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REVIEW ARTICLE

Smart nanomaterials in pharmaceutical analysis

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Life cycle assessment

Abstract Smart nanomaterials have appeared as one of the phenomenal materials to the modern world because of their exceptional thermal, electronic, optical and mechanical properties. Unique characteristics of smart materials make them striking candidates for pharmaceutical analysis which basically determines the quality of drug products via analytical chemistry. The present review discusses smart nanomaterials and their detailed applications in pharmaceutical analysis. A systematic approach for commercial-scale utilization of smart nanomaterials in the pharmaceutical analysis in terms of economic challenges, health & safety concern of nanomaterials and life cycle assessment within pharma industry are comprehended. In the end, the challenges and opportunities for the future development of smart nanomaterials for pharmaceutical analysis in regards to sustainability perspectives are described.

Contents

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1. Introduction

The rapid pace of advancements in the field of nanotechnology has driven innovations in all the disciplines of science including pharmaceuticals where cutting-edge research is carried out for the development of disease diagnosis. Nanotechnology has brought revolution in the field of medicine and an exponential increase has been reported in the nanotechnology related pharmaceutical patents in the last 20 years (Kumar et al., 2013). The pharmaceutical companies are focused on the nanotechnology to find out the solutions for the challenges in the pharmaceuticals and come up with low cost, safe and highly sensitive techniques for drug development. The nanotechnology tools are adding value to the existing products thereby opening new opportunities in the different segments of pharmaceutical R&D (Shah, 2011; du Toit et al., 2007). The focus is on personalized medicine as a new standard of care integrating therapeutics with diagnostics. Based on the utilities of the nanotechnology tools, they have been sorted out into three major categories of pharmaceutical R&D; (1) process development, (ii) product development, (iii) personalized medicine (Kumar, 2010).

The term process development refers to both syntheses of drugs, drug intermediates, and the development of the analytical tools for diagnostics (Martis et al., 2012). For drug discovery or synthesis, a miniaturized automation platform enables the development of high-throughput synthetic routes. The search for breakthrough medicines requires rapid synthesis of complex molecules and testing of their biological hypothesis but the availability of short supply of substrate molecules is a limitation. Miniaturization chemistry to the nanomole scale has come up as a potential solution to this problem. The idea is to do scale synthesis using high precision nanoliter robotics i.e. hundreds of a reaction could be carried out in a single day using as little as 0.02 mg of material per reaction (Buitrago Santanilla et al., 2015). The early identification of synthesized molecules is important during the preclinical development. In the preformulation stage, the availability of the compound is scarce and therefore, formulation development should be performed on the minute quantities of the drug compound. Hence, nanosuspension formulations have been found to be valuable at the screening stage (Van Eerdenbrugh et al., 2008).

Catalysts play a key role in synthetic chemistry as they improve the reaction yields at low temperatures and promote the enantioselectivity. Nanoparticles act as efficient catalysts and support for varied chemical reactions. Ferrite nanoparticles are widely used as nanocatalysts in organic reactions; are easily recovered from the reactions systems and can be reused up to many reaction cycles without the loss of catalytic activity (Abu-Dief and Abdel-Fatah, 2018). The ferrite nanoparticles have high chemical stability and narrow size distribution which are crucial for drug designing (Kralj et al., 2011). The development of nanotechnology tools such as nanodevices and ultrafast imaging tools have revolutionized the quality control during the process development of drug molecules.

The product development involves the discovery and development of new drugs for the treatment of diseases and hence, it is an area of continuous and committed research. The properties such as solubility and solubilization, permeability, lipophilicity, the degree of ionization, gastrointestinal metabolism, stability in biological fluids, systematic pharmacokinetics and pharmacodynamics and protein binding properties are considered while synthesizing new drug molecules (Devalapally et al., 2007). The pharmacological and therapeutic properties of the drugs can be improved and enhanced by the development of drug delivery systems based on lipid and polymer-based nanoparticles (Allen and Cullis, 2004). Aqueous property of any molecule is an important property in the Biopharmaceutical Classification System (BCS) and plays a significant role in the adsorption of passively transported drugs across the gastrointestinal tract (Lipinski, 2000; Amidon et al., 1995). Nanotechnology addresses these issues through the designing of nanodrug delivery systems that are capable of achieving improved biopharmaceutical properties by altering the drug's biopharmaceutics and pharmacokinetics. Polymeric nanoparticles, liposomes, nanoemulsions, micelles and dendrimers are some of the examples of nanodrug delivery systems (Fig. 1). The present era is of nanopharmaceuticals for the early stage disease diagnosis. It is a hope of health care with enormous potential promises for human society. With the creative nanotechnology and nanoscience approaches, nanomaterials with varied shapes, functionalities and distinct physical, chemicals and biological properties have been designed that have a strategic role in the pharmaceutical industry (Moghimi et al., 2011).

In the nanometer range, the surface area of the drug molecule increases and hence, increase in its absorption. Nanodrugs have improved solubility due to the presence of both hydrophilic and hydrophobic environments (Nagy et al., 2012). A number of well-known nanodrugs are already available in the market. Since 1995, 50 nanopharmaceuticals have received Food and Drug Administration (FDA) approval and are currently available for clinical use. Some of the nanodrugs have been summarized in Table 1 (Zhang et al., 2008a; Ventola, 2017).

Personalized medicine was proposed a decay ago to overcome the shortcomings of the current medical practice. It

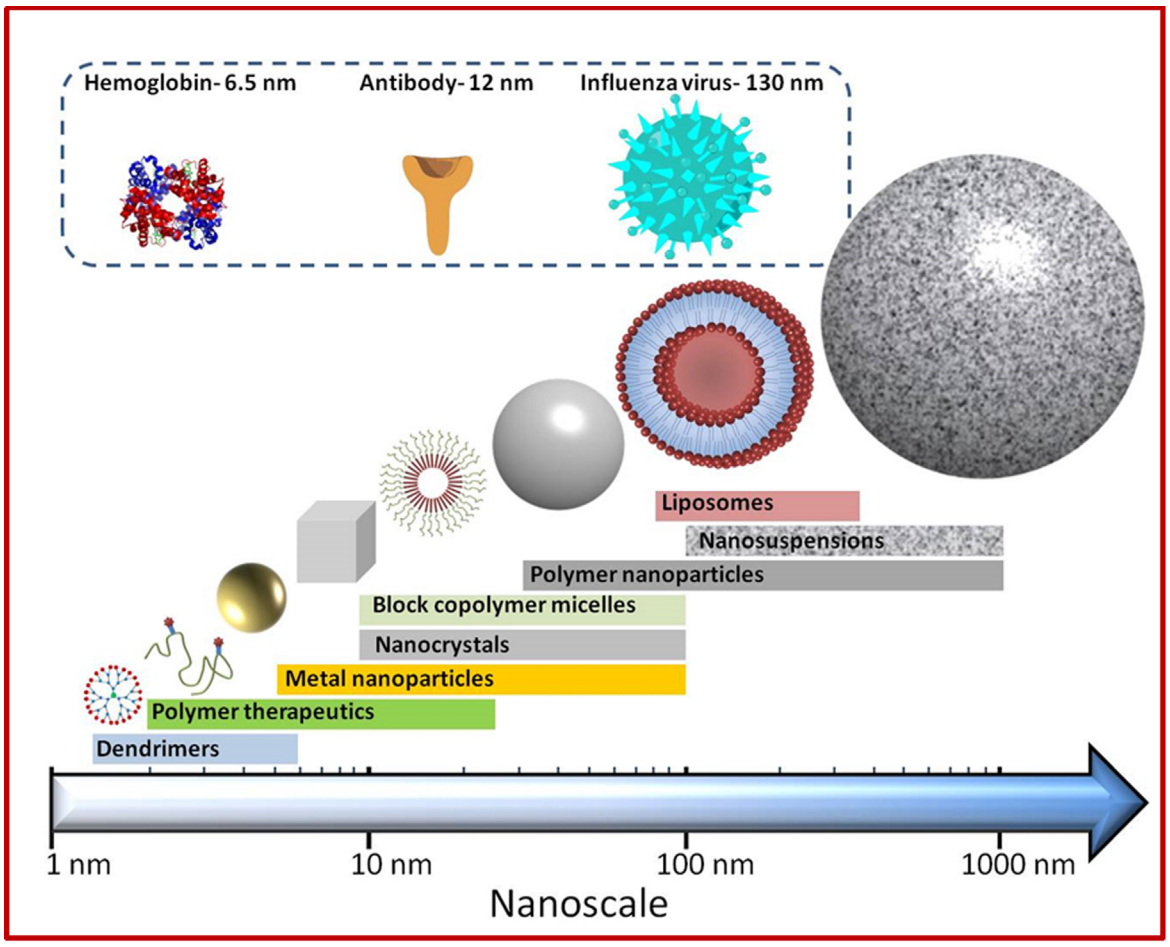


Fig. 1 Different structures of nanomedicines and their approximate sizes (http://www.britishsocietynanomedicine.org/what-is-nanomedicine/).

involves the improved patient stratification process to select subpopulation that has a higher probability of being benefitted from the particularly designed drug therapy and to exclude the high risk individuals from treatment in order to reduce the number of patients suffering from severe side effects. From the industrial point of view, the present personalized medicine is focused on disease diagnostics and risk assessment. It is largely aimed at genomic markers for patient stratification (Reichardt et al., 2016). The present methods coupled with nanotechnology are driving the pharmaceutical industry towards personalized medicine (Fig. 2). Nanoparticle technology has emerged as an effective way of developing the highly specific in-vivo imaging agents that target particularly cancer cells and other components of the tumor microenvironment. The use of nanoparticles as imaging agents has many advantages; (i) large carrying capacities to increase the sensitivity of modalities such as high-resolution MR, (ii) coupling with multiple imaging modalities, thereby enabling non-invasive and intraoperative imaging to ensure complete tumor removal and cancer-free margins, and (iii) can be used as theragnostics to allow monitoring of drug to the tumor site (Shin et al., 2013).

For the development of nanoparticles as effective therapeutic agents, the understanding of tumor microenvironment is important. Cancer or tumor cells are surrounded by complex extracellular fluid, leaky blood vessels, infiltrating immune cells, and stromal cells (Del Vecchio et al., 2010). The tumor cells have abnormal physiological conditions such as hypoxia and acidic extracellular pH (Penet et al., 2008). This creates a barrier for the normal therapeutic agents to act effectively on the cancerous cells and thus, limits their efficacy. The functionalized biocompatible, fluorescent iron oxide nanoparticles have been found to bind effectively in-vivo and in-vitro to secreted protein acidic and rich in cysteine (SPARC) in prostate cancer cells which otherwise effects cell adhesion (Thomas et al., 2011). Thus, nanoparticles could be employed for the designing of personalized treatment strategies. Fluorescent carbon nanoparticles can be used in combination with therapeutic drugs for the treatment of cancer. The carbon nanoparticles act as an effective alternative to the existing drug therapy as these have high water solubility, flexibility in surface modification with various chemicals, excellent biocompatibility, no toxicity, good cell permeability and high photostability (Kumar et al., 2013; Baker and Baker, 2010; Ding et al., 2014).

Lab-on-chip based nanodevices have emerged as potential strategies from the point-of-care diagnostics to tackle the profound issue of global health, especially, in developing countries

Table 1 FDA approved nanodrugs available commercially and in clinical use.

Drug (Cargo)	Nanoparticles (Vehicle)	For	Features of Vehicle
Abelcet (Sigma-Tau)	Liposomes	Fungal infections	Decreased Toxicity
Doxil (Janssen)	Liposomes	Kaposi's sarcoma, ovarian cancer, multiple myeloma	Increased delivery to the disease site, decreased systemic toxicity of free drug
Onivyde (Ipsen Biopharmaceuticals)	Liposomes	Pancreatic cancer	Increased delivery to the tumor site, decreased systemic toxicity
Epaxal (Berna Biotech)	Liposomes	Hepatitis A	Cell-mediated and humoral response, durable immunity against the pathogen, no side-effects in case of infants and children
Cimzia (UCB)	Polymeric	Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	Longer circulation time, greater stability *in-vivo*
Zilretta (Flexion Therapeutics)	Polymeric	Osteoarthritis knee pain	Extended release
Genexol-PM (Samyang)	Polymeric	Metastatic breast cancer	Low toxicity, controlled delivery
Somavert (Nektar, Pfizer)	Polymeric	Acromegaly	Greater protein stability
Estrasorb (Novavax)	Micelle	Vasomotor symptoms in menopause	Controlled delivery
Feraheme (AMAG Pharmaceuticals)	Inorganic	Iron deficiency in CKD	Prolonged, steady release with less frequent dosing
Abraxane (Celgene)	Protein	Breast cancer, NSCLC, pancreatic cancer	Greater solubility, increased delivery to tumor

where there is the greatest need for health technologies. These are portable, highly selective and sensitive towards the disease diagnosis. Lab-on-chip strategies have made a significant contribution to the progress of elimination diseases such as malaria, ebola etc (Kolluri et al., 2017; Kaushik et al., 2016). With the increase in surface area, diffusion distance decreases, the fluid travels through small channels under its own force rather than using pumps, heat capacity reduces leading to fast mass/heat transfer and thus, higher reaction rate. The decrease in size also lowers the sample, reagent, energy consumption and lower waste generation and smaller instrument footprint. Europium (Eu) nanoparticles can emit stable high intensity fluorescence under proper excitation. Biconjugated Eu nanoparticles used as probes have been reported to enhance the sensitivity of microchip immunoassay without the employment of labile catalytic enzymes and detect HIV-1 p24 antigen (Liu et al., 2014a).

