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Review

Recent trends of nanomedicinal approaches in clinics

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ABSTRACT

Nanotechnology has become the indispensable cutting edge science providing solutions to many problems associated with human being. The application of nanotechnology associated to human health "nanomedicine" has revolutionized the drug delivery system by providing improved pharmacological and therapeutic properties of drugs. These advantageous effects of drug loaded nanocarrier systems are embraced by the pharmaceutical industries for the development of different effective nanocarriers. Currently, several drug loaded nanoformulations are approved by the Food and Drug Administration (FDA), and some of them are undergoing clinical trials for the human use. In this review, we have discussed the progress achieved so far for various drug loaded nanoformulations along with few emerging nanoformulations that are about to enter into clinical trials.

1. Introduction

Nanotechnology is a multidisciplinary field which amalgamates science and engineering for the creation of material or system in the nanometer (nm) scale at the level of atom, molecules, and its macromolecular structure (Sahoo and Labhasetwar, 2003; Whitesides, 2005). The prefix "nano" is derived from the Greek word "dwarf". One nm is equal to one-billionth of a meter, which is also about the width of six carbon atoms or group of ten water molecules. The physics and chemistry of bulk materials behave differently in terms of strength, conductivity and reactivity when they are reduced to nanoscale. The application of nanotechnology has been wide spread and much integrated to human health. Various developed nanomaterials are making their ways into our lives in the pharmaceutical and medical applications. For an instance, currently there is no cure and preventive measures for HIV/AIDS but with the help of advancement of nanotechnology various treatment options are now emerging (Mamo et al., 2010). Similarly, cancer and tuberculosis top the list of dreaded diseases in developing countries and with utilization of nanotechnology based formulations tremendous progress towards therapeutic efficacy against these diseases has been achieved (da Silva et al., 2016; Hare et al., 2017). Nowadays, nanotechnology is extensively used in consumer goods, vehicle manufacturers, cosmetic industry, military products etc. For example, in sunscreen lotion, nanoparticles of titanium dioxide and zinc oxide are used which act as a reflector of the harmful sun rays (Newman et al., 2009). Nanotechnology has also varied application in the food industry where various polymers are actively used for the improved food packaging. Recently, polymer nanocomposites (like silica nanoparticles, silicate nanoplatelets, carbon nanotubes, graphenes, starch nanocrystals, chitosan nanoparticles etc.) are the latest materials created which provides flame resistance, better thermal property for enhancing the shelf-life and durability of the packaged food (Duncan, 2011). Similarly, silver nanoparticles are also used owing to their broad spectrum antimicrobial property in food storage bins for safeguarding against food spoilage due to microbial growth (Rhim and Ng, 2007). In textile industry, clay nanoparticles are incorporated in nylon fabrics for the flame retardant property. The nanosilica along with maleic anhydride acts as catalyst for the improvement of wrinkle resistance of silk (Song et al., 2001). Nanocomposite fibers such as, graphite nanofibers, single-wall and multi-wall carbon nanotubes (CNTs), nanosilicates and metal oxide nanoparticles are extensively used in automotive, aerospace and military applications (Schnorr and Swager, 2010). The nanocomposite fibres are evenly distributed in polymer matrix which increases the toughness and makes it abrasion resistant (Sennett and Welsh, 2003). Apart from that, novel CNTs are also developed for multifunctional textiles for providing superior strength, light weight with high electrical conductivity (Schnorr and Swager, 2010). Cerium oxide nanoparticles have been effectively used in advanced technologies as catalytic agent, solid oxide fuel cells, oxygen sensor, high-temperature oxidation protection material and as a component in solar cells (Asati et al., 2009; Martínez-Arias et al., 2005). Besides the commercial application of nanotechnology, this upcoming branch of science has also made its impact in environmental application. The futuristic application of nanotechnology to the environment i.e. "Green Nanotechnology" envisages sustainability to address global issues like energy shortages, scarcity of clean water, and many other

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allied areas (Goel and Bhatnagar, 2014). Green nanotechnology uses the principles of green chemistry, green engineering and industrial ecology to make eco-friendly nanomaterials without toxic ingredients and consumes less energy during the manufacturing process (Goel and Bhatnagar, 2014). Over the years, the promising field of nanotechnology has evolved tremendously exhibiting huge potentialities in diverse areas including human health sector (Sahoo et al., 2007). Nanotechnological application in the field of medical sciences and diagnostics focuses on a major aspect regarding the proper delivery of drugs, diagnostic agents and different therapeutic agents inside the body (Sahoo and Labhasetwar, 2003).

Introduction of nanotechnology has revolutionized the drug delivery aspect towards the therapy and diagnostic under the arena of nanomedicine. The term “nanomedicine” has been coined for the applications of nanotechnology for the treatment, diagnosis and monitoring of disease related to human health (Rizzo et al., 2013). Nanotechnology based approaches provide an opportunity to design novel formulations for the major benefit towards healthcare setting. Nanotechnology scientists are continuously developing pharmaceutical products for different diseases imposing significant impact on current practice of medicine, which in turn enhances patient’s quality of life (Rizzo et al., 2013). Nanotechnological platforms improves drug delivery that are based on several factors of manoeuvring like aqueous solubility, high surface area, control of particle size, biocompatibility, stealth property, target specificity, controlled release etc. (Moghimi et al., 2005; Sahoo and Labhasetwar, 2003). These unique characteristic features of the nanocarriers provide higher therapeutic efficacy, extended plasma half life that lowers the frequency of administration and creates an opportunity to deliver two or more drugs simultaneously as a combination therapy inducing the synergetic effect. Such modality can overcome the shortcomings of the monotherapy by acting upon diverse signaling pathways as well as suppressing multi-drug resistance for an effective therapy (Parhi et al., 2012). According to the market research report of business communication company (BCC) the estimated global nanomedicine market has reached $63.8 billion in 2010 and $72.8 billion in 2011 (Fontaine et al., 2012). With passage of time, several discoveries are continuing in the areas of nanomedicine. Various pharmaceutical companies and academic researchers across the world are exploring this new strategies as an advantageous step for the drug delivery systems (DDS) (Hafner et al., 2014) .If this trend continues then the global nanomedicine market will exhibit a compound annual growth rate (CAGR) of 12.5% between 2015 and 2023 according to the transparency market research .

Over the last two decades, large number of nanomedicines have received regulatory approval as therapeutic and diagnostic agents for the treatment of different cancers (solid tumors and haematological malignancies) and other diseases like; asthma, pain, allergy, infection, high cholesterol, autoimmune disease, fungal infections, macular degeneration, hepatitis etc. (Brannon-Peppas and Blanchette, 2004; Kawasaki and Player, 2005). The approved nanotherapeutics products enlisted in Food and Drug Administration (FDA) agency of United States of America or other related foreign agencies, provide tremendous hope for betterment of human health care. Further ongoing developed nanotechnological products, which are under preclinical and clinical trials are entering the pipeline for venturing into the pharmaceutical market. Looking at the enormous scope of nanomedicine, this review mainly focuses on the developed nanocarriers for drug delivery, gene delivery and diagnostic applications of human health.

2. Role of nanotechnology in clinical application

Drug delivery phenomenon is a challenging aspect of pharmaceutical sciences, where the pharmaceutical drug molecules face numerous challenges after being delivered either parenteral or through an oral route of administration. Post administrations in body, native drugs are subjugated to wide spectrum of internal harsh conditions. Further, presence of different physiological/biological barriers results in suboptimal concentration of the administered drug at the disease site contributing its low efficacy (De Jong and Borm, 2008). The internal physiological condition such as pH, enzymes and intestinal epithelial barriers mostly regulates the intrinsic concentration of the native drug (Parveen and Sahoo, 2008). In this context it has become crucial to devise strategies for the optimal actions of the therapeutics leading to their clinical effectiveness. Drug delivery and related pharmaceutical progress in the milieu of nanomedicine have emerged as the front runners in providing a safe and effective delivery system (Moghimi et al., 2005; Parveen et al., 2012). Basically, the primary objectives of nanoformulations in drug delivery include: (1) precision in targeting and delivering the drug at desired site (2) biocompatibility (3) diminution in toxicity to the normal cells at the same time maintaining therapeutic effectiveness at the desired site (De Jong and Borm, 2008). The engineered nanoformulations increase the aqueous solubility and shield the encapsulated drug thereby preventing its untimely degradation owing to harsh physiological conditions, this elevates the plasma half life of the drug and that in turn regulates their activity. Moreover, the ability of these drug carriers to demonstrate a sustain release phenomena contributes in providing an optimal concentration of drug at disease site in a sustained release manner which prevents the administration of elevated dosages of drug that in turn regulates high toxicity. Additionally, the prospect of site specific release by nanocarriers prevents nonspecific delivery at healthy sites that contributes in regulating toxicity (Fig. 1).

Currently, with the emergence of nanotechnology, different novel drug delivery carriers were developed with the help of biocompatible and biodegradable materials that can significantly be supportive in clinical application (Kayser et al., 2005; Parveen and Sahoo, 2006). In the domain of drug delivery, two different ways (i.e. passive targeting and active targeting) are explored by which the formulated nanoparticles reach the diseases’ sites (Fig. 2). Passive targeting takes the advantage of the inherent size of the nanoparticles and exploits the unique anatomical and pathophysiological abnormalities of tumor vasculature for delivery of payload at requisite site. The nanoparticulate carriers are endocytosed and retained in the tumor tissues by exploiting the hyperpermeable tumor vasculature and impaired lymphatic drainage system resulting in “enhanced permeation and retention (EPR) effect (Acharya and Sahoo, 2011). However, in order to utilize the physio-pathological and anatomical peculiarities of the tumor tissues, the nanocarriers necessitate prolonged circulation in the blood stream. The durability in the bloodstream of nanocarriers is affected by interactions with specific blood circulating components identified as opsonins that results in a conformational rearrangements that induced detection by mononuclear phagocytic system (MPS), through specific membrane receptors (Salmaso and Caliceti, 2013). Thus, surface opsonisation promotes removal of particles from the circulation which may reduce the availability of the drug at the desired site. To bypass the MPS, most passive targeting nanocarriers are surface coated with polyethylene glycol (PEG) a process called PEGylation, for providing “stealth” property (Davis, 2002). Coating of PEG onto nanocarriers reduces the adhesion of opsonins on the nanoparticles making them invisible to phagocytic cells and hence their clearance from blood circulation is evaded (Salmaso and Caliceti, 2013). At present although most clinical trials for anticancer therapy rely on passive targeting, due to its limitation another strategy is being developed to maximize the accumulation of nanoparticles at the preferred site of interest. In order to exploit the increased accumulation of nanoparticles at the diseased site, “active targeting” is adapted that is based on specific ligand-receptor recognition type of delivery (Figure-2). Receptors utilized in this modality are particularly over-expressed in the tumors or diseased tissues while the ligands for specific receptors are conjugated onto the nanoparticulate formulations. Following recognition by receptors on specific cells, these ligand conjugated nanocarrires are endocytosed by receptor mediated endocytosis (Das et al., 2009; Torchilin, 2007), that

