang, H. Xiaoqing, W. Linthicum, et al., Carbon nanotubes induced fibrogenesis on nanostructured substrates, Environ. Sci. Nano. 4 (2017) 689–699.
[221] L. Song, K. Wangb, L. Yan, et al., Nanotopography promoted neuronal differentiation of human induced pluripotent stem cells, Colloids Surf. B: Biointerfaces 148 (2016) 49–58.
[222] K. Wang, A. Bruce, R. Mezan, et al., Nanotopographical modulation of cell function through nuclear deformation, ACS Appl. Mater. Interfaces 8 (2016) 5082–5092.
[223] Dorbeck-Jung BR, N. Chowdhury, Is the European medical products authorisation regulation equipped to cope with the challenges of nanomedicines? Law Policy 33 (2011) 276–303.
[224] M.A. Dobrovolskaia, S.E. McNeil, Understanding the correlation between in vitro and *in vivo* immunotoxicity tests for nanomedicines, J. Control. Release 172 (2013) 456–466.
[225] F. Ehmann, K. Sakai-Kato, R. Duncan, et al., Next-generation nanomedicines and

nanosimilars: EU regulators' initiatives relating to the development and evaluation of nanomedicines, Nanome 8 (2013) 849–856.
[226] R. Gaspar, R. Duncan, Polymeric carriers: preclinical safety and the regulatory implications for design and development of polymer therapeutics, Adv. Drug Deliv. Rev. 61 (2009) 1220–1231.
[227] International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use q8, pharmaceutical development, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Tripartite Guideline, ICH, Geneva, 2009.
[228] R. Gaspar, Therapeutic products: Regulating Drugs and Medical Devices, p. 291À320 Edward Elgar Publishing, 2010.
[229] R. Bawa, Nanoparticle-based therapeutics in humans: a survey, Nanotechnol. L. Bus. 5 (2008) 135–155.
[230] V. Morigi, A. Tocchio, C. Bellavite, et al., Nanotechnology in medicine: from inception to market domination, J. Drug Deliv. (2012) 1–7.
[231] K. Dhama, M. Mahendran, S. Tomar, S. Nandi, Nanotechnology and its applications in biomedicine, biotechnology and animal health, Livest. Line 2 (2008) 21–26.
[232] P. Mohapatra, R.K. Swain, S.K. Mishra, T. Behera, P. Swain, N.C. Behura, G. Sahoo, K. Sethy, B.P. Bhol, K. Dhama, Effects of dietary nano-selenium supplementation on the performance of layer grower birds, Asian J. Anim. Vet. Adv. 9 (2014) 641–652.
[233] P. Mohapatra, R.K. Swain, S.K. Mishra, T. Behera, P. Swain, S.S. Mishra, N.C. Behura, S.C. Sabat, K. Sethy, K. Dhama, P. Jayasankar, Effects of dietary nano-selenium on tissue selenium deposition, antioxidant status and immune functions in layer chicks, Int. J. Pharmacol. 10 (2014) 160–167.
[234] R. Khandia, A.K. Munjal, R.S. Bangrey, R. Mehra, K. Dhama, N.C. Sharma, Evaluation of silver nanoparticle mediated reduction of neovascularisation (angiogenesis) in chicken model, Adv. Anim. Vet. Sci. 3 (2015) 372–376.
[235] H.M. Iqbal, M.V. Angel, Rodriguez, R. Khandia, A. Munjal, K. Dhama, Recent trends in nanotechnology-based drugs and formulations for targeted therapeutic delivery, Recent Pat. Inflamm. Allergy Drug Discov. 10 (2016) 86–93.
[236] M.E.A. El-Hack, M. Alagawany, M.R. Farag, M. Arif, M. Emam, K. Dhama, M. Sarwar, M. Sayab, Nutritional and pharmaceutical applications of nanotechnology: trends and advances, Int. J. Pharmacol. 13 (2017) 340–350.
[237] M. Gopi, B. Pearlin, R.D. Kumar, M. Shanmathy, G. Prabakar, Role of nanoparticles in animal and poultry nutrition: modes of action and applications in formulating feed additives and food processing, Int. J. Pharmacol. 13 (2017) 724–731.
[238] R. Raghav, R. Painuli, D. Kumar, Multifunctional nanomaterials for multifaceted applications in biomedical arena, Int. J. Pharmacol. 13 (2017) 890–906.
[239] S.R.M. Sayed, A.H. Bahkali, M.M. Bakri, A.H. Hirad, A.M. Elgorban, M.A. El-Metwally, Antibacterial activity of biogenic silver nanoparticles produced by Aspergillus terreus, Int. J. Pharmacol. 11 (2015) 858–863.
[240] B.J. Stephen, M. Jain, K. Dhama, S.V. Singh, M. Datta, N. Jain, S. Jayaraman, M. Singh, K.K. Chaubey, S. Gupta, G.K. Aseri, N. Khare, P. Yadav, J.S. Sohal, Nanotechnology based therapeutics, drug delivery mechanisms and vaccination approaches for countering *Mycobacterium avium* subspecies *paratuberculosis* (MAP) associated diseases, Asian J. Anim. Vet. Adv. 10 (2015) 830–842.
[241] M. Bilal, T. Rasheed, H.M.N. Iqbal, H. Hu, X. Zhang, Silver nanoparticles: Biosynthesis and antimicrobial potentialities, Int. J. Pharmacol. 13 (2017) 832–845.
[242] P.R. Raghavan, *In vitro* inhibition of Zika virus by Metadichol®, a novel Nano emulsion lipid, J. Immunol. Technol. Infect. Dis. 5 (2016) 4.
[243] A. Munjal, R. Khandia, K. Dhama, S. Sachan, K. Karthik, R. Tiwari, Y.S. Malik, D. Kumar, R.K. Singh, H.M.N. Iqbal, S.K. Joshi, Advances in developing therapies to combat zika virus: current knowledge and future perspectives, Front. Microbiol. 8 (2017) 1–19.
[244] Y. Matsumura, H. Maeda, A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs, Cancer Res. 46 (1986) 6387–6392.
[245] L.E. Gerlowski, R.K. Jain, Microvascular permeability of normal and neoplastic tissues, Microvasc. Res. 31 (1986) 288–305.
[246] A. Gabizon, H. Shmeeda, Y. Barenholz, Pharmacokinetics of pegylated liposomal doxorubicin, Clin. Pharm. 42 (2003) 419–436.
[247] N.J. Robert, C.L. Vogel, I.C. Henderson, et al., The role of the liposomal anthracyclines and other systemic therapies in the management of advanced breast cancer, Semin. Oncol. 31 (2004) 106–146.