2. Smart nanomaterials

Researchers are putting extensive efforts to study and mimic the characteristics of biological microorganisms to create

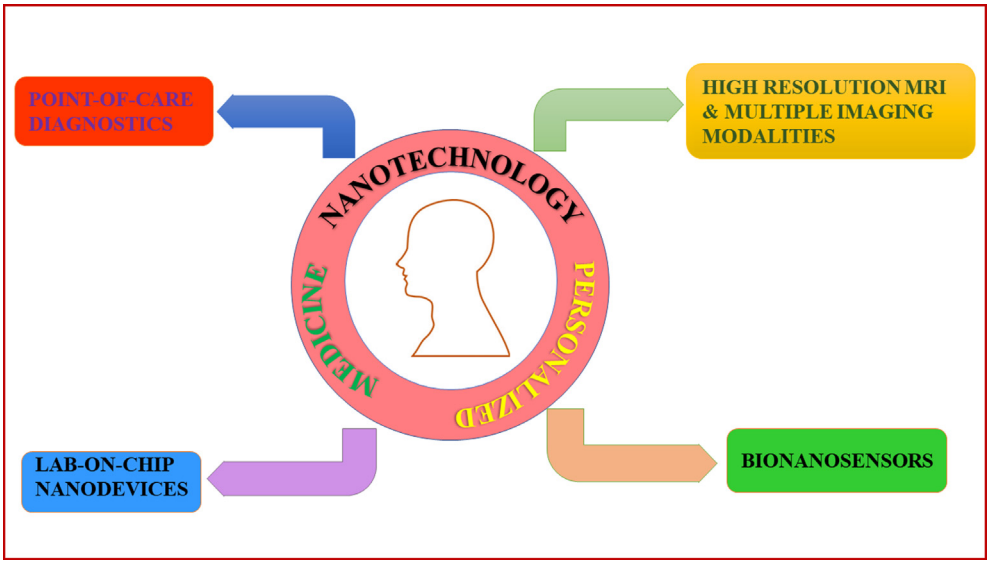


Fig. 2 Nanotechnology tools for personalized medicine.

smart materials. For example, cephalopods (squid, cuttlefish, and octopuses) can change their color by using the tiny muscles in their skin to stretch out small sacs of black coloration (Fig. 3). Zebrafish have also been found to have different camouflaging ability by pumping black pigment fluid under the skin to the surface of the skin. Although synthetic materials lack the ability to change but with the recent advancements in the field of materials science, the natural mechanisms inspire engineers to design smart nanomaterials that respond to external stimuli or their environment. The smart nanomaterials are biomimetic as they can change their properties which enables them to be used in drug delivery and self-healing materials (Yoshida and Lahann, 2008). The examples include the use of smart polymeric materials as artificial muscles which could contract and return to original shape when short-circuited. These can replicate muscular action and can have strong visual effects.

The smart nanoparticles have been classified based on their interaction with their environment; (i) environment responsive nanoparticles, (ii) environment primed nanoparticles. The first class of the nanoparticles sense and respond to their environment. Any disease condition exhibits a change in biochemical properties such as redox potential, pH, enzymatic activity, and homeostatic pathways. These changes can be exploited to immobilize nanoparticles that are administered in the preexisting disease conditions (Kwon et al., 2015). The second class of nanoparticles manipulates the host environment by the administration of radiations (X-rays, infrared, heat), drugs and nanoparticles to enable host-nanoparticle and nanoparticle-nanoparticle interactions.

(i) Environment responsive nanoparticles

The smart polymeric nanomaterials sensitive to stimuli response have been investigated in detail for drug delivery. Since there is an existence of redox potential gradient between the intra- and extracellular space (Meng et al., 2009), various redox responsive polymeric micelles have been obtained successfully (Klaikherd et al., 2009). Polyphosphates are an important class of biomaterials with good biocompatibility, biodegradability and structural similarity to nucleic and teichoic acids (Wang et al., 2001; Zhao et al., 2003). An amphiphilic co-polyphosphate with redox responsive backbone has been employed to construct nanosized micellar drug delivery system having smart redox responsiveness and good biocompatibility and biodegradability, simultaneously. The micelles have a large number of terminal functional groups that bind with the drug molecules/targeting/imaging ligands and are sensitive to environmental responses to release drug especially anticancer drugs into nuclei of tumor cells thereby inhibiting the proliferation of cancer cells (Liu et al., 2011). Hence, responsiveness to the redox environments can be utilized to design effective drug delivery systems for the treatment of disease.

At the cellular or tissue level, there is reduction in pH which has been exploited in many nanoparticle systems where conformational or solubility changes are triggered by acidity along with changes in binding affinity receptor-ligand pairs or the hydrolysis of acid sensitive bonds. In the pharmaceutical field, delivery of poorly water soluble antimicrobial peptides (AMPs) is a challenge. In the literature, a pH-sensitive

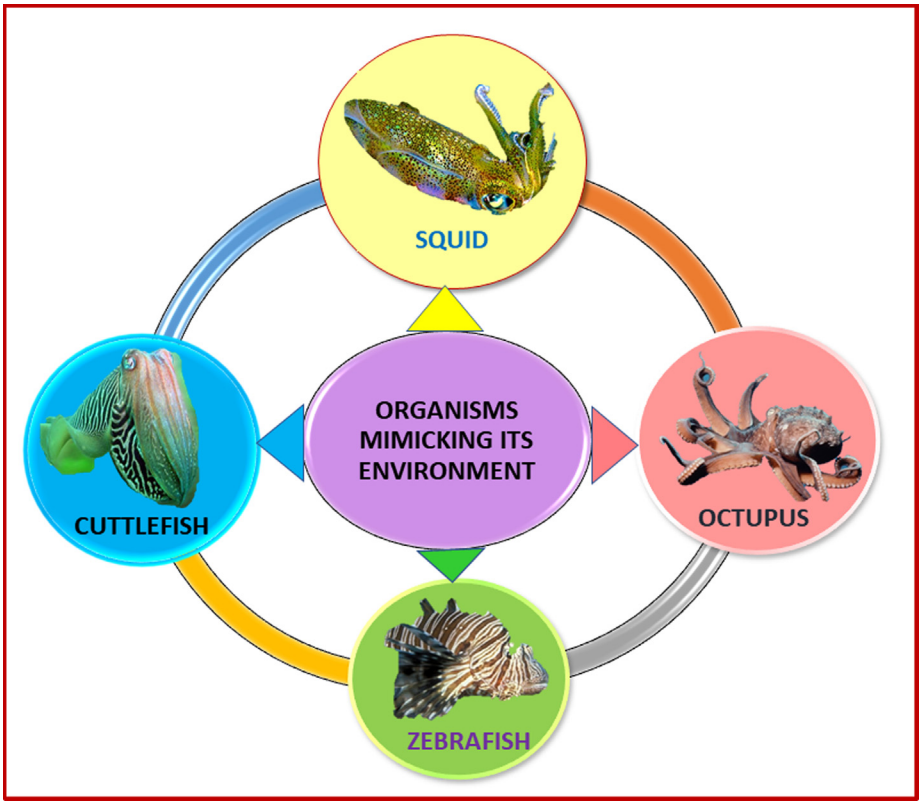


Fig. 3 Organisms that camouflage to mimic their environment.

nanocarrier has been reported to be fabricated with the potential of delivering AMPs and their protection from degradation. The nano-biointerfaces are prepared via the self-assembly of oleic acid (OA) with the human cathelicidin LL-37 in excess water (Gontsarik et al., 2018). It is suggested that the interactions between the AMP and the lipid play an important role in the destruction of the bacterial membranes. In the pH tunable, nanosystems, the protonation and deprotonation of the specific surfactant molecules, such as long chain fatty acid molecules embedded in the self-assembled system, modify the geometric packing of the molecules leading to a change in the nanostructure (Salentinig et al., 2010; Suga et al., 2016).

The decrease of pH in the tumor environment has been harnessed to develop smart nanosystems for the targeted release of chemotherapeutics. Due to inadequate lymphatic drainage in the tumors, there is an accumulation of acidic metabolites (Martin and Jain, 1994). Langer group reported the synthesis of poly (β-amino ester), the solubility of which was directly influenced by the solution pH. They observed that based on the differences between the extracellular and endosomal/lysosomal pH, the microspheres prepared from hydrophobic polymers such as poly (lactic-co-glycolic acid) (PLGA) can be employed in the development of drug delivery devices (Lynn et al., 2001). pH responsive nanomaterials have been used to design sensitive nanosystems for the drug delivery in cancer therapy as they have the ability to stabilize the drug at physiological pH and release the drug when the pH trigger point is reached (Liu et al., 2014b).

A recent promising area of research is the designing of smart nanomaterials whose chemical structure or properties are responsive to the biocatalytic action of enzyme. Enzymes play a critical role in all biological and metabolic processes and their dysregulation is a feature of many diseases. Thus, the smart nanomaterials can sense these enzymes in the host environment and act as a promising tool for diagnostic and therapeutic applications. The enzyme responsive smart nanomaterials include polymer materials (Wang et al., 2010), phospholipids (Wang et al., 2015), and inorganic materials (Popat et al., 2012). Functional mesoporous silica nanoparticles (MSNs) synthesized using alkoxysilane tether, α-cyclodextrin, and multifunctional peptides have been designed to target tumor cells and reduce the side effects of antitumor drug doxorubicin (DOX). The multifunctional peptides were composed of the cell-penetrating peptide of seven arginine (R7) sequence, an enzyme-cleavable peptide of GFLG, and a tumor-targeting peptide of RGDS. When the DOX-loaded MSNs are incubated with tumor cells and normal cells, the nanoparticles could target tumor cells by the specific interactions between RGDS and integrins receptor $\alpha_v\beta_3$ overexpressed on tumor cells, followed by penetrating cell membrane with the aid of R7 sequence. As soon as drug-loaded nanoparticles are inside the cellular membrane, the drug is released quickly due to the

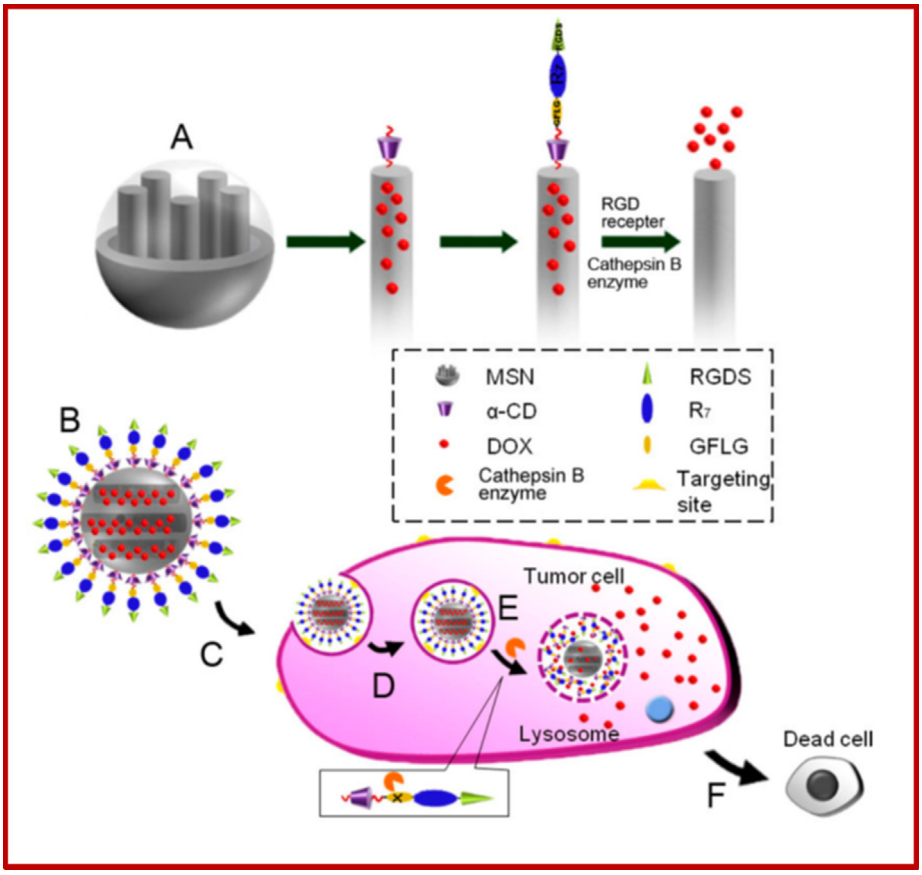


Fig. 4 (A) Functionalization procedure of the MSNs. (B) Drug-loaded MSNs under physiological condition. (C) RGDS-targeted to the tumor cell. (D) Endocytosis into a specific tumor cell. (E) Cathepsin B enzyme-triggered drug release in the cytoplasm. (F) Apoptosis of the tumor cell. Reprinted from reference Sahle et al., 2017.

breakage of GFLG peptide cleaved by cathepsin B, resulting in enhanced antitumor activity. This effective enzyme-responsive nanoparticle based drug delivery system has a great potential in the field of nanomedicine (Fig. 4) (Cheng et al., 2015).