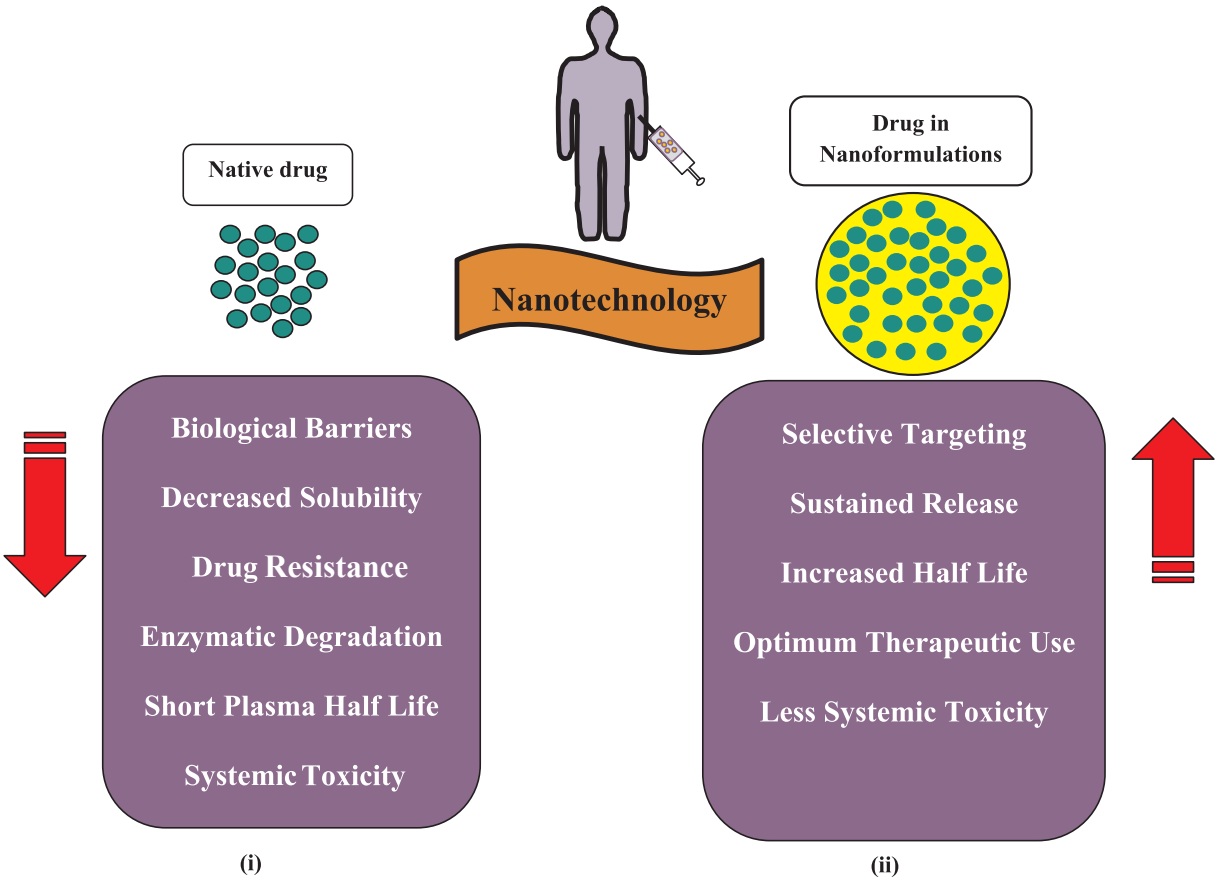

Fig. 1. (i) Hurdles faced by the native drug after systemic administration. (ii) Impediments faced by native drug are surpassed by drug in nanoformulations leading to optimum therapeutic efficiency.

are available at the desired location. The enormous well-known benefit of active targeting has resulted in some clinically validated nanoproducts till date. Moreover, stimuli-responsive and triggered release is another modified form of active targeting wherein, the encapsulated payload is released through a trigger present in the disease site, thus minimizing the risk of systemic exposure to healthy tissue (Wang et al., 2014). Triggering is a stimuli-dependent phenomenon; development of suitable initiators plays a key role in the release of encapsulated contents in sustained manner. Many methods are used to trigger the release of encapsulated contents which can be categorized into internal (pathophysiological/patho-chemical condition) and external (physical stimuli such as temperature, light, ultrasound, magnetic force and electric fields) stimuli thus enhancing the therapeutics in a site-specific manner (Fig. 2). Such a regime of drug delivery evokes greater spatial and temporal control in the therapy by controlling the phase, structure, configuration and other characteristics which can be changed under certain *in vivo* or *in vitro* stimulus (Esser-Kahn et al., 2011). Stimuli-responsive drug release not only reduces premature drug release but also improves drug release efficiency at target sites (Fig. 2). Moreover, stimuli-responsive drug alters drug bio distribution, reduces toxicity while improving therapeutic outcomes due to the ability to deliver therapeutic doses of drug at the site of interest (Esser-Kahn et al., 2011). Despite many advances that have been accomplished, the field of stimuli-responsive triggered release of nanoformulations still faces many challenges, one of which includes dependency upon a single type of stimulus for triggered release (You et al., 2010). In this context, developing a material that is responsive to more than one stimulus may become beneficial for drug delivery along with diagnosis and imaging.

3. Range of nanoformulations in clinical platforms

Various type of nanoparticulate formulations have been developed as a potential strategy to deliver the drugs, recombinant proteins and nucleotides etc (Fig. 3). In the following section different categories of nanoparticulate carriers and their applications in therapy has been discussed.

4. Pegylated proteins, polypeptides and polymeric nanoformulations

Polyethylene glycol (PEG) is a water soluble macromolecule, which can be used for numerous applications in drug delivery formulations. It is often considered as a gold standard polymer for different biological applications owing to its higher solubilising ability, easy end group modifications, low intrinsic toxicity and higher physical and thermal stability to the encapsulated drugs (Parveen and Sahoo, 2006). In fact, protection of encapsulated drugs by PEG can be attributed to its ability to form “conformational cloud”. Conformational cloud is mostly generated by the flexible PEG polymer chains which posses the capability of forming many different conformations as it switches from one conformation to another which shields the drug molecules against interaction with blood components or opsonization followed by uptake by the reticuloendothelial system. This activity in turn lowered interaction of PEG with body components results in its low immunogenicity and antigenicity.

The polymer based drug delivery specifically includes polymeric drugs, polymer-drug conjugates, polymer-protein conjugates and polymeric non-viral vectors, macromolecular drug conjugates, aptamer conjugated nanoformulations, which are approved by FDA for different