Many physiological functions are regulated by homeostatic mechanisms and this has inspired the fabrication of homeostatic nanoparticle systems with the incorporation of sensor, effector or negative feedback system. The basic principle is the binding of the nanoparticles directly with the detected ligand (Fig. 5D). These type of nanoparticle systems have been employed in the delivery of insulin to regulate glucose levels in the body. Currently, patients with diabetes must maintain glucose levels either by controlled monitoring or taking oral insulin. Thus, a method of insulin delivery that could respond to glucose levels without outside input can be beneficial for diabetes management. A "Smart Insulin," is a commercially developed nanoparticle formulation that releases insulin based on lectin-mediated glucose binding (Veiseh et al., 2015).

(ii) Environment-primed nanoparticles

In some cases, there are disease conditions where disease may not bring changes that can be targeted by the nanoparticles. In this class, nanoparticles bring change in the host environment. The change can also be brought by administration of energy or small molecules that are delivered in the multistage treatment as part of the self-regulating cycle especially in the cancer nanotechnology.

MicroRNAs are the most promising candidates due to their vital role in tumorigenesis and significant expression difference. In the malignant tumor cells, microRNAs are in low abundance and therefore, the drug release triggered by them is greatly hindered. Stimuli responsive DNA Y-motif has been designed for the co-delivery of small interference RNA (siRNA) and doxorubicin (Dox) in which the cargo release is achieved via enzyme-free cascade amplification with endogenous microRNA as a trigger and ATP (or H+) as fuel through toehold-mediated strand displacement. For controlled release in tumor cells, nanocarriers are constructed with stimuli-responsive Y-motifs, gold nanorods and temperature-sensitive polymers, whose surfaces could be reversibly switched between PEG and RGD states *via* photothermal conversion. The PEG corona on the surface of nanocarriers protect the coupled Y-motifs from nuclease degradation thereby favoring their accumulation at the tumor sites. The gold nanorods heat the surrounding environment under mild near infrared radiation (NIR) and facilitate the specific receptor-mediated endocytosis by tumor cells (Zhang et al., 2016).

2.1. Synthesis of smart nanomaterials

In the field of biomedical research, the nanotechnology-based approaches have led to the development of therapeutic drugs and pharmaceutical formulations. To come up with the effective diagnostic treatments for the different diseases (cancer, HIV, hepatitis, coronary heart diseases etc.) and to improve the quality of human life, ongoing innovations in the field of drug design and delivery depend on nanotechnology. The most utilized nanocarriers are based on nanoparticles including liposomes, dendrimers, polymeric nanoparticles, inorganic, and

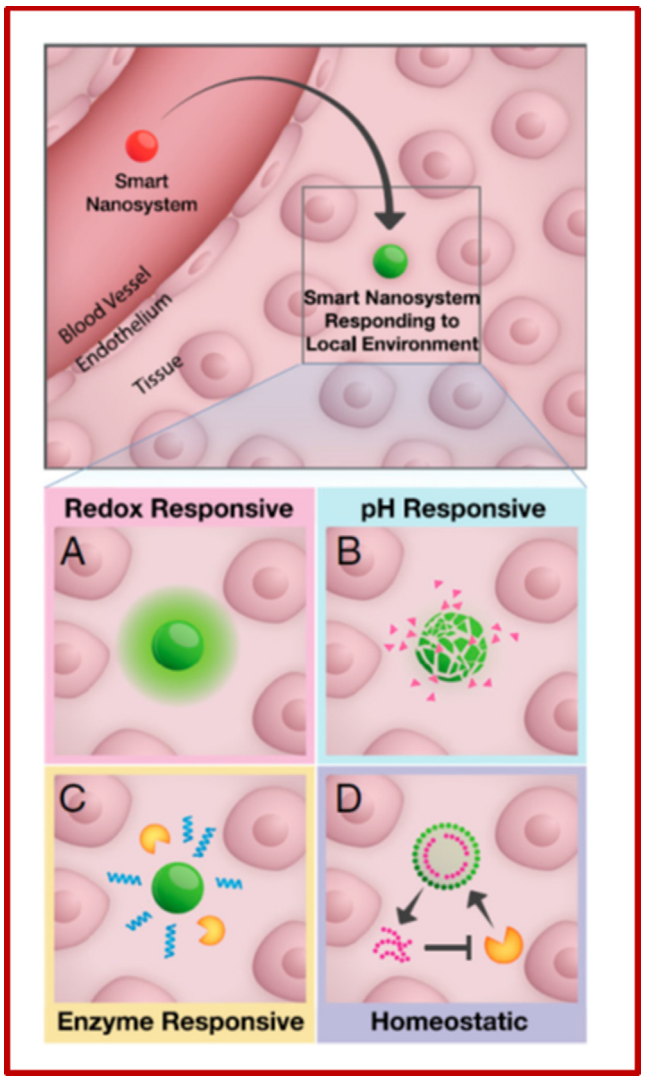


Fig. 5 Smart nanosystems in circulation (red) can sense their local environment and are responsive (green) to (A) redox, (B) pH, (C) enzymes, (D) homeostatic regulation. Reprinted from reference Kwon et al. (2015).

metal nanoparticles, carbon nanotubes, lipid nanoparticles, core-shell nanoparticles, mesoporous silica nanoparticles etc (Karimi et al., 2016). Therefore, the synthesis methods nowadays is primarily focused on the rational development and applications of nanoparticles as effective drug carriers and imaging agents.

Scarabelli group has explained about the four distinct stages involved in the development of any nanodevice and these are interconnected (Scarabelli et al., 2017) (Fig. 6).

1. Preparation and conceptualization of a systematic staring idea(s) required for the fabrication of the nanodevice.
2. Creation and assembly of different components into the desired structure.
3. Systematic and detailed characterization of the final obtained structure.

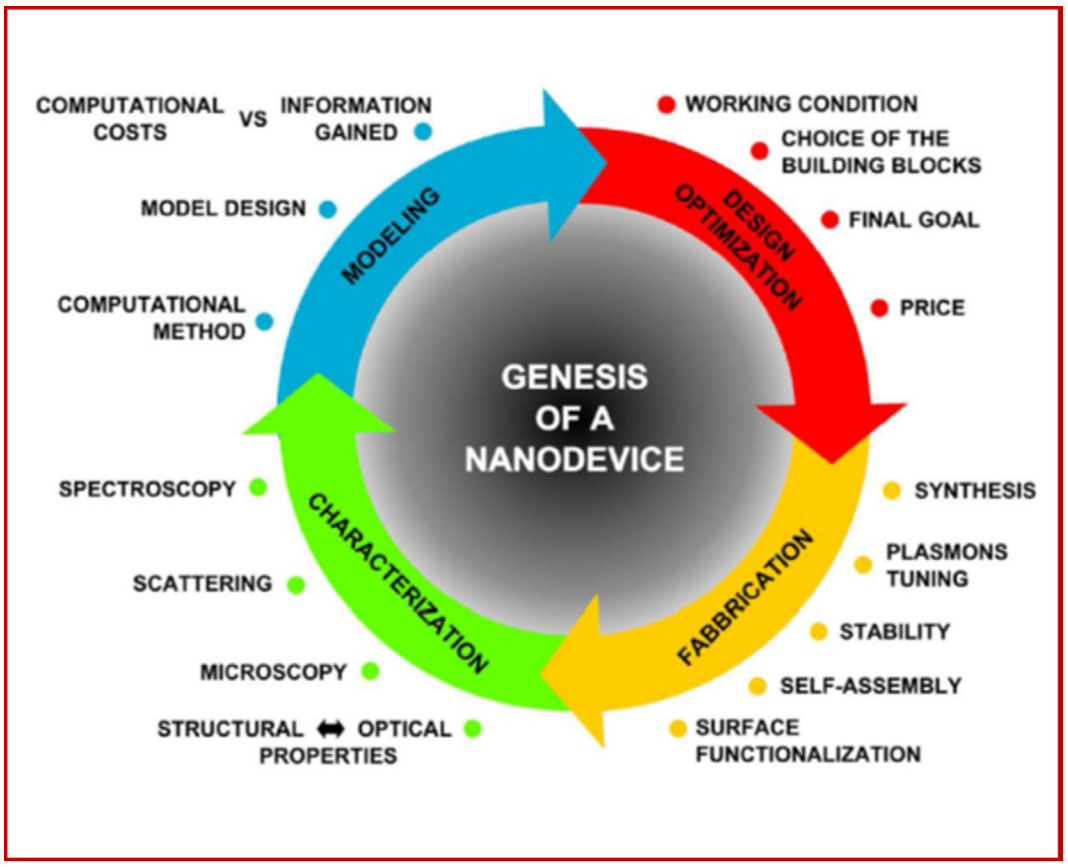


Fig. 6 Schematic representation of an "improvement loop" that leads to the development of new material/device. Reprinted from reference Scarabelli et al. (2017).

4. Interpretation of the experimental data based on the existing or new theory.

The four stages in Fig. 6 have been organized in the form of a "loop" where each step takes forward for the designing of new functional nanomaterial.

Magnetic nanoparticles (MNPs) are an excellent class of materials that have good biocompatibility and excellent magnetic responsiveness (Wang et al., 2013). A novel type of MNPs with smart polymer brushes have been reported with the selective adsorption and separation of chiral amino acid (AA) enantiomers. The MNPs have been synthesized by grafting linear poly(N-isopropylacrylamide-co-glycidylmethacrylate) (poly(NIPAM-co-GMA)) chains attached with numerous β-cyclodextrin (CD) functional molecules on the surface of Fe_3O_4 nanoparticles by the surface-initiated atom transfer radical polymerization (SI-ATRP) technique and subsequent ring opening reaction (Fig. 7). The grafted polymer act as brushes and β-CD units play a key role in the chiral separation of AA enantiomers. These smart nanoparticles demonstrate excellent thermo-sensitive adsorption and separation results and the MNPs can be regenerated by simply changing the operation temperature under the effect of the external magnetic field (Song et al., 2016).

Mussel inspired polymer coated superparamagnetic iron oxide nanoparticles (SPIONs) have been designed with anticancer drug (BTZ) incorporated within the nanoparticles by thermal decomposition method. The multiple catecholic groups are introduced along the polymer chains by using a biocompatible copolymer poly (2-hydroxyethyl methacrylate-co-dopamine methacrylamide) p(HEMA-co-DMA) (abbreviated as HEDO) synthesized via radical polymerization to accommodate several anchoring groups that can bind with nanoparticles as well as borate-containing anticancer drug BTZ. The drug loaded nanoparticles act as hypothermic agents by delivering heat when an alternating magnetic field is applied and act as chemotherapeutic agents when the anticancer drug bound to catechol moieties is released in a pH dependent manner (Sasikala et al., 2015).

The ability of smart nanoparticles to deliver drugs and act as imaging agents in response to disease-specific or physiological signals requires simultaneous control over the shape and size during the synthesis of nanoparticles. The current methods have limitations to fabricate shape and size-specific nanoparticles that can impart environmentally-triggered release mechanisms for in-vivo, in-vitro transport, biodistribution, and therapeutic efficiency (Ferrari, 2005). Step and flash imprint lithography (S-FIL) leads to the fabrication of stimuli-responsive, easily harvestable nanoparticle in the size range below 50 nm. The biodegradable acrylated peptides and polyethylene glycol (PEG) macromers are incorporated in the matrix of nanoparticle and help in the triggered release of encapsulated drugs. S-FIL is a high-throughput, commercially available nanomolding process that utilizes the topography of topaz template to mold macromers that can crosslink into patterns on a silicon wafer (Glangchai et al., 2008). PEG

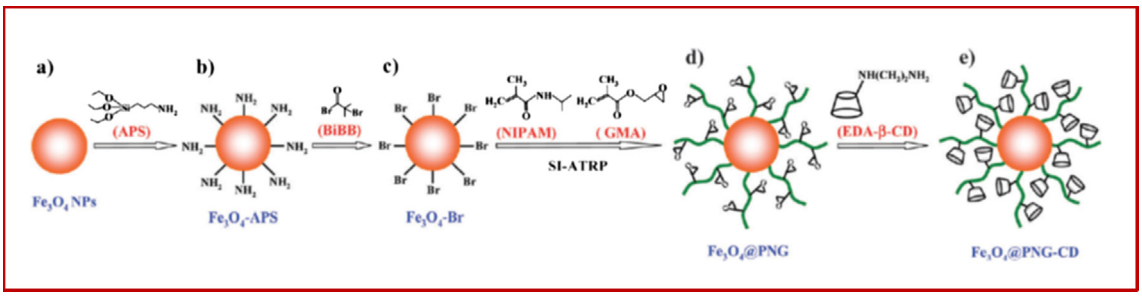


Fig. 7 Synthesis of the Fe_3O_4@PNG-CD smart chiral MNPs. Reprinted from reference Song et al. (2016).

conjugation to nanoparticle surfaces such as lipid nanoparticles protects against particle clearance in the blood thereby generating long circulating carriers (Kawano et al., 2006; Awasthi et al., 2003).

Flame technology has been employed widely for the synthesis of nanostructured materials. This technology is a low investment process with improved scalability. In this process, energy is generated chemically that drives the reactions for particle formation. The radiation and convection methods are used to remove the released energy rapidly for the preparation of nanoparticles (Strobel and Pratsinis, 2007).