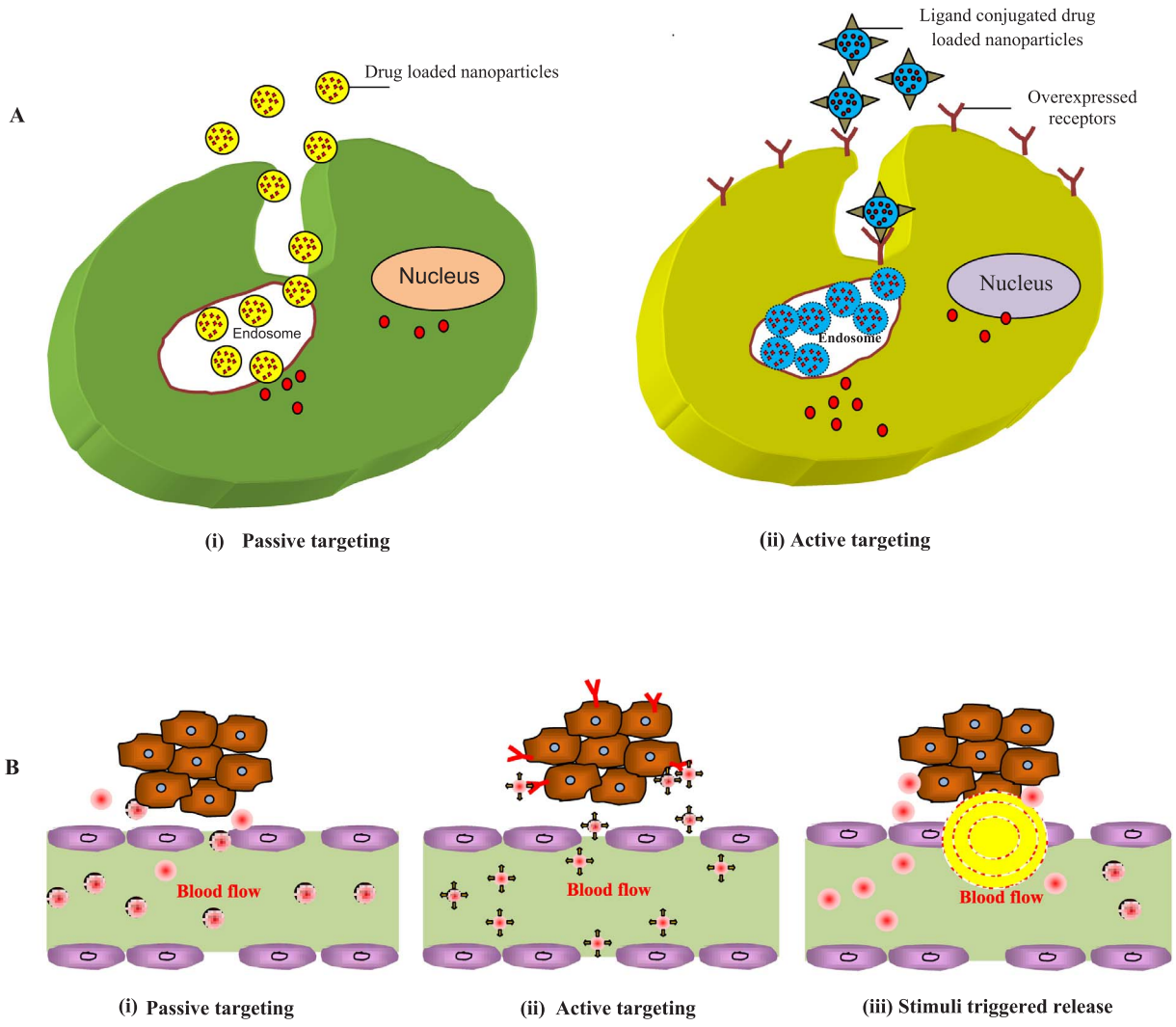

Fig. 2. Schematic depiction of mode of cellular uptake of nanoformulations in cells; A (i) Passive targeting exploits the morphological anomalies of the diseased/tumor cells for accumulation of drug loaded nanoparticles by endocytosis. (ii) Active targeting utilizes recognition of ligand conjugated drug loaded nanoformulation by overexpressed receptor present in the surface of cells for site specific delivery by receptor mediated endocytosis, B (i) Extravasation of drug loaded nanoparticles through fenestrated blood vessels leading to passive targeting towards diseased/ tumor tissues. (ii) With the help of functionalized ligands, drug loaded nanoparticles extravasates through fenestrated blood vessels and reached the diseased/ tumor tissues in great numbers, (iii) Designed stimuli responsive drug loaded nanocarriers can pass through fenestrated blood vessels and release it either by internal stimuli or external trigger.

diseases are summarized in Table 1. Wicki et al., have extensively discussed about the developed nanoformulations that are under different phases of clinical trials (Wicki et al., 2015).

5. Nanoparticulate formulations: An overview

5.1. Nanoparticles

Polymeric nanoparticles consist of nanosized solid particles made up with natural or synthetic polymers, in which the drug is encapsulated, adsorbed or conjugated to the constitutive polymer. The drug can release from the nanoparticles either by the process of diffusion or degradation of the polymeric matrix. Owing to the advantages of nanoparticles, research has always focused on translating these nanoparticles towards clinical use. One of the polymeric nanoparticles based product in the market for the treatment of various cancers is albumin protein bound paclitaxel formulation (Abraxane®). After intravenous administration, the nanoparticles rapidly dissociates into soluble albumin bound complexes which is readily bio -available and is swiftly transported throughout the body without the risk of capillary blockage to the tumor sites using endogenous albumin pathway (Desai et al., 2006). BIND-014, a tumor prostate-specific membrane antigen (PSMA)–targeted nanoparticles (containing docetaxel) formulation has garnered attention in the field of cancer therapy. Von Hoff et al., have evaluated the clinical outcome of the above formulation in different cancer patients and it was found to have shown super anticancer activity in multiple cancer types (Von Hoff et al., 2016). The results of phase I trial of BIND-014 support its further investigation in phase II studies, which are currently ongoing.

5.2. Micelles

Polymeric micelles are self assemblance of amphiphilic polymers having the hydrophobic segment towards the core and hydrophilic segments on the outer shell for the suitable encapsulation of the hydrophobic drugs. Micelles have been extensively used as a carrier for

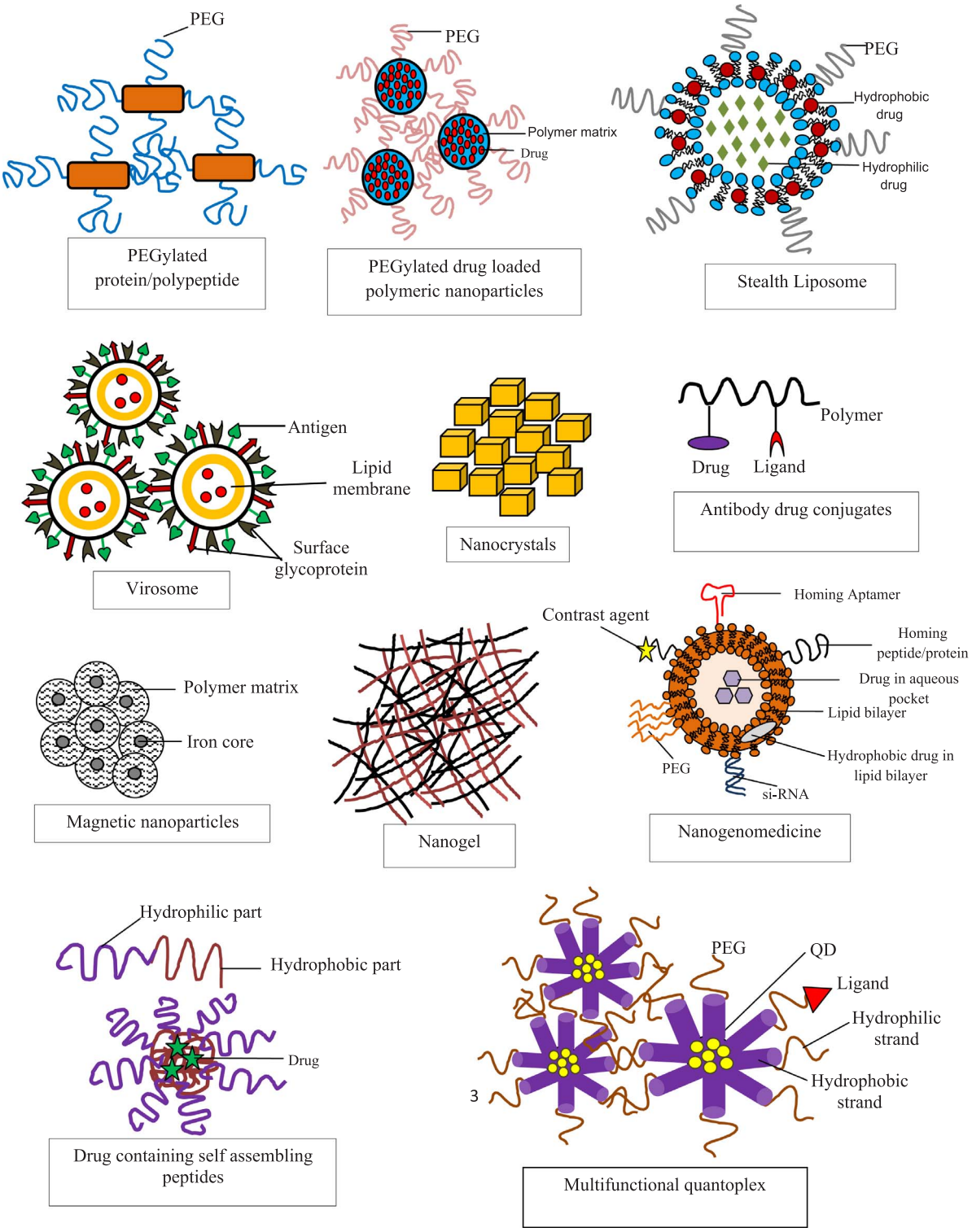

Fig. 3. Schematic representation of various nanoformulations based drug delivery system in clinical use. PEGylated protein is the attachment or amalgamation of polyethylene glycol (PEG) polymer chains to protein molecules or macrostructures and polymeric nanoparticles. Modification of liposome with PEG polymer yields "stealth" liposomes in which the hydrophobic drugs can be entrapped in the lipid layer whereas hydrophilic drugs can be entrapped in the core. Virosomes are lipid based synthetic vehicle composed on viral surface glycoproteins to which drugs can be encapsulated and ligands can be conjugated. Nanocrystals are absolute drug nanocrystals without any carrier material. Antibody-drug conjugates are formed when drug is coupled to antibody using polymer as a linker. Magnetic nanoparticles are iron oxide nanoparticles coated with polymeric matrix, where the drug can be entrapped and ligand can be conjugated. Nanogels are crosslinked polymeric network where drug molecules can be entrapped in the polymeric matrix. Nonviral polymeric vehicle known as "nanogenomedicine" are capable of delivery of gene/si-RNA/peptide/contrast agent along with drugs. Self-assembling peptides undergo spontaneous assembly to form ordered nanostructures where drug can be encapsulated. Multifunctional quantum dot (QD) encapsulated nanocarriers "quantoplex" are capable of realtime imaging.

anticancer therapy; some of them are currently used in preclinical or clinical development. A polymeric micellar formulation of paclitaxel (Genexol-PM®) illustrated superior cytotoxic activity against various human cancer cells e.g. breast, colon, ovarian and non-small cell lung cancer compared to Taxol®. Due to this better efficacy, Genexol-PM® has been approved in South Korea for breast and non-small cell lung

Table 1
Various PEGylated proteins, polypeptides, polymer based, aptamers conjugated nanoformulations; partly adapted from reference van der Meel and Hennik (2017), Weissig et al. (2014).