In the flame-assisted spray pyrolysis (FASP), an external flame is used as a heating source for the low enthalpy-content spray solution of inorganic precursors. For high enthalpy-content organic solution, flame spray pyrolysis (FSP) uses the small pilot flame source to ignite and sustain spray combustion. Vapor-fed aerosol flame synthesis (VAFS) is the process of combustion of volatile precursors in hydrocarbon, hydride or halide flame. Here, complete precursor evaporation leads to the formation of solid nanoparticles (see Fig. 8).

A comparative study of the methods mostly employed for the synthesis of smart nanomaterials in research and other applications has been summarized in Table 2.

2.2. Characterization techniques

The development of smart nanosystems with increased complexities requires improved and sophisticated characterization techniques (Fig. 9). In this section, an overview of smart nano-

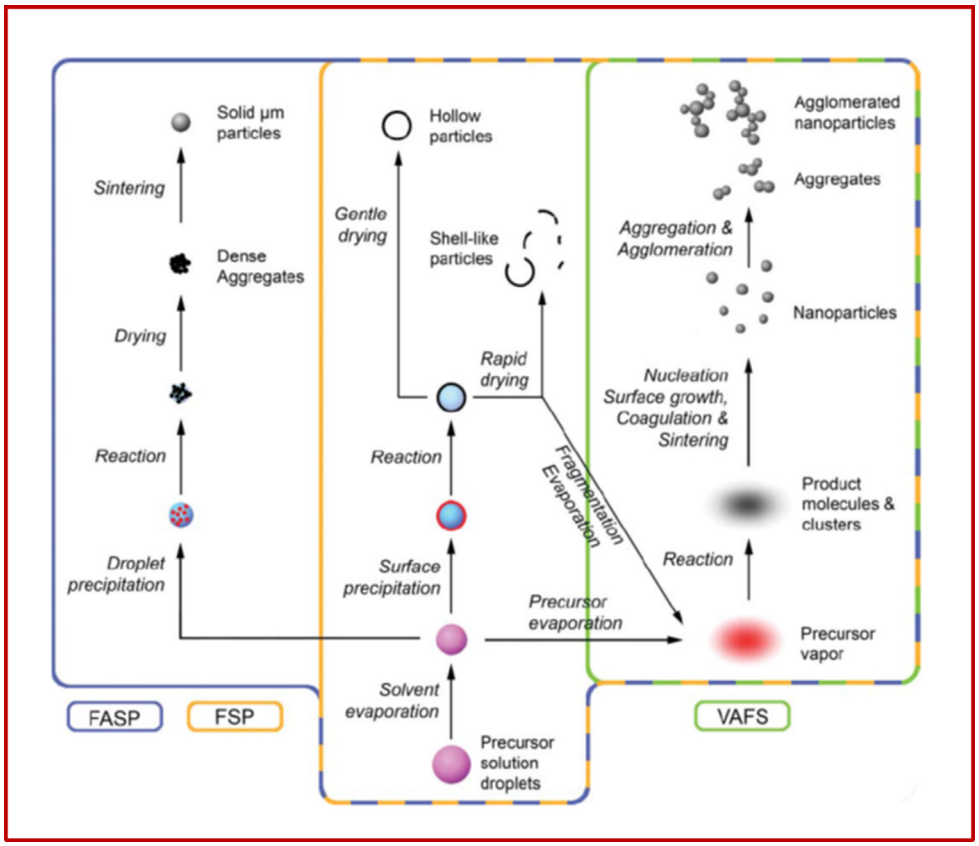


Fig. 8 Schematic for particle formation mechanisms during flame assisted spray pyrolysis (FASP), flame spray pyrolysis (FSP) and vapor-fed aerosol flame synthesis (VAFS). Reprinted from reference Strobel and Pratsinis (2007).

Table 2 Advantages and limitations of synthesis methods employed for the fabrication of smart nanomaterials.

Method	Advantages	Limitations	References
Gas-phase deposition	• Feasible	Problem in controlling the size of nanoparticles	Cuenya (2010)
Electron beam lithography	• Well controlled interparticle spacing	Require highly complex and expensive instruments	Lin and Samia (2006)
Microwave	• Reduced reaction or preparation time • Small and narrow particle size distribution	Sometimes leads to poor dispersion of nanoparticles	Liu et al. (2007) and White et al. (2009)
Pulsed layer ablation/Laser ablation in liquid	• Facile, simple and effective route for contamination free nanoparticles • Facilitates greater control of particle geometry • Absence of catalysts	Low production	Zeng et al. (2012)
Supercritical fluids	• Organic solvents not required • Efficient control of particle size	Requires high temperature and critical pressure Limited solubility of precursors in the supercritical phase	Zhang and Erkey (2006) and Ali et al. (2016)
Flow injection	• Homogenous • Reproducible	Requires continuous or segmented mixing of reagents	Salazar-Alvarez et al. (2006)
Biological (microbial incubation)	• Reproducible • Scalable • High yield • Low cost	Time-consuming	Narayanan and Sakthivel (2010)

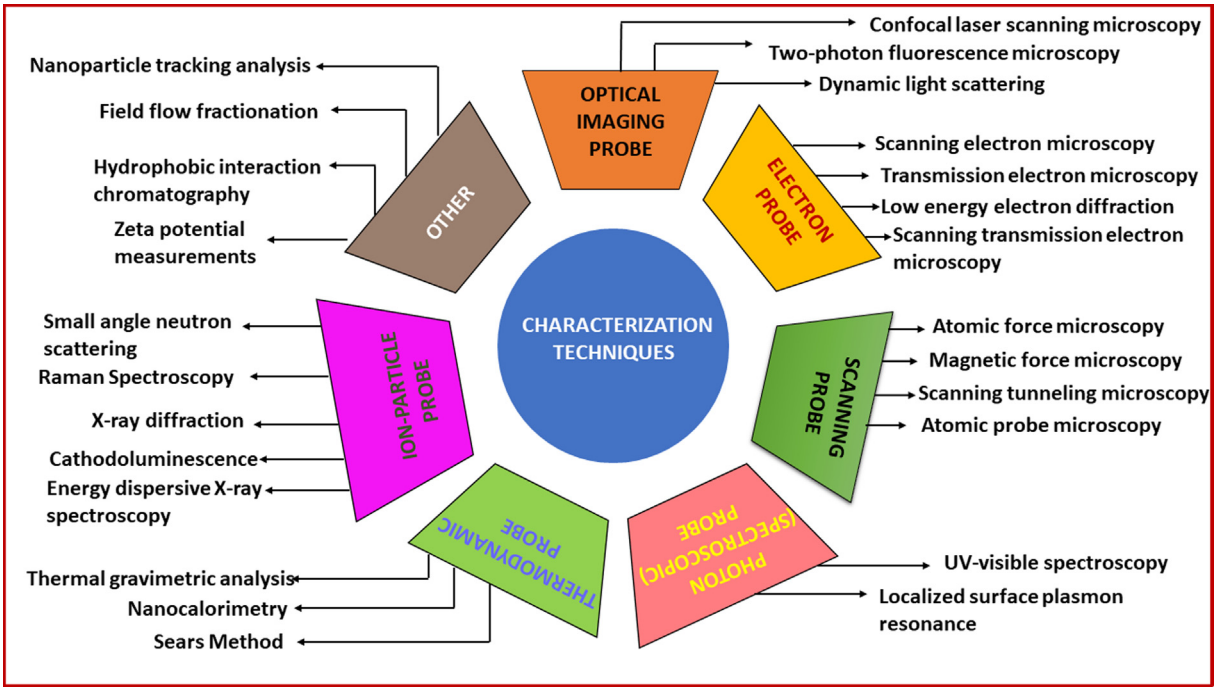


Fig. 9 Different smart nanoparticle characterization techniques.

materials characterized by different instrumentation techniques has been stated.

Nanogels are thermoresponsive nanoparticles prepared by using thermoresponsive polymers that can undergo conformational changes from an extended/hydrophilic coil to a globular/hydrophobic state on heating above a certain temperature known as lower critical solution temperature (LCST). These are loosely crosslinked polymer chains arranged in the three-dimensional network. These nanogels have been characterized by transmission electron microscopy (TEM) and atomic force microscopy (AFM) (Fig. 10) (Sahle et al., 2017). The size of the nanogels decreased by a factor of 2–3 times in the TEM images as compared to the hydrodynamic diameter of nanogels obtained from dynamic light scattering. This is attributed to the drying of nanogels during the drying process in the sample preparation for TEM. The size of nanogels is bigger in AFM

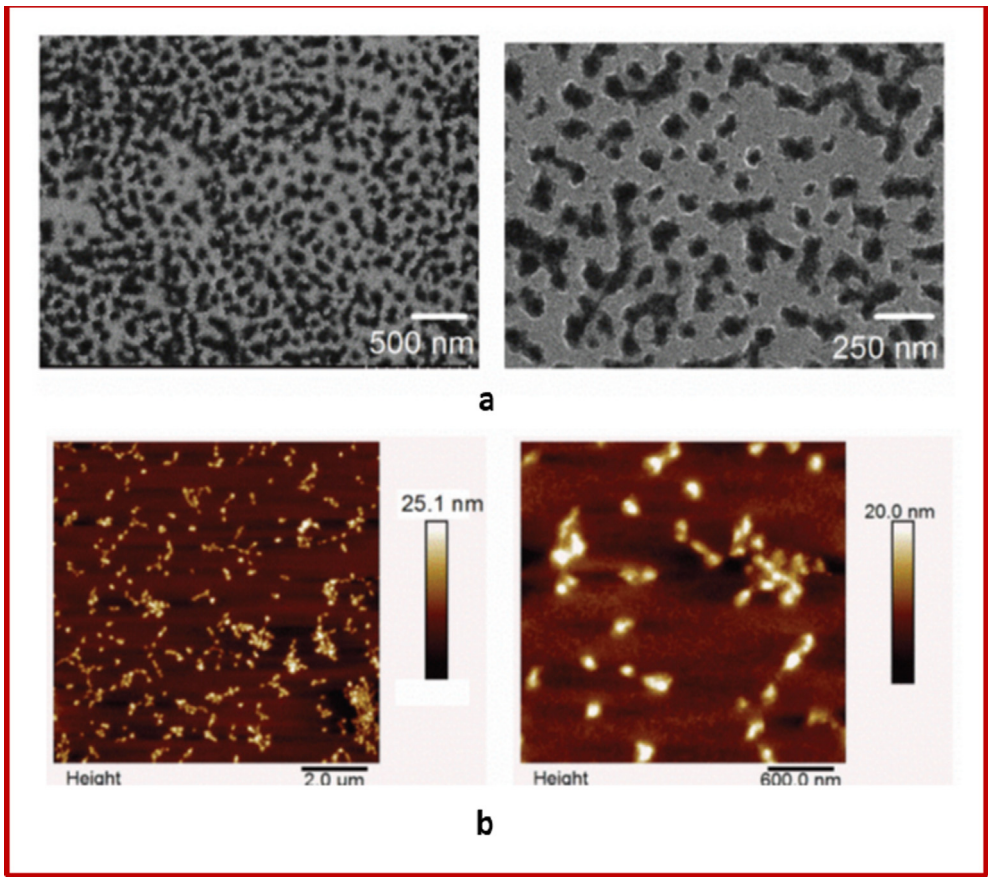


Fig. 10 Different microscopy images of selected nanogels obtained at two different magnifications: (a) TEM and (b) AFM images. Reprinted from reference (Sahle et al., 2017).

images as compared to TEM images. This can be attributed to less amount of water being removed from the sample in AFM.

The vault nanocapsules have been determined by electron microscopy (EM), dynamic light scattering experiments, and UV–vis turbidity analysis. Nanovaults are used in multiple biomedical and biotechnological applications. These are highly conserved ribonucleoprotein complexes with high molecular weight and found in high concentration in almost all eukaryote cells. The vaults are conjugated with polymers ultimately forming nanovaults which could undergo aggregation on heating above the lower critical solution temperature (LCST) (Matsumoto et al., 2013). UV–vis turbidity analysis shows the thermoresponsive properties of the conjugates. The study shows that the polymer is covalently bonded to the protein and the polymer confers thermal responsivity to the vault. In Fig. 11a, the polymer has LCST of 30.5 °C with a sharp phase transition. When the polymer is conjugated with the vault, the LCST increased to 35.9 °C due to the proximity with the protein. The phase transition is broad due to the distribution of the number of polymers and attachment sites.

Uniform SiO_2 coated Fe_2O_3 nanoparticles with superior colloidal stability and dispersibility facilitates their incorporation in alginate hydrogel microbeads. The hyperthermia performance of these nanoparticles has been studied in the presence of alternating magnetic fields. The magnetic properties of the beads have been determined by a multi-segment hysteresis loop measurement in the vibrating sample magnetometer (VSM). The presence of SiO_2 coated Fe_2O_3 nanoparticles in the alginate beads leads to their low coercivity near to superparamagnetic behaviour (Teleki et al., 2016).

Table 3 illustrates some of the techniques used for the characterization of smart nanoparticles. Application of nanoparticles in drug delivery and targeting can be determined conveniently using various sophisticated tools.

3. Applications of smart nanomaterials

The applications of smart nanomaterials in different areas has been depicted in the form of a chart in Fig. 12. Some of the important applications focused in the field of pharmaceuticals are discussed in the subsequent sections.