Nanoformulations (Trade name/generic name)	Drug/Active agent	Indications	Approval
PEGYlated proteins, polypeptides nanoformulations			
Adagen® (Pegademase bovine)	PEGylated adenosine deaminase	Enzyme replacement therapy for treatment of severe combined immunodeficiency disease (SCID) associated with deficiency of adenosine deaminase	FDA 1990
Cimzia® (Certolizumab pegol)	PEGylated anti-tumour necrosis factor–alpha (TNF-α)	Treatment of Crohn's disease, rheumatoid arthritis, psoriatic arthritis	FDA 2008
Neulasta® (Pegfilgrastim)	PEGylated recombinant methionyl human granulocyte colony-stimulating factor	Reducing neutropenia of cancer patients	FDA 2002
Oncaspar® (Pegaspargase)	PEGylated L-asparaginase	Treatment of acute lymphoblastic leukemia	FDA 1994
Pegasys® (Peginterferon alfa-2a)	PEGylated interferon	Treatment of chronic hepatitis B and C	FDA 2002
PegIntron® (Pegylated interferon alfa-2b)	PEGylated interferon	Treatment of hepatitis B and C	FDA 2001
Somavert® (Pegvisomant)	PEGylated human growth hormone mutein antagonist	Treatment of acromegaly	FDA 2003
Omontys® (Peginesatide)	PEGylated synthetic peptide mimicking the structure of erythropoietin	Treatment of anemia associated with chronic kidney disease	FDA 2013
Movantik® (Naloxegol) (Methoxy capped heptaethylene glycol conjugated to naloxol)	PEGylated naloxol	Treatment of opioid-induced constipation in patients with chronic non-cancer pain	FDA 2014
Krystexxa® (Pegloticase)	PEGylated recombinant porcine-like uricase	Treatment of severe chronic gout	FDA 2010
Mircera® (Methoxy polyethylene glycol-epoetin beta)	PEGylated form of erythropoetin	Treatment of anemia associated with chronic renal failure	FDA 2007
PLEGRIDY™	PEGylated form of interferon beta-1a	Treatment of people with relapsing forms of multiple sclerosis	FDA 2014
Adynovate® Antihemophilic Factor (Recombinant)	PEGylated antihemophilic factor VIII	Treatment of hemophilia A patient	FDA 2015
Polymeric Nanoformulations			
Copaxone® (Glatiramer acetate)	Random polymer composed of four amino acids found in myelin basic protein	Immunomodulator drug for treatment of multiple sclerosis	FDA 2002
Genexol-PM® Methoxy-PEG-poly (D, L-lactide) taxol	Copolymeric micellar formulation of paclitaxel	Treatment of metastatic breast cancer, pancreatic cancer	South Korea 2006, Phase-III trials in US
Renagel® (Sevelamer Hydrochloride)	Sevelamer consists of polyallylamine that is crosslinked with epichlorohydrin	Treatment of hyperphosphatemia	FDA 1998
Renvela® (Sevelamer Carbonate)	Sevelamer consists of polyallylamine that is crosslinked with epichlorohydrin	Treatment of hyperphosphatemia	FDA 2007
Zinostatin stimalamer®	Copolymer of styrene-maleic acid and an antitumor protein neocarzinostatin	Treatment of primary hepatocellular carcinoma	Japan 1994
Abraxane®	Albumin bound paclitaxel	Treatment of advanced breast, non-small-cell-lung and pancreatic cancer	FDA 2005
BIND-014	Poly (styrene-alt-maleic acid)-Docetaxel	Treatment of squamous cell non-small cell lung cancer	NCT02283320 (Phase II) Completed
Aptamer nanoformulations			
Macugen® (Pegaptanib)	PEGylated anti VEGF aptamer	Treatment of neovascular age related macular degeneration	FDA 2004

cancers and is currently undergoing Phase III trials in the US (Table 1).

6. Liposomal formulations

Liposomes are self-assembling structures composed of a lipid bilayer that entirely surrounds an aqueous core and are able to deliver different kind of hydrophobic drugs and biomolecules (Allen and Cullis, 2004). Liposomes have become the first nanomedicine delivery system to build the transition from concept to clinical application. The pioneering work of numerous liposome researchers led to emergence of technical advancements in developing different type of liposomes (PEGylated liposomes or triggered release liposomes or liposomes containing nucleic acid polymers or ligand-targeted liposomes or drug loaded liposomes) which have proved successful in numerous clinical trials as delivery vehicles of many anti-cancer, anti-fungal and antibiotic drugs, gene medicines, and anti-inflammatory drugs (Allen and Cullis, 2013). Release of the drug has an important implication in therapeutic activities and the drug entrapped in liposomes becomes bioavailable only when it is released from the system to have optimum therapeutic activity (Allen and Cullis, 2004). Development of liposomal drugs preferably alters the pharmacokinetics (PK) of the native drug. Quite a few anticancer drug loaded liposomes are in clinical domain among which the first PEGylated liposomal formulations of doxorubicin (Doxil®) is approved by FDA for treatment of Kaposi's sarcoma, ovarian cancer, multiple myeloma, metastatic breast cancer. Besides this some other liposomal formulation are summarized in (Table 2). Various developed nanoformulations which are currently under phase-1 or phase-II or phase-III trials are extensively discussed (Wicki et al., 2015).

Table 2
Various liposomal nanoformulations; partly adapted from reference (van der Meel and Hennik, 2017; Weissig et al., 2014).

Nanoformulations (Trade name/generic name)	Drug/Active agent	Indication	Approval
Doxil® (PEGylated liposomal doxorubicin)	Doxorubicin hydrochloride	Treatment of kaposi sarcoma, multiple myeloma, ovarian cancer	FDA 1995
Myocet® (Non-pegylated doxorubicin)	Doxorubicin hydrochloride	Treatment of metastatic breast cancer	European Union 2000
DaunoXome® (Liposomal daunorubicin)	Daunorubicin citrate	Treatment of Kaposi sarcoma	FDA 1996
AmBisome® (Fungizone)	Amphotericin B	Treatment of systemic fungal infections	FDA 1997
DepoCyt® (Cytarabine liposome)	Cytarabine	Treatment of lymphomatous malignant meningitis	FDA 1999/2007
DepoDur®	Morphine sulfate	Treatment of post surgical pain	FDA 2004
Mepact® (Muramyl tripeptide phosphatidyl-ethanolamine)	Mifamurtide	Treatment of non-metastatic osteosarcoma	European Union 2009
Marqibo® (Vincristine liposomal)	Vincristine sulfate	Treatment of acute lymphoid leukemia	FDA 2012
Onyvide® (Liposomal formulation)	Irinotecan	Advanced (metastatic) pancreatic cancer	FDA 2015
Vyxeos™ (Liposomal formulation)	Cytarabine and daunorubicin	Treatment of acute myeloid leukemia	FDA 2017
CPX-1 (Liposomal formulation)	Irinotecan HCL and floxuridine	Advanced colorectal carcinoma	NCT00361842 (Phase II) Completed
ThermoDox® (Thermosensitive liposomal formulation)	Doxorubicin	Hepatocellular carcinoma	NCT02112656 (Phase III), Recruiting
MM-302 (Antibody liposomal drug conjugate)	Antibody (HER2) and Doxorubicin	Advanced HER2 positive breast cancer	NCT02213744 (Phase III) active

7. Antibody drug conjugates

Conjugates of small molecular drugs with antibody are known as antibody drug conjugates (ADC), that are used as a new class of targeted therapeutics for the treatment of cancer and other diseases (Duncan, 2006). ADCs not only prolong the *in vivo* circulation time from several minutes to several hours, but also reduce cellular uptake to the endocytic route which enhances passive delivery of drugs to the diseased tissues (Duncan, 2006). Although the benefit of active targeting is well-known, therapeutic antibody in the form of ADC is conceptualized to deliver cytotoxic drugs directly to the tumor cells. There are also antibodies, which are highly specific to cancer antigen but lack therapeutic effect. For the use of therapeutic purpose, the chosen antibody should be able to avoid aggregation as well as maintain the stability and affinity for targets upon conjugation. The discussed ADCs are enlisted in (Table 3). Other developed ADCs currently under phase-1 or phase-II or phase-III clinical trials are extensively discussed elsewhere (van der Meel and Hennik, 2017; Wicki et al., 2015).

8. Virosomes as nanoparticle

Virosomes are the liposomal carrier for delivery of drugs or vaccines comprising of viral surface glycoproteins, viral lipids without their genetic material (Yoo et al., 2011). These viral peplomers (glycoprotein spike of viral envelope) support the recognition and attachment to its specific target. The central cavity of the virosome can accommodate variety of therapeutic agents including drug molecules, nucleic acids and proteins. The viral lipid bilayer and glycoproteins play an important role in the homogeneity, structural stability, targeting and prevent the carrier from the adverse biological reactions in the body. For the vaccine and drug delivery purposes, the surface glycoproteins of influenza virus, hepatitis viruses and vesicular stomatitis virus have been successfully incorporated (Babar et al., 2012). With the advent of such modality, researchers focused on application of these drug delivery vehicles in clinical settings which led to development of many virosome based nanoproducts. Rexin-G is the first genetic medicine for cancer, which consists of retro vector bearing a construct of cytocidal cyclin G1 for targeted gene therapy. The virosomal nanoparticle formulation of Rexin-G demonstrated high affinity for collagen-binding region, derived from coagulation von Willebrand factor (vWF) that is genetically engineered into the retrovector's surface protein (Dritschilo et al., 2006). Rexin-G has demonstrated its potent anti-angiogenic properties and selective tumoricidal activity. The potential safety and efficacy of Rexin-G has resulted in its approval in Philippines in 2007 for the treatment of all solid tumors. Moreover, FDA has granted phase III status of Rexin-G for pancreatic cancer, osteosarcoma and soft tissue sarcoma. Different virosome based vaccine delivery which have been developed and approved are enlisted in (Table 3). Besides clinically accepted virosomes, research is still ongoing for the development of other potential viruses for cancer therapy.

Virus mediated cancer treatment offers several advantages for cancer therapy, as the cancer cells have impaired anti-viral defence which permit virus to target cancer cells while sparing the healthy cells. Pox viruses such as myxoma or vaccinia strains are extensively studied for cancer therapy because of the presence of specific cancer cell features (blockage of apoptotic pathways, uncontrolled division and immune evasion) (Kirn and Thorne, 2009). Different groups have evaluated the role of JX-594 poxvirus, (an oncolytic virus) as an anti-tumor agent. This oncolytic virus was injected intratumorally and intravenously to patients of metastatic liver cancer and advanced solid tumors respectively (for phase I trials). Following administration, this virus homed successfully in the tumor tissues and demonstrated dose related antitumor activity whereas, the normal tissues were observed negative for viral replication (Breitbach et al., 2011; Park et al., 2008). Another study was carried out using Herpes simplex virus (HSV) type 1-derived, Granulocyte-macrophage colony-stimulating factor (GM-CSF)-expressing virus (Talimogene laherparepvec) [T-Vec] in randomized first phase III trial. The vector was capable of inducing direct lysis of the tumor cells and further stimulated the immune response by GM-CSF. Overall results in patients demonstrated prolonged survival. This study confirmed the potentiality of T-Vec to become the first oncolytic virus for cancer therapy (Wicki et al., 2015).

Table 3
Various Antibody/Protein–drug bound/conjugates, micelle, virosomes based and nanocrystal based nanoformulations; partly adapted from reference (Hafner et al., 2014; van der Meel and Hennik, 2017).

Nanoformulations (Trade name/generic name)	Drug/Active agent	Indication	Approval/USTrial ID
Adcetris®	Brentuximab Vedotin	Treatment of Hodgkin's lymphona, anaplastic large cell lymphoma	FDA 2011
Kadcyla® (Ado-trastuzumab emtansine)	Trastuzumab connected to a drug called DM1	Treatment of metastatic breast cancer	FDA 2013
Ontak® (Denileukin diftitox)	Engineered protein combining Interleukin-2 and Diphtheria toxin	Treatment of cutaneous T-cell lymphoma	FDA 1994
Gendicine®	Recombinant adenovirus expressing wildtype-p53	Treatment of head and neck squamous cell carcinoma	People's Republic of China 2003
Rexin-G®	Retrovector bearing cycline G1construct	Treatment of all solid tumors	Philippines 2007
Inflexal®V	Virosomal influenza vaccine	Immunization against influenza	Switzerland 1997
Epaxal® (Hepatitis A-vaccine)	Hepatitis A virus inactivated	Immunization against hepatitis A	Europe, 2003
Exparel®	Bupivacaine liposome injectable suspension	Amide-type local anesthetic for post-surgical analgesia	FDA 2011
Rapamune®	Rapamycin	Immunosuppressant	FDA 2000
Emend® (Aprepitant)	Antiemetic compound (Neurokinin1 receptor antagonist)	Treatment against nausea and vomiting	FDA 2003
Megase®	Megestrol acetate	Treatment of appetite loss, weight loss and advanced breast and endometrial cancer	FDA 1993
Zypadhera®	Olanzapine	Treatment of schizophrenia	FDA 2009
Semapimod®	Guanylhydrazone	Inhibition of macrophage activation and production of several inflammatory cytokines	NCT00038766 (Phase II)
Paxceed®	Paclitaxel	Treatment of rhematoid arthritis	NCT00055133 (Phase III)
CriPec®	Docetaxel	Treatment of solid tumors	NCT02442531 (Phase I)
NK105	Paclitaxel	Metastatic recurrent breast cancer	NCT01644890 (Phase III) ongoing
SGN-CD33A (Vadastuximab talirine)	Azacitidine	Treatment of Acute myeloid leukemia	NCT02785900
IMMU-132 (Sacituzumab govitecan)	Antibody RS7 is attached to SN38 (active metabolite of irinotecan) targets TROP-2 antigen	Treatment of epithelial cancers	NCT01631552
CMC-544 (Inotuzumab Ozogamicin)	CD22- antibody coupled to calicheamicin	Acute lymphoblastic leukemia	NCT01564784 (Phase III) ongoing

9. Nanocrystals

Drug nanocrystals are the crystals in the nanometer range which are composed of 100% drug without any excipient or associated carrier system. The most important feature of the drug nanocrystals are increased saturation solubility and accelerated dissolution velocity that leads to fast and proper drug absorption (Keck and Muller, 2006). Different methods are engaged for formulation of drug nanocrystals such as milling, high-pressure homogenization and precipitation. Depending on the production method, they can also be partially or completely amorphous. Rapamune® containing sirolimus (SRL, rapamycin), was the first nanocrystal product which entered the market in the year 2000. Rapamycin has antiproliferative effect that inhibits several cytokines induced signal transduction pathways by complexing the mTOR (mammalian Target of Rapamycin). The second product which was introduced in 2001 for the treatment of emesis following Rapamune®'s successes was Emend®. The nanocrystal Emend® (aprepitant) has high affinity antagonist effect on human substance P/neurokinin 1 (NK 1) receptors and therefore is beneficial for chemotherapy-induced nausea and vomiting. Another nanocrystal Tricor® (fenofibrate) is used primarily as an adjunctive therapy for hypercholesterolemia or mixed dyslipidemia in adult patients. Different companies using nanocrystal technology have developed various nanosuspensions, tablets, capsules of many poorly soluble drugs which are enlisted below (Table 3).

10. Nanoformulation for gene therapy and immunotherapy

Gene therapy is a form of therapy that uses genes to treat or prevent different diseases. Through the emergence of nanotechnology, there was great advancement of gene therapy that pushes for the production of nanoscale gene based medicines (Anselmo and Mitragotri, 2016; Babar et al., 2012). Various liposomal nanoformulations are currently approved and few of them are under clinical trials (Table 4). Gene silencing by RNA interference (RNAi) has become key tool for therapeutics as it allows specific knockdown of the target genes (Fig. 4). However, delivering the genetic material *in vivo* faces many challenges because of their instability and vulnerability to intracellular RNAses (Elbashir et al., 2001; Gavrilova and Saltzmanb, 2012). Nanoparticulate based drug/gene delivery has become one of the promising approach as it offers stability, controlled release, high payload, easy surface modification, transport and targeting by overcoming the obstacles faced by native RNAi (Anselmo and Mitragotri, 2016; Woodrow et al., 2009).

Therefore, using nanoparticulate vehicle for selective gene silencing, either through siRNA or miRNA shows potency towards various diseases including cancer. These newer class of nanogenomedicines can specifically target the cancer cells through homing agents, resulting in effective delivery of the same by both passive and active targeting system (Hollins et al., 2007; Omidi et al., 2003). For this approach, various lipids and polymers are conjugated to the specific receptors (antibody, peptide, aptamers) by chemical conjugation methods using various bi-functional cross-linkers (Hermanson, 2008) (Table 4). For prolong circulation of the nanogenomedicines, conjugation with PEG has been most effective as it reduces the protein adsorption *in vivo* as well as the avoidance of RES based clearance (Guo and Huang, 2011). Recently, siRNA protected by RNAi/Oligonucleotide Nanoparticle Delivery (RONDEL) technology has demonstrated impacts on its targeted destination (Heidel and Schluep, 2012). The majority of the nanocarriers used for gene therapy are liposome based; few selected liposomal nanoformulations for gene therapy are enlisted in (Table 4).

MicroRNAs (miRNAs) are a class of small, single-stranded noncoding RNAs that primarily function at the posttranscriptional level. Study of miRNA has advanced our understanding of many of the fundamental processes of cancer biology and the molecular mechanisms underlying tumor initiation and progression and its surrounding

Table 4
Gene therapy and immunotherapy using liposomal nanoformulations; partly adapted from reference (Anselmo and Mitragotri, 2016; Barar and Omidi, 2012; Shi et al., 2017).

Nanoformulations	Drug/Active agent	Indication	US trial ID
Liposomal formulation of EGFR antisense	EGFR antisense	Advanced head and neck cancer	NCT00009841, Completed
Cholesterol-FUS1-liposomes	Erlotinib, Dexamethasone	Stage IV, lung cancer	NCT01455389 (Phase1/II), Active
Liposome encapsulated c-raf antisense oligonucleotide	c-raf antisense oligonucleotide	Advanced solid tumors	NCT00024648 (Phase-1), Completed
Neutral Liposomal Small Interfering RNA Delivery	siRNA-EphA2	Advanced solid tumors	NCT01591356 (Phase1)
Liposome-BikDD Nanoparticles	C-VISA BikDD	Advanced pancreatic cancer	NCT00968604 (Phase 1), Completed
Vitamin A coupled lipid nanoparticle conjugated to siRNA	siRNA-HSP4	Hepatic fibrosis	NCT02227459, Completed
Lipid nanoparticles	shRNA-stathmin1	Advanced metastatic and/or metastatic cancer	NCT01505153 (Phase I)
Lipid nanoparticle of siRNA to knockdown the disease-causing TTR protein	Patisiran, TTR protein	Amyloidosis	NCT02510261 (Phase III) NCT01961921 (Phase II) NCT01960348 (Phase III)
Lipid nanoparticle formulation with two siRNAs	KSP and VEGF	Solid tumors	NCT01158079, Completed
Liposomal formulation with siRNA to knockdown protein of vascular endothelium	Atu027, PKN3	Pancreatic cancer	NCT01808638 (Phase I/II)
Lipid nanoparticle formulation of siRNA against PLK1	PLK1	Hepatocellular carcinoma	NCT02191878 (Phase I/II)
Liposome containing RNAi therapeutics to target the HBV genome	Target three sites on HIV genome	Hepatitis B	NCT02631096 (Phase II)
Lipid nanoparticles Oncogene silencing	Myc	Solid tumors, multiple myeloma, lymphoma, or hepatocellular carcinoma	NCT02110563 (Phase I) NCT02314052 (Phase I/II)
Lipid nanoparticles encapsulated single-stranded DNAi	PNT100:BCL-2	Lymphomas	NCT02378038 (Phase II) NCT02226965 (Phase II) NCT01733238 (Phase II)
Neutral liposomes encapsulated growth factor protein-2 antisense oligodeoxynucleotide	L-Grb2 AS	Leukemias	NCT01159028 (Phase I)
Liposome encapsulated with plasmid	RB94 plasmid DNA anti-transferrin receptor antibody (TfRscFv)	Solid tumors	NCT01517464 (Phase I)
Liposomes encapsulated micro RNA	miR-34	Liver cancer	NCT01829971 (Phase I), terminated
SGT-53 Cationic liposome encapsulating wildtype p53	Wild type p53 gene (plasmid DNA) encapsulated in a liposome and functionalized with anti-transferrin receptor single-chain antibody fragment (TfRscFv)	Solid tumors, glioblastoma, pancreatic cancer	NCT02354547 (Phase I) NCT00470613 (Phase I) NCT02354547 (Phase I) NCT02340156 (Phase II)
Immunotherapy			
Liposome-vaccine	Synthetic 25 aminoacid derived from MUC1	Non-small cell lung cancer	NCT00409188 (Phase III) Completed
Liposome	Recombinant HER2 (dHER2) antigen and A515 adjuvant	Metastatic breast cancer	NCT00952692 (Phase I and II) Completed
Liposomal	Multi tumor associated antigen	Advanced stage ovarian, breast, prostrate cancer	NCT01095848 (Phase I) Completed
Liposome	Melanoma antigen	Malignant melanoma	NCT01052142 (Phase I) Completed
Lipid nanoparticles	Plasmid DNA	Relapsed or refractory leukemia	NCT00860522 (Phase I)