3.1. Electrochemical analysis

The use of nanoparticles in the biochemical analysis has been reduced to the following; (i) the surface of the nanoparticle is modified with a highly selective protein, amino acids, etc., (ii) the modified nanoparticles are introduced into the test object (sensing of analytes) where interaction takes place between

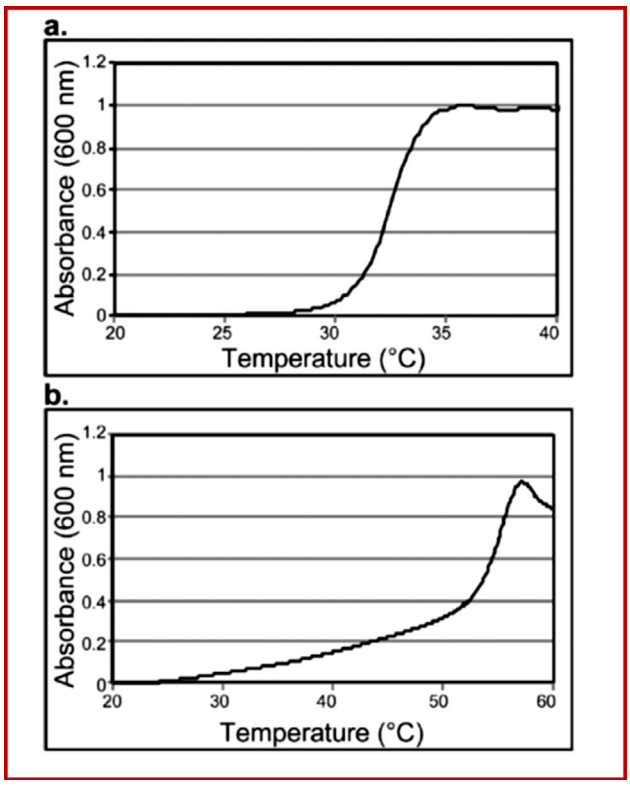


Fig. 11 UV–vis turbidity study of (a) polymer, and (b) conjugate. LCST is 10% of the maximum absorbance. Reprinted from reference (Matsumoto et al., 2013).

Table 3 Various characterization tools for the smart nanoparticles (Bhatia, 2016).

Parameter	Characterization tool
Carrier-drug interaction	Differential scanning calorimetry
Charge determination	Laser Doppler Anemometry Zeta potentiometer
Chemical analysis of surface	Static secondary ion mass spectrometry Sorptometer
Drug stability	Bioassay of drug extracted from Nanoparticles Chemical analysis of drug
Nanoparticle dispersion stability	Critical flocculation temperature (CFT) Particle size and distribution Atomic force microscopy
Particle size and distribution	Atomic force microscopy Laser diffractometry Photon correlation spectroscopy (PCS) Scanning electron microscopy Transmission electron microscopy
Release profile	In vitro release characteristics under physiologic and sink Conditions
Surface hydrophobicity	Rose Bengal(dye) binding Water contact angle measurement X-ray photoelectron spectroscopy

nanoparticles and the analytes, and (iii) the interactions are studied via different electrochemical techniques that provides to reach high selectivity and sensitivity (Vertelov et al., 2007).

The surface of an electrode modified with nanoparticles increases the surface area of an electrode and thus, the modified electrode has more sorption capacity than the normal electrode (Hernández-Santos et al., 2002). The glassy carbon electrode (GCE) modified with multi-walled carbon nanotubes (MWCNs) and ZnO nanoparticles has was reported to sense silymarin molecule with electrochemical signals 2-fold higher than bare GCE. Density functional theory (DFT) calculations showed that charge transfer between the silymarin and ZnO nanoparticles was responsible for the electrochemical sensing of analyte (silymarin) (Sharma et al., 2018).

With the development of nanobiosensors, which are capable of characterizing and quantifying biomolecules, there have been great advancements in the field of biology and medicine. Hydrogel nanoparticles have been found to have promising applications in catalysis, drug delivery and other biotechnological areas (Schexnailder and Schmidt, 2009). Hydrogels are cross-linked polymer networks swollen with water in the presence of nanoparticles. These have been successfully used as electrochemical biosensors due to their superior sensor performance and moreover, they minimize the overall cost of the sensor (Hasanzadeh et al., 2014). The large interfacial area allows the immobilization of the biomolecules and increases the biometric identification probability. These 3D-nanomaterials provide several advantages which pave their way in the field of biosensors;

(1) Large specific surface area over 2D/1D nanomaterials due to the presence of nanoscale-pores in the interconnected porous structure.
(2) Excellent conducting properties of polymers due to the presence of a π-conjugate backbone that promotes the rapid electron transfer.
(3) Good biocompatibility of hydrogels promoting the immobilization of biomolecules and keeping their bioactivity intact.
(4) Excellent processability that leads to any desired shape on gelation. The synthesis procedure is simple, and no surfactants or templating agents are required.

Based on the above advantages, a sensitive label-free amperometric biosensor based on polypyrrole (PPy) hydrogel and Au nanoparticles have been designed for the sensitive and low detection limits of Carcinoembryonic antigen (CEA) biomolecule (Fig. 13). Au NPs play an important role in increasing the electrical conductivity and promote electron transfer whereas PPy hydrogel promoted the dispersion of Au NPs in the polymer matrix (Rong et al., 2015).

Graphene-based electrochemical sensors have received a great deal of attention due to their excellent ability to detect organic molecules (Wang et al., 2009; Varghese et al., 2009). The large surface area renders enhanced electron transfer process. It provides an extremely attractive support for the incorporation of nanoparticles. In one of the study, Au nanoparticles with varied amounts were embedded in the few-layer graphene sheets. The platinum electrode was modified with this composite (graphene + Au NPs) to detect adenine, one of the DNA bases. The enhanced electrochemical oxidation of adenine was attributed to the kinetics of the interfacial charge transfer at the surface of the modified platinum electrode (Biris et al., 2013).

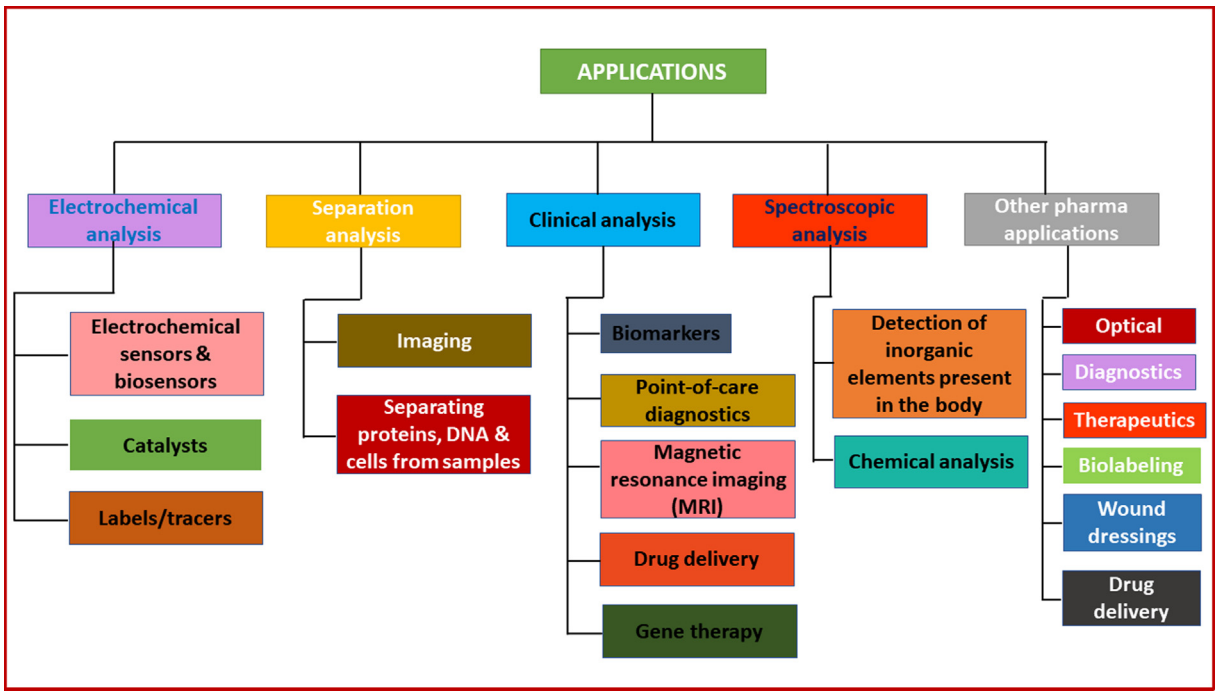


Fig. 12 Applications of smart nanomaterials.

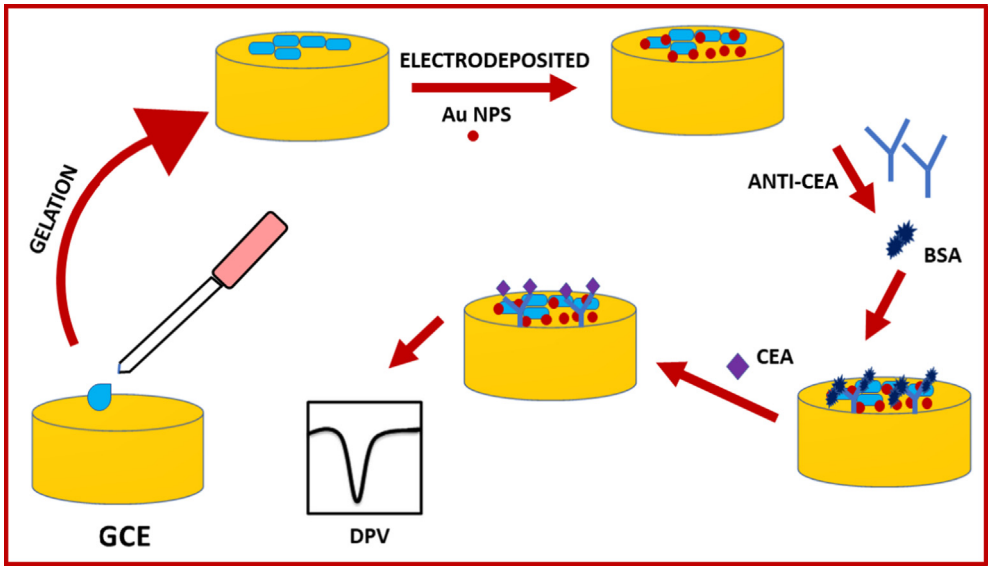


Fig. 13 Schematic illustration of the electrochemical immunoassay protocol. Modified from reference (Rong et al., 2015).

Plasmonic nanoparticles have been found to accelerate electrochemical reactions. When a nanostructured material interacts with the photons that match the resonance energy of the collective oscillation of the surface valence electrons, there is an occurrence of excitation of localized surface plasmon resonance (LSPR) (Chou et al., 2012). Due to LSPR, strong electromagnetic field and a high concentration of energetic carriers (electron-hole pairs) is generated at the surface of nanoparticles (Kale et al., 2014). The enhanced electromagnetic field generated makes the plasmonic nanoparticles an ideal platform for many potential applications. The glucose electrocatalysis occurs in the presence of Au NPs where the direct plasmon accelerated chemical reaction (PAER) takes place. The charge carriers (holes) generated upon LSPR excitation assists the electrocatalytic oxidation of glucose due to their matched energy levels (Wang et al., 2017).

3.2. Separation analysis

Au NPs have been used in the capillary electrophoresis (CE)-based analysis because of the enhanced separation resolutions (Zhang et al., 2008b). The NPs also act as a pseudo-stationary phase in the presence of poly (ethylene oxide) (PEO) for the

Table 4 Smart nanomaterials used in isolation and identification of CTCs.

Nanomaterials	Advantages	References
Magnetic nanoparticles	Cellular internalization, biocompatibility, magnetic separation, easy scale-up	Ming et al. (2017) and Wu et al. (2013)
Gold nanoparticles	High stability, laser-controlled simultaneous detection, and ablation, biocompatibility, no blood sampling issue	Bhattacharyya et al. (2012) and Zhang and King (2017)
Nanopillars, nanowires, nanofibers	Interactions with extracellular features, increased surface area, potential thermosensitivity	Hou et al. (2013) and Kim et al. (2010)
Quantum dots	Quantitative detection with high sensitivity, Potential for surface marker-dependent separation, Stable fluorescence intensity	Myung et al. (2016) and Lee et al. (2013)
Graphene oxide	Ultrahigh specific surface area for multiplex functionalization, Increased surface area, Interactions with extracellular features, Excellent thermal, electric conductivity, and its optical transmittance	Cruz et al. (2016) and Li et al. (2015a)

separation of double-stranded DNA. The interaction between DNA and PEO is enhanced in the presence of NPs thereby improving the sieving ability of PEO without any change in its viscosity. The separation of acidic and basic proteins using a capillary filled with surfactant capped Au NPs has been reported (Yu et al., 2006) along with high separation efficiencies for a variety of analytes (Liu, 2009). A simple approach has been demonstrated for the fabrication of highly efficient columns coated with octadecylamine-capped Au NPs for open tubular capillary GC (Qu et al., 2008). The stationary phase NPs are applied to the GC separation of many analytes.

Monodispersed silica nanotubes with desired shape and size have been reported to be synthesized via template-assisted synthesis. These nanotubes have inner voids that can be filled with species ranging from large protein molecules to small molecules and the inner and outer surfaces of the nanotube can be functionalized. One of the applications of the nanotubes is the smart nanophase extractor to remove the small molecules from the solution. Since the outer surface of the nanotubes is hydrophilic and inner surface is hydrophobic, these are ideal candidates for extracting the lipophilic molecules from the aqueous solutions. The antibody functionalized nanotube provides an ultimate extraction selectivity. The antibody produced against the drug, 4-[3-(4-fluorophenyl)-2-hydroxy-1-[1,2,4]-triazol-1-yl-propyl]-benzonitrile (FTB) binds selectively with the RS enantiomer and the Fab fragments of the antibody are immobilized on the inner and outer surfaces of the silica nanotubes (Mitchell et al., 2002).

The frightening aspect of cancer is its ability to spread with metastasis causing 90% of cancer related deaths (Gupta and Massague, 2006). The process of metastasis involves the escape of tumor cells from the tumor site and enter the main bloodstream, move to the secondary site, erupt and proliferate form secondary tumor colonies (Chambers et al., 2002). Once the tumor cell has left the primary environment and entered the blood, it averts the immune response and gains protection against the stress caused by the fluid flow. The fate of cancer cells at the secondary site varies; some of the cells may proliferate and some may be dormant or even die. Thus, only a small percentage of cells grow into micrometastases and among this also, few will grow into full blown macrometastatic lesions. This process takes place parallel to the development of the primary tumor and even before the tumor is initially detected. The isolation and identification of these cells (circulating tumor cells, CTC) of vital interest to come up with a complete diagnosis of cancer (Yoon et al., 2014). Various technologies have been developed for the isolation and identification of CTCs, however, there are challenges associated with CTC enumeration. Magnetic nanoparticles functionalized with anti-EpCAM (biomarker) are used to bind with the selected cells in the presence of a magnetic field (Hoshino et al., 2011). This is known as immunomagnetic separation of CTCs. The unique physical properties of nanomaterials make them promising candidates in the field of cancer research (Table 4).

3.3. Clinical analysis

Among different applications of nanomedicine, the most promising ones are in the field of biomedical sciences. These applications have an impact on the human health as these are targeted towards the disease diagnostic methods that are rapid and inexpensive. Some of the areas where nanomedicine is already in use are (Jotterand, 2007);

(i) New types of drugs either based on human genome or structural genome.
(ii) Targeted drug delivery.
(iii) Nanoscale biostructures, which include artificial bone, tissue engineering, and cell therapy.
(iv) Nanobots.
(v) Several types of nanodevices.

To enhance the therapeutic effects and reduce the side effects, the drug molecules should be selectively targeted at the disease site in the body and accumulate there for a prolonged time in the body in a controlled manner. Drug delivery refers to the development of approaches, formulations or techniques required to transport any pharmaceutical compound safely within the body in order to achieve the effective therapeutic effects (Hrubý et al., 2015). In this regard, nanoscale based smart drug delivery systems (DDSs) have opened new opportunities in the field of pharmaceuticals. Nanoparticle based DDSs accumulate and binds specifically to the disease target with controlled release behaviour. The design of nanomaterials as efficient drug carriers should address the following key issues (Liu et al., 2016); (i) biocompatibility and biodegradability, (ii) excellent stability at physiological pH, (iii) high drug loading capacity with no toxicity, and (iv) industrial scale-up of nanomaterials for clinical applications. The stimuli responsive smart DDSs deliver the drug at specific tissues in the systematic administration. These do not freely

extravasate during the blood circulation and are released at the targets where the nanocarriers accumulate by active or passive targeting strategy (Mura et al., 2013).

An immunoassay is a biochemical test that measures the presence or concentration of a macromolecule or a small molecule in a solution using an antibody or an antigen. The key feature is to produce a measurable signal in response to a binding effect. Screen-printed electrodes (SPEs) have attracted attention as immunosensors due to their miniaturized size, low cost fabrication and large-scale production. A single drop of sample i.e. only a few microliters of a solution is used to perform all the immunological steps thereby reducing the consumption of the reagent. SPEs are coupled with nanoparticles which improve the sensitivity of these electrodes (Arduini et al., 2016). Silver nanoparticles modified SPE has been used for the preliminary screening of cystic fibrosis which is a common genetic disease caused by the autosomal recessive gene known as the cystic fibrosis transmembrane conductance regulator (CFTR) gene (Kerem et al., 1989). It affects the multiple organs including the lungs and intestines leading to the irregular transport of sodium and chloride ions across the epithelial cells (Rowe et al., 2005). It is reported in the literature that the oxidation of silver is sensitive to chloride ion concentration (Brolo and Sharma, 2003). Sweat chloride levels are crucial to the diagnosis of cystic fibrosis. A layer of silver nanoparticles is deposited on the working electrode of SPE and anodically stripped off to generate Ag cations. the anodic stripping voltammetry of silver nanoparticles yields a single silver oxidation peak in the absence of chloride ions whereas two voltammetry stripping peaks (one for AgCl and other for the oxidation of Ag to Ag(I) ions) are observed in the presence of chloride ions. The silver chloride peak is used for the quantitative determination of chloride concentration (Toh et al., 2013).

Alzheimer's (AD) and Parkinson's disease (PD) are the most common neurodegenerative diseases that have affected 26 million and 1.6% of the world population, respectively (Brookmeyer et al., 2007; de Rijk et al., 2000). This has posed a growing challenge for the patients, caregivers, clinicians, and society. The current treatment relies on the clinical symptoms and thus, the diagnosis depends on the proficiency of the treating physician. Nanoparticle based sensors are used to distinguish groups of AD and PD patients from a healthy control group. The diagnostic approach relies on the identification of patterns of volatile organic compounds (VOCs) in the exhaled breath (Song et al., 2010). The disease related changes in the blood chemistry may be transmitted to the alveolar exhaled breath via the lungs even in the initial stages of the disease. The sensor undergoes rapid and reversible changes in electrical resistance on being exposed to characteristic VOCs. Therefore, breath prints could be the basis for the development of simple, cost-effective, non-invasive biomarker using nanoparticle based sensors (Tisch et al., 2013).

3.4. Spectroscopic analysis

Ag nanostructures possess excellent surface plasmon resonance (SPR) properties and therefore, Ag NPs are capable of ultra-sensitive analysis down to single molecule level in surface enhanced Raman scattering (SERS) (Li et al., 2012). However, several factors should be taken into consideration when using bare Ag nanostructures; (i) the probes/analytes in direct contact with the surface of Ag can cause an interference in the spectroscopic analysis, (ii) The mechanism of SPR mediated chemical reactions is complex due to the dual functions of Ag nanostructures: local electric fields amplifiers and as "hot carrier" donors (Kumar et al., 2015), (iii) Ag is easily oxidized under ambient conditions thereby leading to decrease in plasmonic enhancement. The Ag nanoparticles are coated with graphene to improve their plasmonic performance (Erol et al., 2009). Shell isolated Ag nanostructures have been reported to exhibit remarkable plasmonic properties with high stability even after 16 months of storage (Li et al., 2015b). The smart Ag nanostructures have advantage of acquiring high quality Raman signal and can be further expanded to surface-enhanced fluorescence used for biological imaging and sensing (Tam et al., 2007).

One of the studies reported the application of core-shell colloidal material consisting of Au nanoparticles coated with thermally responsive poly-(N-isopropylacrylamide) (pNIPAM) microgel (Au@ pNIPAM) for the detection of all types of analytes. The Au core presents the enhanced properties whereas, the pNIPAM shell swell or collapse as a function of temperature. This phenomenon helps to trap molecules and bring them close to metal core for enhanced SERS signal and enabling the rapid detection of molecules or analytes (Alvarez-Puebla et al., 2009).

The nanomaterials have been widely used in imaging with features including improved brightness, inertness of the nanomaterials to the microenvironment and even distribution. As compared to molecular probes, the nanomaterials are not cytotoxic and do not suffer from non-specific binding by cellular biomacromolecules or unwanted sequestration. Number of nanoparticles are commercially available that are used in high throughput screening (Wolfbeis, 2015). Co-encapsulated magnetic photon-upconverting polymeric nanoparticles have been used in bimodal imaging (fluorescent/magnetic resonance). Nanoparticles with layered structure UCNP@$mSiO_2$–Ln (dbm)4, where UCNP stands for upconversion nanoparticle, $mSiO_2$ stands for mesoporous silica, Ln is trivalent ion (Eu, Sm, Er, Nd, Yb) and dbm represents the organic ligand complexed with Ln have acted as excellent multimodal imaging agents (Fig. 14) (Sun et al., 2014).

3.5. Other pharma applications

Hydrogel forming polysaccharides have attracted attention in the designing of Ag nanoparticles with varied morphologies and sizes. Polysaccharide based hydrogels are smart materials widely used in cosmetics, pharmaceuticals, and daily life (Hoffman, 2002; Good et al., 2004). Hydrogels have been employed as capping or templating agents for the fabrication of Ag nanoparticles. One of the potential hydrogel forming polysaccharide is glucuronoxylan (GX). It has been used as a carrier for the targeted release of different drugs due to its pH responsive on-off switching (Muhammad et al., 2016; Ashraf et al., 2017). Ag nanoparticles have been synthesized using GX at alleviated temperature via diffuse sunlight assisted green method (Muhammad et al., 2017). GX-Ag nanoparticles are used in wound healing dressings (Fig. 15). The hydrogel layer does not allow the bandage to fix in the wound area due to moisture and therefore, patient compliance can be

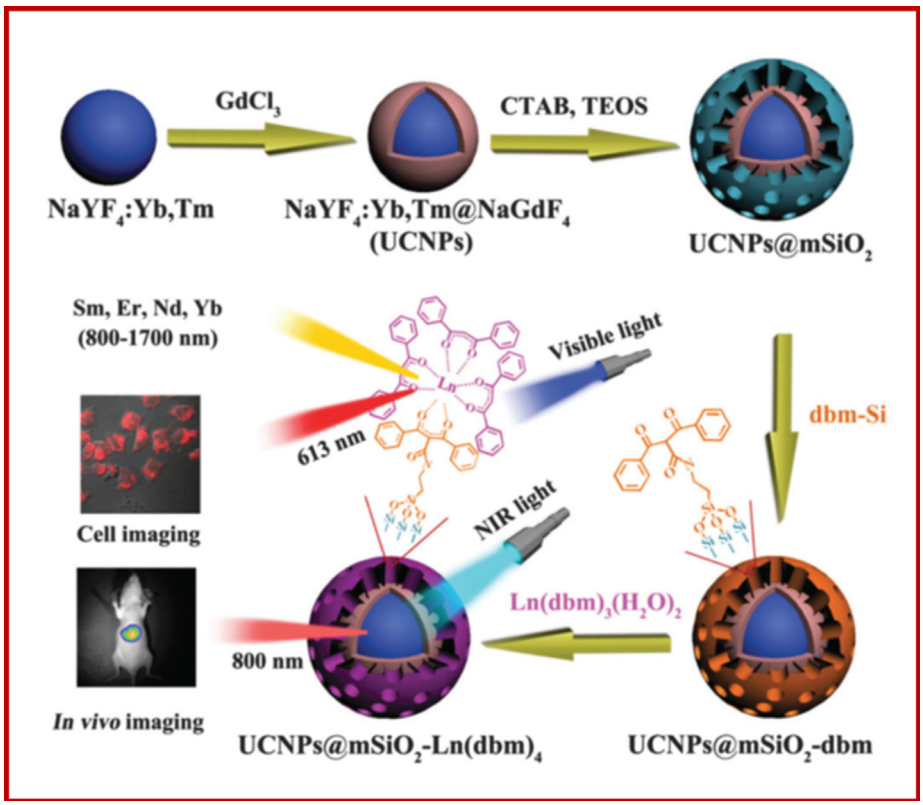


Fig. 14 Schematic of the preparation and structure of multifunctional mesoporous NPs containing both upconversion and magnetic nanophosphors (with an architecture of the type NaYF4:Yb,Tm@NaGdF4) and covered with a conventional luminescent lanthanide complex (Ln-dbm) for use in upconversion and downconversion luminescence imaging and as T1-weighed MRI contrast agents. Reprinted from reference (Sun et al., 2014).

achieved by developing such bandages. The mechanism of wounds is based on the collagen content and tensile strength of epithelium tissues. The rapid wound healing tendency is due to the cross-linking of the collagen fibers.

Diabetes is one of the most dreadful and major health problem in the world showing an alarming increase. Around 25% of diabetic patients are at elevated risk of developing foot complications (diabetic foot ulcer, DFU) (Vellayappan et al., 2016). If not treated earliest, there is always a risk of limb amputation. In the patients with DFU, the wound healing process is impaired. Different approaches have been used to treat DFU but these have limitations. With the rapid advancements in the field of nanomedicine, nanoparticles have shown remarkable results in wound healing process. DFU shows good response when γ-Fe_2O_3 nanoparticles are used (Ziv-Polat et al., 2010). There is an acceleration in the wound healing process. The healing process is impaired due to the late cellular infiltration and granulation tissue formation, decreased angiogenesis, reduced collagen and its organization (Yue et al., 1987). When there is inflammation, the neutrophils and macrophages invade the wound and increase in number within 1–3 h of wounding, generating superoxide radical anions. The process is commonly known as "respiratory burst". In addition, reactive oxygen species (ROS) are generated by pro-inflammatory cytokines (Meier et al., 1989). The production of ROS is a component of the innate immune system to clean the wound from invading bacteria. But if ROS is at elevated level, it can cause severe tissue damage (Cerutti and Trump, 1991). Nanoparticles act as free radical scavengers. CeO nanoparticles have been utilized in the treatment of DFU as these are active free radical scavengers (Zhang et al., 2002). Different applications of nanomaterials have been summarized in Table 5.