EGFR: epidermal growth factor receptor; EphA2: ephrin type-A receptor 2; C-VISA BikDD: liposome consists of a pancreatic-cancer-specific expression vector "VISA" (VP16-GAL4-WPRE integrated systemic amplifier) and a pancreatic-cancer-specific promoter CCKAR (cholecystokinin type A receptor) (CCKAR-VISA or C-VISA), BikDD, a mutant form of the potent proapoptotic gene Bik (Bcl-2 interacting killer), PLK1: (Polo-like kinase1) , HIV (Human immunodeficiency virus); Myc: (Myelocytomatosis); HSP47: (Heat shock protein 47) ; TTR: (Transthyretin); KSP: (Kinesin spindle protein) and VEGF: (Vascular Endothelial Growth Factor); PKN3: (Protein Kinase N3); eIF5A^{K50R}plasmid eIF5A siRNA, Atu027, Kirsten Rat Sarcoma (KRAS), miR-34 (Micro RNA 34), Grb-2: (Growth Factor Receptor Bound Protein-2); Proprietary 24-mer single stranded, phosphodiester DNA, which is a part of the B-cell lymphoma2 (Bcl-2); MUC: Mucinous glycoprotein 1.

microenvironment. In this context, miRNAs have mostly been considered as potential non-invasive biomarkers and as therapeutic targets for many diseases (Bouchie, 2013). It is becoming evident that an emerging hallmark of cancer is the dysregulation of miRNAs, both in the tumor itself and in the surrounding microenvironment therefore using miRNAs as therapeutic agents has become the call of the hour (Pérez-Díaz et al., 2014). The nanoparticle based delivery approach appears as an attractive strategy for miRNA delivery because it avoids several of the concerns used for viral delivery systems, such as off-target effects like immunogenicity, inability to specifically target to tumor and toxicity (Haraguchi et al., 2009; Thomas et al., 2003). Su et al. found that lipid nanoparticles that contained 2′fluoro-modified anti-miR-122 significantly inhibited tumor growth (Su et al., 2011). Similarly, biodegradable polymer nanoparticles containing anti-miRNAs were developed to inhibit miR-155 in a mouse model of pre-B-cell lymphoma (Babar et al., 2012). Nanoparticles conjugated with targeting molecules for specific binding have also been designed and tested for miRNA delivery (Babar et al., 2012). For example, Huang et al. designed transferrin-conjugated anionic lipopolyplex nanoparticles carrying miR-29b which showed specific binding to AML cells exhibiting significant *in vitro* and *in vivo* anti-leukemia activities (Huang et al., 2013). Although none of the formulations are in clinics, there is hope that such a strategy may get translated as personalized medicine in near future.

From last few decades immunotherapy has become essential for

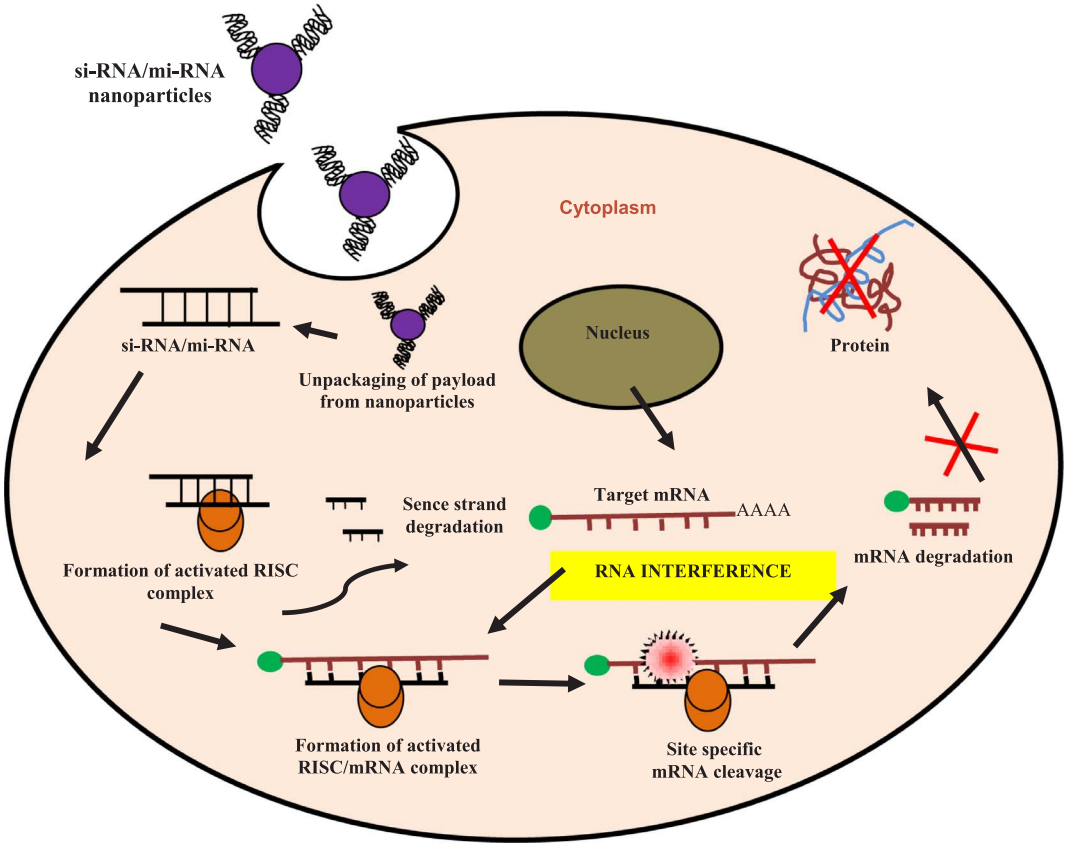

Fig. 4. Core process of RNA interference. Double stranded miRNA and siRNA are processed and one of the single strand is incorporated in RNA-induced silencing complex (RISC) a multi protein complex. The single strand acts as a template for RISC to recognize complementary mRNA. One of the proteins of RISC, argonaute activates and cleaves the mRNA and the protein synthesis is blocked leading to RNA interference, a key process of gene silencing.

treating certain types of cancer as it works in either by boosting immune system or directing the immune system to attack cancer cells (Smith et al., 2013). Utilization of nanotechnology for the immunotherapy is also gaining momentum for cancer therapy. Especially liposomal nanoformulations are becoming attractive for the development of synthetic vaccines, adjuvant carriers for the preferential uptake, elevated tissue penetration and/or access to lymphatics. Recently Shi et al. have reported some of the liposomal nanoformulations for immunotherapy which are under different stages of clinical trial (Shi et al., 2017) (Table 4).

11. Inorganic nanoformulation for therapy and imaging

Inorganic nanoparticles have made tremendous progress in biomedical applications related to drug delivery and imaging. Different inorganic nanomaterials such as magnetic nanoparticles or gold or silicon etc. nanoparticles have added significant contribution towards cancer therapy and imaging (Huang et al., 2011). Magnetic materials have been used for various biomedical applications. The unique physical properties of magnetic material (e.g. iron oxide) endows it to serve both as imaging probes and drug delivery vehicle for diagnosis and treating the diseased lesions (Singh and Sahoo, 2014). Superparamagnetic nanoparticles (SPION) developed from iron oxide nanoparticles possess ultrafine size, biocompatibility and magnetic properties that can be steered with an application of external magnetic field for imaging and therapy (Clément et al., 1998; Dilnawaz et al., 2012; Dilnawaz et al., 2010). Currently, number of clinically approved SPIONs are used for biomedical imaging (Table 5). Dextran coated SPION (Feridex®) was approved by FDA in 1996 as a contrast agent for magnetic resonance imaging (MRI). With the MRI detection system, the lesions of liver, spleen and diseased tissues become better distinguishable from the normal surrounding tissues. However, later the production of Feridex® was discontinued in 2008 due to unwanted side effects (Clément et al., 1998; Weissig et al., 2014). Ferumoxytol (Feraheme™) is the new carbohydrate (polyglucose sorbitol carboxymethylether) coated SPION used for the treatment of anaemia patients with chronic kidney disease in clinical settings. Ferumoxytol releases iron inside the MPS; thereafter the iron either enters intracellular storage of the iron pool or transferred to plasma transferrin (Schwenk, 2010). It also acts as blood pool contrast agent and is currently under the development for the inclusion as novel imaging agent for MRI-based diagnosis of cancer and cardiovascular diseases (Prince et al., 2003). Recently, Zanganeh et al. reported the therapeutic effect of ferumoxytol on the growth of an early mammary cancer, lung cancer metastases in liver and lungs due to macrophage polarization into pro-inflammatory M1 phenotypes. Further, intravenous ferumoxytol treatment before the tumor induction prevents liver metastasis. These results suggested that application of ferumoxytol could protect the liver from metastasis (Zanganeh et al., 2016).

Another magnetic nanoformulation, aminosilane-coated SPION or NanoTherm® was developed by MagForce (Berlin, Germany) for diagnosis, imaging and therapy which can be administered for treating solid tumor mass like glioblastoma, prostrate and pancreatic cancer. Exposure to oscillating magnetic field can elevate the intratumoral temperature and can directly destroy the tumor cells by means of thermal ablation (Weissig et al., 2014). Recently, a new parenteral iron formulation in matrix structure; iron isomaltoside 1000 (Monofer®) and ferric carboxymaltose formulation (Injectafer®) are developed with reduced immunogenic properties (Jahn et al., 2011). These formulation matrixes enabled a controlled and slow release of iron avoiding the consequences of free iron toxicity (Jahn et al., 2011; Zager et al., 2002). Very recently, the first clinical trial with hafnium oxide nanoparticles (NBTXR3) as radiosensitizer for soft tissue sarcoma has been started in

Table 5
Various inorganic nanoformulations; partly adapted from reference (Hafner et al., 2014; Shi et al., 2017; van der Meel and Hennik, 2017).