In summary, smart nanoparticles have different applications in the field of pharmaceuticals. The applications are dependent on the size of the nanoparticles, their surface modifications and interactions with different analytes. Among different analysis techniques, electrochemical methods are used to study the interaction between nanoparticles and different analytes with high sensitivity and selectivity.

Considering the applications of nanoparticles, magnetic nanoparticles have been found to be promising candidates in the field of cancer research. Nanoscale based smart drug delivery systems (DDSs) have paved their way in the field of pharmaceuticals as these bind specifically to the disease in target and have controlled release behaviour.

Due to their small size, low cost of fabrication, screen-printed electrodes (SPEs) are used in conjugation with smart nanoparticles to act as immunosensor. The nanoparticle modified SPEs are used for the preliminary diagnosis of diseases such as Alzheimer's and Parkinson's disease. Ag nanoparticles have been employed for ultra-sensitive analysis as they possess surface plasmon resonance properties (SPR). The SPR property is further enhanced by coating nanoparticles with graphene. For bimodal imaging, magnetic nanoparticles are covered with lanthanides to form a luminescent complex.

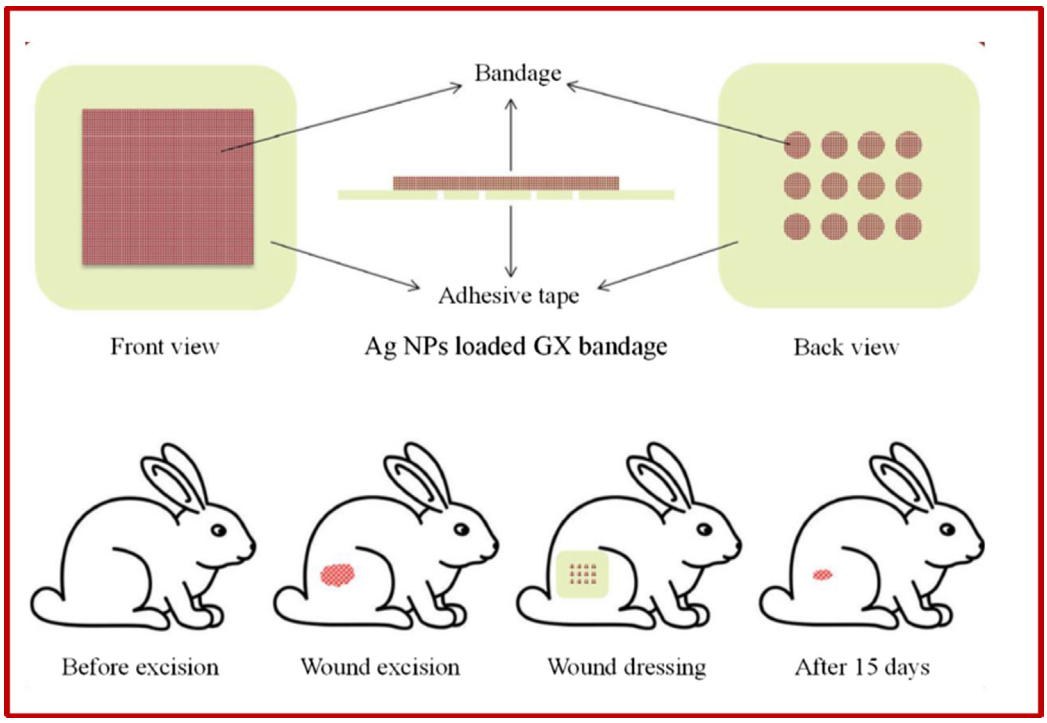


Fig. 15 Schematic diagram showing the preparation of wound dressing and wound treatment. Reprinted from reference (Muhammad et al., 2017).

Table 5 Applications of smart nanomaterials in pharmaceuticals.

Nanoparticle types	Characteristics	Applications	References
Polymeric	Biocompatible, biodegradable, offer complete drug protection.	Excellent carrier for controlled and sustained delivery of drugs.	Linlin et al. (2007), Nicolas et al. (2013) and Singh et al. (2014)
Quantum dots	Semi-conducting, bright fluorescence, high photo-stability.	Long term multiple colour imaging of liver cells, labeling of breast cancer marker, imaging of cells and tissues.	Luo et al. (2014) and Luo et al. (2013)
Carbon nanotubes	Excellent mechanical strength and unique electrical properties.	Gene delivery, peptide delivery.	Moretti et al. (2016)
Dendrimers	Highly branched and monodispersed polymer system.	Controlled and targeted delivery of bioactive.	Cuu Khoa et al. (2017)
Metallic nanoparticles	High surface area, stable, non-toxic.	Drug and gene delivery, sensitive diagnostic assays, radiotherapy.	Jaque et al. (2014)
Micelles	High drug entrapment, payload, stability.	Targeted active and passive drug delivery, diagnostic value.	Ahmad et al. (2014) and Lee et al. (2011)
Liposomes	Biocompatible, versatile, easy functionalization.	Active drug and gene delivery, delivery of proteins and peptides.	Sawant and Torchilin (2010) and Offerman et al. (2014)
Iron oxide nanoparticles	Superparamagnetic	MRI, intracellular monitoring.	Qiao et al. (2009) and Demirer et al. (2015)
Silica nanoparticles	Silanised and coated with oligonucleotide.	Nanobiosensor for trace analysis, detection of DNA, destruction of tumor by binding to malignant tumor cells.	Florek et al. (2017) and Perez et al. (2017)

Fe_2O_3 and CeO nanoparticles are reported to be used to heal diabetic foot ulcer (DFU) as they act as free radical scavengers.

4. Commercial scale utilization

The chemical industry products are an outcome of designing a set of properties within a material. The present industrial development considers nanoparticles as an extended toolbox containing unique properties which were difficult to realize earlier. From an economic point of view, any industry makes profits or revenue by focusing on adding new properties and modifications to the existing materials. This has brought a large impact on academic research, specifically, in the area of nanomaterials (Stark et al., 2015). Nanomaterial manufacturing is one of the most promising fields and is now a growing

economy (Diallo et al., 2013). Nanomaterials have been widely used in different industrial sectors and among them pharmaceutical industry is an emerging at a very fast pace. The global nanomedicine market is driven by emerging innovative technologies for drug delivery, various healthcare applications, and cost-effective therapies. The field of nanomedicine has revolutionized the current disease diagnostic techniques and treatment. The global nanomedicine market is classified into drug delivery, diagnostic imaging, vaccines, regenerative medicine, implants, and others. The global nanomedicine market accounted for $111,912 million in 2016, and is anticipated to reach $261,063 million by 2023, registering a CAGR of 12.6% from 2017 to 2023.

With the major advancements in the field of nanoscience and nanotechnology, National Institute of Health (NIH) promoted a National Nanotechnology Initiative (NNI) program in 2000 to promote the nanoscience related research in Health Science. The extensive funding from the government sector stimulated the launch of interdisciplinary research. With the new concept of 'nanomedicine', the field of nanoscience was quickly adapted by pharmaceutical scientists and thus, creating 'nanopharmaceuticals' (Weissig et al., 2014). In 2016, the size of the global nanomedicine market was estimated to be USD 138.8 billion. With the ongoing developments in nanorobotics and increased funding, the projects related to the treatment of cancer cells using nanorobots is anticipated to drive the process through to 2025. The presence of about 40% products in phase II of clinical development is anticipated to be commercialized over the coming decade (https://www.grandviewresearch.com/industry-analysis/nanomedicine-market).

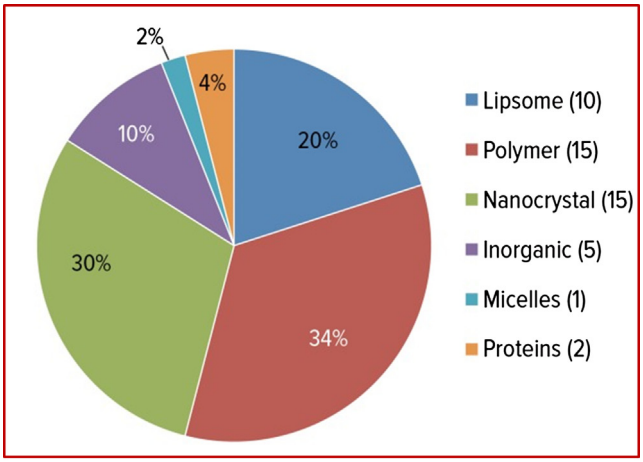
Fig. 16 depicts the types of nanoparticles that have been approved by Food and Drug Administration (FDA) and those which are at the investigational stage till.

4.1. Economic challenges

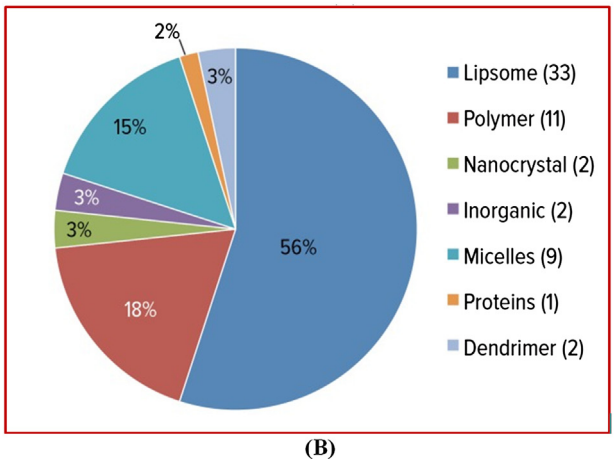
Nanomedicine plays a pivotal role in disease diagnosis and treatment across the entire healthcare spectrum. However, the market size, economic value, and areas of application remain unclear. The five major areas of nanomedicine have been identified by the European Scientific Foundation (ESF) (Bowman and Gatof, 2015);

(i) Analytical tools
(ii) Nanoimaging
(iii) Nanomaterials and nanodevices
(iv) Novel therapeutic and drug delivery systems
(v) Clinical, regulatory and toxicological issues

According to experts, there are no scientific hurdles that can block the entry of nanomedicine products in the market because most of the technologies are now in the mature state. However, there seem to be external factors that hinder the commercialization of nanomedicine. Some of the factors are; (i) availability of capital, (ii) technology transfer management universities, (iii) intellectual property landscape, (iv) regulatory issues. In Europe, less venture capital funding is available as compared to USA where about 52% venture capital has gone to nanobiotechnology start-ups. This sector is seen as a great business venture with promising high returns or investments.



(A)



(B)

Fig. 16 (A) Types of nanoparticles in approved drug available for clinical use, (B) Types of nanoparticles in investigational drugs. Reprinted from reference (Ventola (2017)).

At the university level, the commercialization can be improvised by taking the following into consideration (Wagner, 2008);

(i) Universities should offer business courses that provide scientists with the essential know-how to run a start-up company.
(ii) Senior management personnel should be involved in the management teams or the advisory panels of start-ups at an earlier stage than it is currently the case.
(iii) Establishment of more, and more professionally managed technology transfer centers at universities.

The commercialization of nanomedicine products is crucial and for this investments for major pharmaceutical and medical devise corporations is required as these have the means to finance clinical trials for novel drugs and diagnostic devices. Though scientists claim that there technologies are fruitful for the commercialization but representatives from the pharmaceutical companies caution that the technologies are not mature enough so that investments can be made. Therefore, this leads to very slow uptake of any biotechnology by the

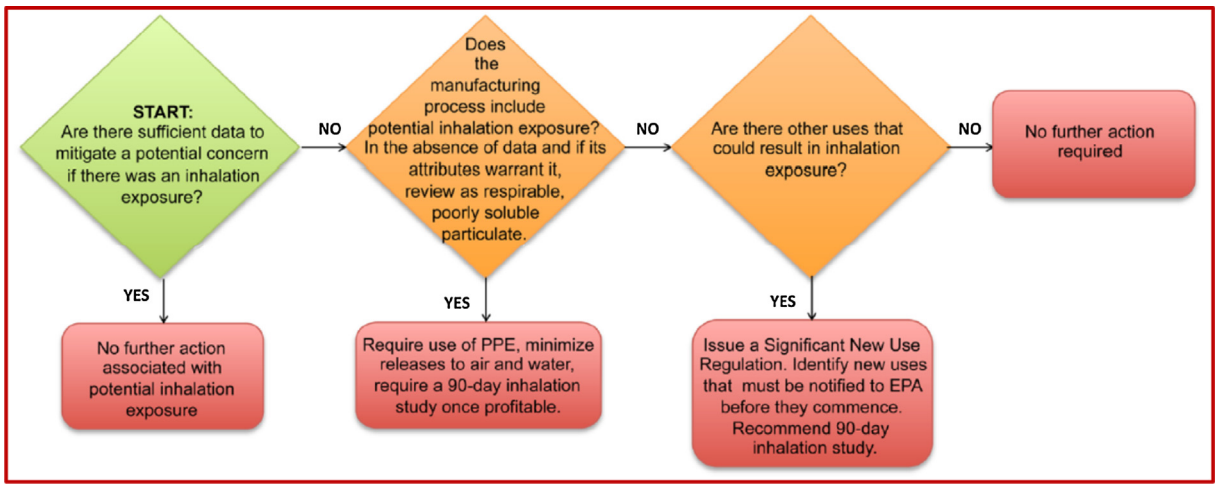


Fig. 17 Decision-tree approach currently used by the EPA to characterize risk potential of carbon nanotubes (CNTs). The decision tree above provides an example of a regulatory program where CNTs are currently characterized by their risk and exposure potential under the Toxic Substances Control Act section 5 program. Currently, inhalation testing is requested most frequently as a result of concerns for worker exposure. Testing required as a result of risks to the general population or consumers, rarely if ever, has occurred to date for CNTs. Reprinted from reference (Godwin et al., 2015).

pharmaceutical companies. Thus, these companies wait for the cutting-edge technology that shows potential to move ahead with the financial investment. The companies will not take initiatives if the nanomedicine innovations have no major impact and increase future costs if they;

(i) Aim at diseases of minor cost relevance i.e. diseases of less relevance.
(ii) Comes as add-on technology offering only a limited health benefit.
(iii) Result in additional procedures without substantial health effects (e.g. more diagnostic procedures).