Nanoformulations	Drug/Active agent	Indication	Approval
Feridex®	Dextran coated iron oxide nanoparticles	MRI contrast agent, discontinued from 2008	FDA 1996
Feraheme™ (Ferumoxytol)	Carbohydrate coated iron oxide nanoparticles	Treatment of anaemia associated with chronic kidney disease	FDA 2009
Monofer®	Iron isomaltoside 1000	Treating anaemia	European Union 2009
Injectafer®	Ferric carboxymaltose coated iron oxide nanoparticles	Treating anaemia	FDA, 2013
NanoTherm™	Aminosilane coated iron oxide nanoparticles	Local ablation in glioblastoma, prostate, and pancreatic cancer	European Union 2010
Aurimune (CYT-6091)	PEGylated colloidal gold for tumor necrosis factor (rhTNF) delivery	Solid tumors	Phase I/II
AuroLase	Gold-coated silica nanoparticle	Photothermal ablation therapy for head and neck cancer	Phase I
NanoXray (NBTXR3)	Hafnium oxide nanoparticle	Radiotherapy for solid tumors	Phase I
Cornell dots(C-dots) (Silica nanoparticles)	^{124}I-cRGDY–PEG–C dots	Positron emission tomography (PET)–optical dual-modality imaging for integrin-expressing cancers	NCT01266096 (Phase-I)
Graphene nanosystem	Doxorubicin and tumor-necrosis-factor (TNF)-related apoptosis-inducing ligand (TRAIL)	Non small cell lung cancer	–
Single walled carbon nanotubes	Human telomerase reverse transcriptase (hTERT) siRNA	Prostate cancer	–
Molybdenum disulfide nanosheet	Doxorubicin	Breast cancer	–
Gold nanorod	Doxorubicin	Cervical cancer	–
Colloidal silver nanoparticles(Sovereign Silver, Bio-Active Silver Hydrosol)	Silver nanoparticles	Chronic rhinosinusitis	NCT03243201 (Phase 1, January 2018)
Nanosilver	Silver nanoparticles	Inflammatory disease	NCT02408874 (withdrawn) 2017
Acticoat	Silver nanoparticles	Antibacterial	FDA 2005
Acticoat Flex™	Nanocrystalline silver coating	Antimicrobial wound dressing, diabetic, surgical	K153723, premarket notification, Europe, 2016

patients (Maggiorella et al., 2012). Other inorganic nanoparticles such as PEGylated gold-TNFα nanoparticles: CYT-6091 (Aurimune) for cancer therapy (Libutti et al., 2010) whereas, few others are in the development process (Table 5). Utilization of green synthesis technology for formulating gold nanoparticles is being attempted and its application in various biomedical research is undergoing.

Silver nanoparticles (AgNPs) have been extensively studied for many decades due to their unique features and wide range of applications as antiseptic, antimicrobial, anti-inflammatory agent (Konop et al., 2016). There are a variety of methods to synthesize AgNPs including physical and chemical methods (Chudasama et al., 2010). Colloidal silver nanoparticles (AgNPs) were synthesized by gamma radiation using poly (vinyl alcohol) (PVA) or silk fibroin (SF) from cocoons of silk worms as stabilizers and chitosan (CS) which were then evaluated for their excellent mechanical and antibacterial properties against S *aureus* and *P aeruginosa*. Result suggested that these synthesized AgNPs can potentially be applied for antibacterial wound dressing (Uttayarat et al., 2015). Archana et al. synthesized chitosan-Poly vinyl pyrolidone-nano silver oxide (CPS) which demonstrated better wound healing ability as compared to other dressing materials (Archana et al., 2015). Silver nanoparticles were efficiently synthesized *in situ* using ultra violet (UV) with $AgNO_3$ as precursor and chitosan/polyethylene oxide as reducing agent and protecting agent, respectively. These antibacterial nanofibers displayed excellent antibacterial activity against gram-positive (Staphylococcus aureus) and gram-negative (Escherichia coli) bacteria (Wang et al., 2015). Pérez-Díaz et al. reported the antibiofilm efficacy of chitosan gel formulations loaded with AgNPs on strains of clinical isolates, as well as their cytotoxic effect on human primary fibroblasts. The chitosan gel loaded with AgNPs prevented the formation of biofilm by killing them hence they can be used for prevention and treatment of chronic wounds (Pérez-Díaz et al., 2016).

Although chemical routes are effective for synthesizing AgNPs, but it suffers from toxicity. Therefore, to avoid toxicity, green synthesis methods were developed as an alternative by using natural compounds or plant components. Aloe vera leaf extract has multiple biochemical properties. In a recent report, silver nanoparticles (AgNPs) were synthesized from Aloe vera extracts for biomedical applications against pathogenic bacteria *S. epidermidis* and *P. aeruginos*a (Tippayawat et al., 2016). In another study Kasithevar et al. prepared AgNPs from aqueous leaf extract of *Alysicarpus monilifer* and evaluated its antibacterial efficacy against multi-drug-resistant Methicillin-resistant *S aureus* and coagulase-negative *Staphylococci* isolates from HIV patients (Kasithevar et al., 2017). Siddiqui et al. recently synthesized PEG coated AgNPs through green synthesis by using honey or β-d-glucose which illustrated better antibacterial activity (Siddiqui et al., 2017). In another study, Aboelfetoh synthesized AgNPs using green marine algae which displayed superior antibacterial activity at lower concentration against *S aureus*, *P aeruginosa*, *Shigella* sp., *S typhi*, and *E coli* (Aboelfetoh et al., 2017).

12. Emerging nanoformulation for clinical trials

Although various nanoformulations have entered into different phases of clinical trials but they do not have the ability for real time monitoring of the disease. Keeping this perspective in mind, several other nanocarriers are also entering clinical trials for drug delivery as well as imaging.

13. Nanogels

Nanogels (nanoparticles composed of hydrogel) are three dimensional network formed from cross linked hydrophilic polymers either by chemical (covalent) or physical (Vander Waals and electrostatic bonding) process. These nanogels can swell in hydrophilic medium and have the ability to entrap large quantity of DNA, RNA, proteins and drugs envisioned for drug/gene delivery (Kashyap et al., 2005). Nanogels have received considerable attention for the past few decades in biomedical application such as drug delivery, gene delivery, wound

management and tissue engineering (Kashyap et al., 2005). Nanogels are preferably used for delivery of siRNA as it overcomes the challenges associated with siRNA delivery like its poor stability in the cytosol along with low cellular uptake efficiency (Dykxhoorn and Lieberman, 2006). In this regard, branched polyethyleneimine (PEI) is considered as a potential carrier for siRNA delivery because of its highly positive charge which enabled it to form complexes with the negatively charged siRNA through strong electrostatic interaction, as a result, the siRNA is protected against enzymatic degradation and its cellular uptake is enhanced via endocytosis for subsequent gene silencing effect (Merdan et al., 2002). In this context, Mimi et al. reported a gelatine-PEI-core–shell nanogel based siRNA delivery vehicle having higher gene silencing effect than commercially available transfection agent, Lipofectamine™ 2000, suggesting it to be a promising nanogel carrier for siRNA delivery (Mimi et al., 2012). Naeye et al. demonstrated better therapeutic effect by using PEGylated dextran hydroxyethyl methacrylate nanogels. These nanogels loaded with siRNA (EGFP) caused significant EGFP knockdown in a human hepatoma cell line (Naeye et al., 2010). In another study, Khaled et al., reported the therapeutic efficacy of inorganic silica core cationic poly (2-diethylaminoethyl methacrylate) pH-responsive nanogel for intracellular delivery of siRNA (CXCR4 protein). These siRNA loaded nanoparticles significantly decreased the expression of this protein in a human breast cancer cell line and demonstrated preferential accumulation at the tumor site in an orthotopic human breast cancer mouse model with a reduction of CXCR4 expression (Khaled et al., 2016).

14. Self assembling peptide as nanodelivery system

Recently, self-assembling peptides have been explored as new nanobiodelivery material due to their high resistance to proteolytic degradation and non-toxic nature which make them an ideal candidate for biomedical applications for the delivery of insoluble molecules or negatively charged nucleic acids in drug or gene delivery applications. Bawa et al. demonstrated the use of self-assembling peptide (EAK16-II) to stabilize the hydrophobic anticancer drug ellipticine in aqueous solution. The above nanoformulation illustrated superior cytotoxicity due to enhanced cellular uptake in human lung carcinoma A549 cells compared to native drug (Bawa et al., 2011). Naskar et al. reported the efficiency of multivesicular structures from self-assembling water-soluble synthetic amphiphilic dipeptides containing glutamic acid residue at the C-terminus, which are sensitive towards calcium ions. These vesicles have the capacity to encapsulate anticancer drugs, fluorescent dyes and cyclic adenosine monophosphate (cAMP) within the cells keeping their biological functions intact. These nanodelivery systems disrupt after sensing the calcium ions and thus release the encapsulated cargo (Naskar et al., 2011).

15. Quantum dots and near infrared dye nanoformulation

Nanotheranostic aspect of nanomedicine which amalgamates cancer therapy and imaging has been adapted for achieving superior cancer diagnosis by using quantum dots (QDs) and, near-infrared (NIR) dyes. QDs are the semiconductor inorganic nanomaterials (e.g. Cd and Se) utilized as imaging agent in cancer nanomedicine because of its excellent fluorescent properties. Moreover, the wide application of QDs in biology is due to its less photobleaching ability in comparison to organic dyes (Resch-Genger et al., 2008). The photophysical properties and broad absorption spectrum coupled with narrow emission spectrum of the QDs and its ability to be simultaneously excited by a single wavelength renders it ideal for multiple molecular targets (Medintz et al., 2005). QDs can be labelled with drug carriers such as liposomes, nanoparticles, and dendrimers for simultaneous drug delivery and imaging (Das et al., 2015; Pan and Feng, 2009). For active biological applications, QDs can be modified by ligands or entrapped with polymers to improve aqueous solubility, specificity, size as well as visualization in tissues. Recently, our group reported the bioimaging ability of aptamer conjugated QDs encapsulated polymeric nanoformulation and antibody functionalized QDs encapsulated in lipid based nanoformulation as an effective imaging agent for cancer therapy (Das et al., 2015; Parhi and Sahoo, 2015). NIR dye based nanoformulation is highly sensitive with multi-detection capability that is currently used for the early cancer detection. Zintchenko et al. have developed “quantoplex” that comprises of polyethylenimine (PEI) nanocarriers having plasmid DNA and incorporated NIR-emitting cadmium telluride (CdTe) for real-time tracking in living animals. Upon intravenous injection to nude mice, the quantoplexes accumulated rapidly in the liver and peripheral regions resembling lymph nodes, followed by clearance via the liver within hours to days (Zintchenko et al., 2009).