4.2. Health and safety concerns of nanoparticles

For nanotechnology to become a sustainable technology, it is important that the products going into the market have passed thoroughly all the regulatory concerns and are safe and effective. Categorization strategies are needed to enable the regulators and industry to predict the potential risks to prioritize testing and minimize the time consuming and expensive *in-vivo* studies or traditional risk assessments (Stone et al., 2014).

The characterization of nanomaterials coupled with alternative testing strategies can be used to expedite hazard characterization and risk analysis thereby allowing for integrated environmental and occupational health and safety (EHS) decision making for nanoparticles. Carbon nanotubes have gained lot of interest and attention in the global market, but challenges have arisen related to this material. These can be addressed by the emergence of new tools and approaches for alternate testing of materials or facilitating grouping, ranking and read-across for manufactured nanomaterials (Godwin et al., 2015).

Environmental Protection Agency (EPA) treatment of carbon nanotubes (CNTs) is described in the flowchart (Fig. 17). EPA has considered CNTs risks under the "Respirable, Poorly Soluble Particulate" category. If CNTs fall under this category and it poses risk, then a 90-day inhalation study is requested. Both SWCNTs and MWCNTs fall under Significant New Use Regulation (SNUR), and any company wishing to use CNT in a new manner, must provide notice to EPA 90-days before starting the new use. This provides an opportunity to EPA to review the use and determine if it may present an unreasonable risk so that appropriate action may be taken. But this approach poses a challenge as it does not provide a methodology to manufacturer and regulator to determine that new CNT is similar to the previous submissions based on the predicted risk potential of the existing CNTs. Therefore, they cannot confirm that whether new CNTs pose a potential risk or not (Godwin et al., 2015).

Risk management strategies proposed by different researchers to establish a safe environment when working with nanomaterials have been summarized in Table 6 (Oksel et al., 2016).

4.3. Life cycle assessment within the pharma industry

With the increasing demand for new drugs, the pharmaceutical industry faces challenges with the aspect of development time to reduce time to the market. Environmental aspects also play an important role in the early phase of process development. In the active pharmaceutical ingredient (API) process, it is important to rethink, redesign and optimize strategic processes as early as possible (Ott et al., 2014).

There are specific issues that are taken into account in the four different phases of the nanoproduct life cycle (Fig. 18).

LCA is performed on the nanoproducts to answer the questions related to the environmental performance of the nanoproducts, such as (Klöpffer et al., 2007);

(i) Comparison of the lifecycles of nanodevices/products with conventional devices/products.

Table 6 Risk prioritization and management tools for nanoparticles.

Tool	Description	Protocol (P)/ Modelling (M)/Database (D)	Reference
CB Nanotool	A control banding tool for nanotechnology researchers/risk assessment and management	M	Zalk et al. (2009)
Stoffenmanager Nano	Employers and employees/Prioritize health risks and implementation of control measures	M	Van Duuren-Stuurman et al. (2012)
ANSES Nano	A control banding tool for managing the potential risks of ENMs	M	Riediker et al. (2012)
Swiss precautionary matrix	Employees, consumers and the environment/Source identification and risk reduction	M	Liguori et al. (2016)
NanoSafer	Occupational exposure assessment	M	Subramanian et al. (2015)
NanoRiskCat	A conceptual decision support tool for risk categorization and ranking of nanoparticles	M	Hansen et al. (2014)
MARINA	Environmental fate/exposure assessment	M	Bos et al. (2015)

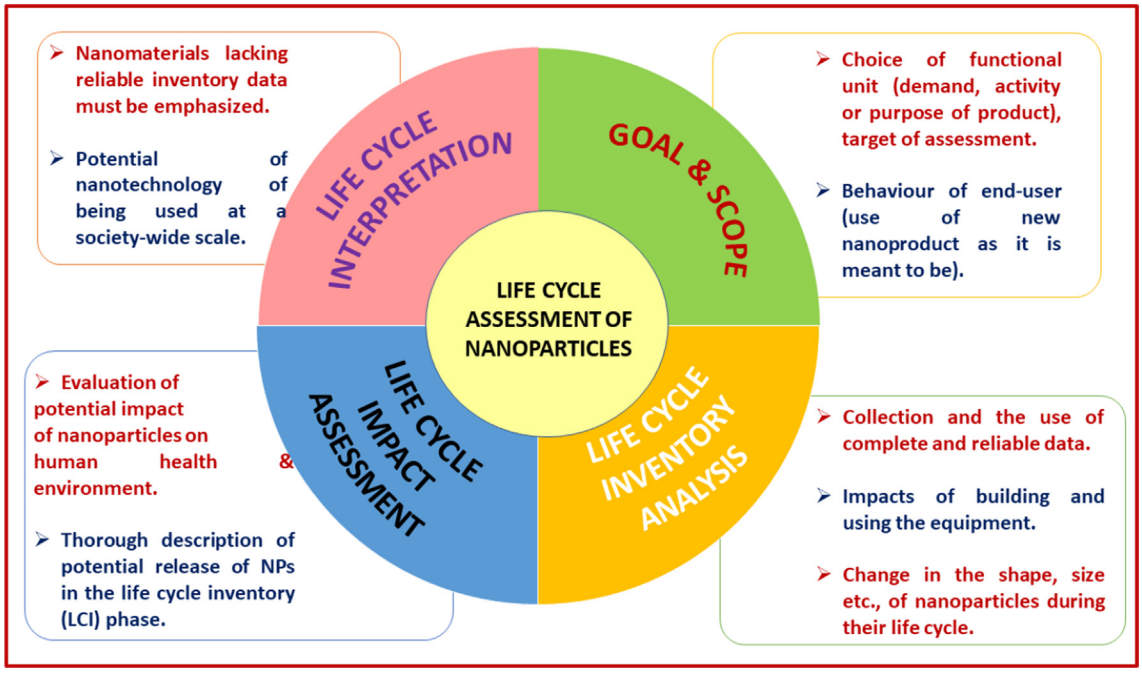


Fig. 18 Different phases of nanoproduct life cycle.

(ii) Savings in the energy efficiency as compared to those of conventional products.
(iii) What phase in the lifecycle (manufacturing or end-of-life) dominates energy use?
(iv) any issues in end-of-life management that are specific to nanomaterials, especially recovery and reuse or recycling.
(v) What are the key eco-toxicity and human-toxicity potentials for nanomaterials?
(vi) How risk assessment (RA) methods can be integrated into LCA of nanomaterials?
(vii) Are there trade-offs between potential eco-toxicological and human toxicity impacts and a potential environmental gain related to global change and other pressing environmental problems?
(viii) Geographical impact of the nanoproducts as compared to those of conventional products.

LCA studies on the nanoproducts (nanodrugs/nanodevices) are performed by the companies as well as by the consultants and academia. Government-supported institutions may play a secondary role through assistance, e.g., by building databases, funding research and providing funds for method development and improvement.

In the pharmaceutical industry, the following are the benefits of conducting LCA of nanodrugs or nanodevices (Klöpffer et al., 2007);

(i) LCA results influence the decision in product design, marketing, development and manufacturing. The behaviour of any product in the subsequent lifecycles is predetermined by the design of the product.
(ii) LCA is applied as a screening tool for different technologies to support the classical R&D decision process.

(iii) The environmental performance of the nanoproducts is proactively investigated by the companies to avoid hindrance to innovation and provide evidence of compliance with legislation and derive the value of LCA work.
(iv) LCA provides a sound basis for the marketing of nanoproducts.
(v) The results provide information regarding environmentally efficient products minimizes production costs.
(vi) The results help the companies to foresee and avoid any environment related problems during the production/sales operations.
(vii) Strategic decision-making in investment and production capacities could be supported by the LCA results.

5. Modern society and sustainable pharma analysis

Pharmaceutical companies are increasingly imparting a lot of importance on becoming more sustainable by developing drugs/medicines that are same medicinal value but has less impact on the environment. The design, usage, and all the practices surrounding the pharmaceutical play a key role in minimizing their impacts on the environment and increasing the sustainability of the healthcare. Advancements in the medicine field such as drug design, personalized medicine, targeted drug delivery, nanomedicine, medical genetics, formulations and worldwide initiatives (medications management and pharmaceutical care) are bringing sustainability in quality health care close to reality (Daughton and Ruhoy, 2009).

Fig. 19 represents the sustainable development which can be divided into three sectors; (i) pharmaceuticals, (ii) environment, and (iii) health care. These three sectors are interconnected and therefore, this model has a conceptual simplicity in terms of sustainable pharma analysis. The classification of impacts on human society based on these three categories makes the analysis straightforward. When these three sectors are balanced, they lead to sustainable development of the human society.

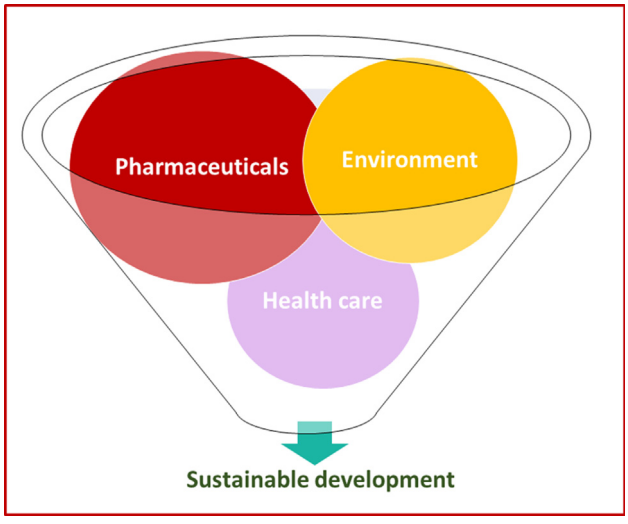


Fig. 19 Model showing an interconnected view of sustainable development.

With the rapid research progress in the field of nanobiotechnology and stable nanomaterials, the present pharmaceutical industry is primarily focused on inventing medicines, specially nanomedicines to allow patients to live longer, healthier, and more productive lives. The industry is committed to bring key nanomedicines to patients with minimal environmental impact. In recent years, the pharmaceutical industries have paid more attention towards the productivity improvement, reduction in waste, quality improvement, and control on both the research and development (R&D) and manufacturing areas. These are not only driven by considerations in cost-reduction but also increasing awareness of sustainability (Jiménez-González et al., 2011). In 2005, the American Chemical Society (ACS) Green Chemistry Institute (GCI) and several global pharmaceutical corporations founded the ACS GCI Pharmaceutical Roundtable (GCIPR or the Roundtable). The mission of the Roundtable is to catalyze the implementation of green chemistry and engineering into the business of drug discovery, development, and production. Several measures have been proposed to encourage chemists and engineers to design pathways of drug design that are greener, safer and more sustainable (Jiménez-González et al., 2013).

6. Conclusion

Smart nanomaterials have become an important subject of research since their detection. Smart nanomaterials with unique properties are offering exciting prospects to modern scientific research. In this review, characterization and application of smart nanomaterials in pharmaceutical analysis with commercial scale utilization are covered. Overall, this review provides an updated overview of technological and economic challenges for commercial applications of smart nanomaterials. A serious debate on these challenges is required to overcome and consider high-performance and cost-effective usage of smart nanomaterials.

The core aim of the modern research is to close the gap between laboratory studies and practical applications. Most of the research on smart nanomaterials in the pharmaceutical analysis is carried in literature is limited to lab scale and hence research on a commercial scale is recommended. As a result, commercialization of nano-based products is very crucial and requires huge investments from major pharmaceutical and medical devise corporations. Likewise, optimistic methodologies are required to motivate policy makers to design the applications of smart nanomaterials in sustainable systems. At present, the opportunity of smart nanomaterials in pharmaceutical analysis at industrial scale seems to be still growing at lower levels of its ability. Nevertheless, it is expected in the near future that smart nanomaterials in the pharmaceutical analysis will play a major role in next-generation pharmaceutical technologies and devices.

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