16. Smart functional nanomaterials

Although many different types of nanoparticles have entered into clinical trials, research is still ongoing for the development of smarter, functional nanomaterials for maximizing the therapeutic efficacy. Nanoparticles based on stimuli response that provide insight into the complex biological microenvironment gives new dimension to the diagnostic opportunity. In this regard, switchable nanoparticles are developed that respond to internal and external stimulus (Lehner et al., 2013). Internal stimuli, such as pH, redox potential, enzymatic activity or temperature sensitive nanomaterials are developed that are less detrimental to healthy tissues in comparison to non-sensitive materials (Tagami et al., 2011). External stimuli such as temperature, light, radiation or ultrasound-sensitive nanosystem have been developed for getting additional clinical benefit. A few external controlled nanoparticulate system e.g. photodynamic therapy has been developed (Visudyne®, Photofrin®, Levulan® and Kerastick®) for age-related macular degeneration, actinic keratosis and esophageal cancer (Christie and Kompella, 2008; Keam et al., 2003). Redox sensitivity based antibody linked drug named Mylotarg® developed by the Celltech Group and American Home Products was first approved by FDA in 2000 for the treatment of acute myelogenous leukemia but later was withdrawn from market in 2008 (Lo Coco et al., 2006). Jiang et al. developed a cellular protease (furin) mediated graphene nanosystem for co-delivering cytokine (TRAIL) and anticancer drug doxorubicin for effective sequential release in plasma membrane and nucleus (Jiang et al., 2015).

Special nanomaterials such as single-walled carbon nanotubes (SWNTs) are now emerging for biomedical applications, because of their interesting physical and chemical properties. Wang et al., has successfully developed a promising anticancer system of single-walled carbon nanotubes (SWNTs) for combination of RNAi and near-infrared (NIR) photothermal therapy. SWNTs were chemically functionalised with polyethylenimine, conjugated with tumor homing NGR peptide and loaded with hTERT siRNA for enhanced antitumor activity (Wang et al., 2013). Xiao et al. explored the possibility of targeted cancer thermo-chemotherapy using DNA-based platform. NIR-responsive nanoparticles are comprised of gold nanorod, DNA strands for loading drug, PEG and the targeting ligand. This platform specifically delivers and releases the drug upon NIR irradiation and effectively inhibits tumor growth through thermo-chemotherapy both *in vitro* and *in vivo* studies (Xiao et al., 2012). In another study for the first time Liu et al. exploited PEGylated molybdenum nanosheets (MoS2) for the photothermal therapy and chemotherapy using anticancer drugs. The strong near-infrared absorbance of MoS2 along with the drug provided excellent synergistic anti-tumor effect upon systemic administration in animal studies (Liu et al., 2014). Soon some of these nanomaterials can enter for the clinical trials.

17. Challenges in transition of nanoparticle from benchside to bedside

Increased market penetration of nanomedicinal products in clinical

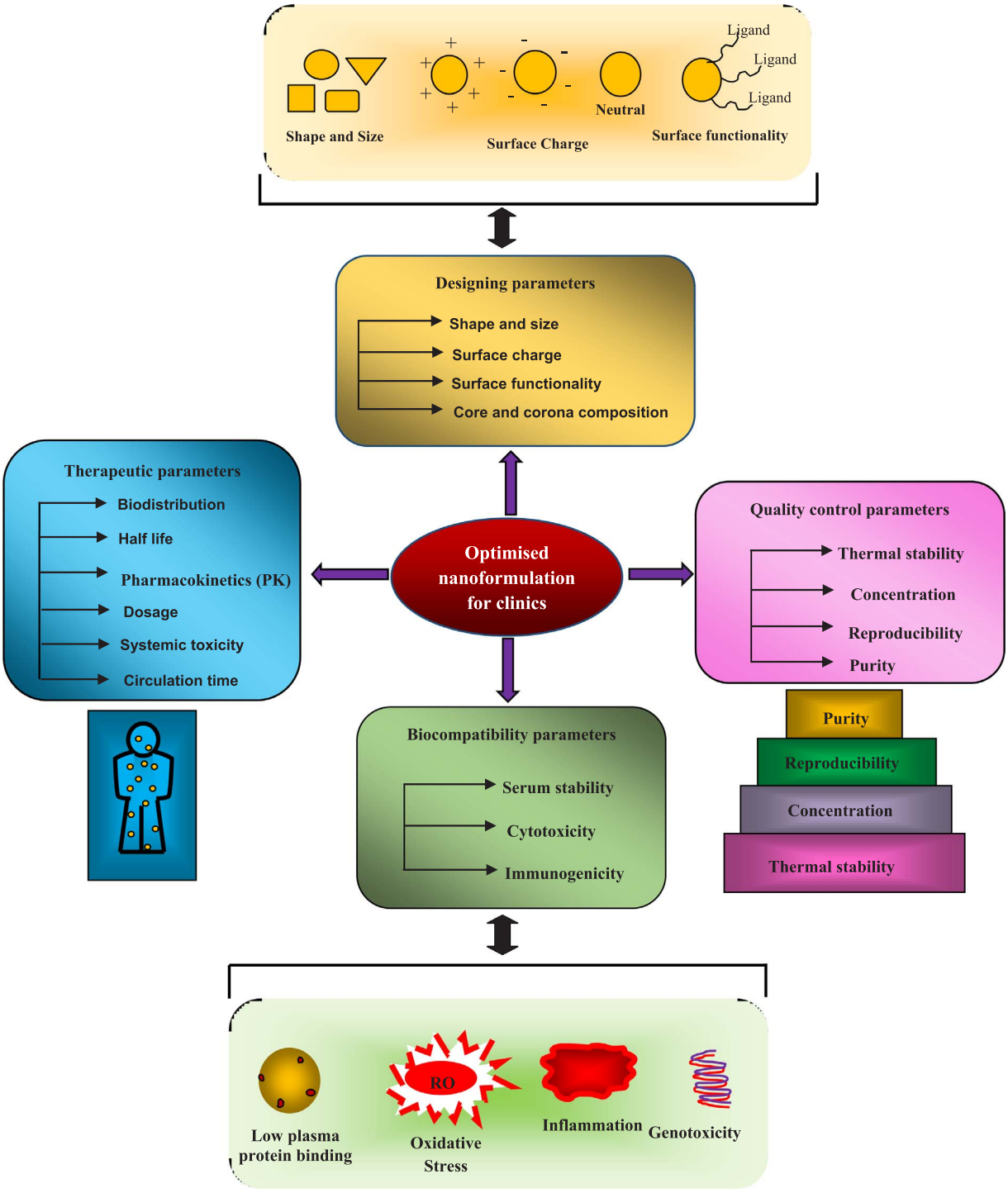

Fig. 5. Different regulative parameters are to be taken into consideration for devising an optimized nanoformulation for clinical application.

trials have driven the nanopharmaceutical market growth. The beneficial effects of the nanomedicines has also been currently advantageous in many ways for designing impactful second-generation of nanopharmaceuticals in upcoming years. Although we have witnessed rapid progress in the application of nanotechnology in the areas of drug delivery, several hurdles still remain which impede the smooth shift of nanomedicine from laboratories to clinics.

Physico-chemical characterisation are the key and critical parameters that regulate the activity and safety of nanoformulation produced within acceptable pharmaceutical tolerances and hence represent as the foremost hurdle for the success of nanotherapy (Fig. 5). Moreover, the therapeutic index of nanoformulations is also related to their specific physico-chemical characteristics which is equipment dependent and its complexity creates challenges for commercial development of nanomedicines. The nanoparticles produced in laboratories are not always characterized up to the standards set for clinical evaluation. In this setting, it would be very dicey to predict the clinical efficacy of the formulation. Therefore, devising suitable analytical tests for characterization of the formulated nanomedicines remains a challenging aspect. Moreover, for devising an optimized nanoformulation, it is prerequisite to consider several parameters like shape, size, charge, length, stability and targeting ligand simultaneously. As each

component of these parameters serves a specific function, it would be essential to quantify each component and establish relationships and interactions between these parameters concurrently rather than assessing each parameter separately which is the standard code of assessment followed in laboratories.

Parallel to the emergence of nanomedicine, the field of nanotoxicology has also gained momentum. In fact, the adverse effects of nanomedicines have been witnessed by deaths from respiratory and cardiovascular disease (Brook et al., 2004). Inflammation due to nanoparticles is the common factor that binds together these adverse effects. Similarly, several other toxicological studies have demonstrated that presence of nanoparticles in blood can elicit experimental thrombosis and platelet aggregation. Cationic nanoparticles (gold and polystyrene) can also induce hemolysis in experimental conditions. Moreover, studies using intratracheal instillation of high doses of nanotubes demonstrated chronic lung inflammation, including foreign-body granuloma formation and interstitial fibrosis (De Jong and Borm, 2008). As toxicity concerns of nanoparticles poses as a significant parameter to determine the success of any nanoproduct, certain parameters are recognized by researchers (like size, zeta potential and solubility of nanoparticles) which should be taken into concern for assessing the toxicity of the nanoformulations. Discrepancies observed in composition in batch to batch during manufacturing could affect the toxicities of nanoparticles. Besides, there is an insufficient understanding of the connection between physicochemical properties of nanoparticle and its role in clinical pharmacokinetics. Moreover, the conventional animal models used by researchers do not provide ample information regarding biodistribution of nanoparticles and its toxicity issues in humans. It has therefore become necessary to develop an inclusive list of tests which meets clinical standards to determine the toxicity of the nanoparticle formulations.

Another challenge posing as a major hindrance for success of nanomedicine is the large scale production of nanomaterials for commercialization purpose under Good Manufacturing Practices (GMP) conditions. A number of nanodrug delivery technologies may not be well suited for large scale production due to tedious methods of preparation or high cost of raw materials used for formulating particles, which may limits the deployment of nanoproducts for health care purpose. Moreover, nanomedicines are often initially developed in the laboratory and substantial gap exists between the productions in academic as well as industrial settings. In academic settings, usually micrograms or milligrams of product are produced, whereas, grams or kilograms are necessary for pre-clinical screening, clinical trials, and clinical use. In this regard, scaling up of any laboratory process is hard and batch-to-batch reproducibility is not easy; because subtle variations in the manufacturing procedure can significantly alter the product characteristics and its therapeutic outcome. In addition, implementation of a robust quality control system is the essential key to ensure successful nano-manufacturing (Ragelle et al., 2016).

18. Conclusion

Nanoparticle-based drug delivery has been actively developed to treat complex diseases with an increased efficacy and reduced side effects leading to unprecedented benefits for the clinical outcome. As therapeutic delivery systems, nanoparticles not only allow targeted delivery and controlled release but also assist in detection on the molecular scale to help identify abnormalities such as precancerous cells, and disease markers that cannot be detected with traditional diagnostics. Much of the work on nanomaterials for drug delivery is extremely promising and some of them are undergoing phase II/III clinical trials. Rigorous research engagement and development of novel nanomaterials would result in the multifunctional nanoparticles to enter the clinic in the near future.

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