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Nanoscience and Nanotechnology: Issues and Applications in Agri-Food, Biomedical, and Environmental Sciences

Saikh Mahammed Athar Alli

Department of Pharmacy, V.B.S. Purvanchal University, Jaunpur, Uttar Pradesh, India.

Nowadays nanotechnology based on nanoscience was exploited extensively in every sphere of science and technology so as to get a product with desired and improved performances; whose utility was subsequently became controversial. The work was aimed to project the technology; the potential utility of nanoscience and nanotechnology based products specifically in the field of agri-food, medicine, pollution abatement; and the associated societal issues. Presently nanotechnology had become a thrust area of research in sectors like: agro-food, medicine, pollution abatement, electronics, electrical, and so on. Publications related to pronounced effects/properties vis-à-vis ecotoxicity and toxic effects were the research outcomes of nanoscience and nanotechnology. Present review work was aimed to look at technical aspects and, societal and ecological issues related to nanotechnology and development of nanotechnology based products, specifically in the health and allied science, so as to aid in designing system with highest prosperity. In this respect data related to basic information on current practice in nanotechnology and societial issues were gathered from databases, compiled and analysed. Presented data will help researchers working in the pharmaceutical, agri-food, and other allied sectors for enhancing potentiality, utility, continuances, and future directions for nanotechnology based products.

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**Corresponding Author Email:* atharodi@gmail.com

INTRODUCTION

Global technological competition and breakthroughs, primarily driven by science and engineering, had resulted in unification of the science and the features of nature at nanoscale (NSc) had leaded for a new foundation for knowledge, innovation, and integration of technology [1,2] thereby resulting in production of novel materials and devices with properties never envisioned before called ‘nanomaterials’ (NMs) with ‘nanotechnology’ (NTy). [2,3] NTy possesses great potential to generate products with novel properties in various domains and having expectation for enhanced importance in the near future.[4] Transparent sunscreens; stain-resistant clothing; self-cleaning glass; paints; sports equipment; biotechnology products; and electronic items like memory and storage devices, display, optical, and photonic technologies; were the several consumer products marketed as ‘nanotechnology-based products’ and its introduction potentially was broadening. Possible utilities of the NTy were also exploited for producing safer, more nutritious, and more appealing foods; for improving performance of the medications by devising more effective and efficient systems [3,5] and for protecting environment through pollution prevention, treatment, and cleanup of long-term problems at hazardous waste sites; and replacing current practices for site remediation.[6]

With NTy, NMs having novel and desired properties were created that possesses potentially great benefits vis-à-vis may also result in unwanted risks. [7] Currently, possible benefits over possible risks of this technology were known. NMs may differ by biological and chemical properties with respect to the macro form of the same, thus may affect so many aspects of human life and environment. [8] and their consequences on human and environmental health became a concerns.[9,10] Studies emphasizing possible adverse effects of NMs on health and environment, and assessing their life cycle were very infancy; leading to inconclusive opinion associated with lack of data.[11] Some NMs upon expose to humans or the environment may have damaging potentiality, [12]and cannot be accessed due to lack in the knowledge of dosage and exposure for traditional risk analysis models. [8] Questions/concerns on the safety issues includes their fate in human leading to variation in metabolism creating challenges in dosing; their fate and ecological consequences followed to their dispersion and shading into environment from the composite material associated with aging and degradation; their regulation and labelling associated with unavailability of sufficiently hard facts, [13,14] and so on. As like during the introduction of genetically engineered crops, proponents of NTy were reviewing the concerns and difficulties related to reliability on assessing the potential utility, the safety, and the societal and the ethical issues, prior to their continuances. Potential risks of NTy were poorly understood that might escort to unintended consequences like irreversible damage. [8] Combating issues related to functional improvements, costs, and safety of NTy will be focus point for its success and acceptance. [3]

This was an in-extensive review of literature, and was projected to present a background and overview of publications related to basic information on current practice and utility of NTy with most emphasis in health science and allied subjects, issues adjoining use of NTy, and future directions.

NANOSCIENCE AND NANOTECHNOLOGY

A material may have diverse optical, electrical, magnetic, mechanical and chemical properties at assorted size scales; was the basis of development of NTy. [15] Over past two decades, scientists and engineers had been mastering the intricacies at NSc level, that is manipulation of structures at the atomic level, had developed new technical methods for more precise and controlled production of novel materials and devices; termed as NMs with the technology 'NTy'. [2,3] 'Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometres, where unique phenomena enable novel applications' [16].

OVERVIEW ON APPLICATIONS OF NANOSCIENCE AND NANOTECHNOLOGY

NTy will be useful in detecting toxins, pathogens, and spoilage in foods and food processing facilities through development of sensitive biosensors; for delivering specific amounts of nutrients directly to the needy tissues and cells, in the fields of nutrition and nutritional supplements; localizing and monitoring diseases in humans; revealing bioterrorism agents; detecting environmental toxins through development of sensitive biosensor materials that detects very small amounts of toxins, pathogens, volatile compounds, and diverse organic compounds present in body fluids or environmental samples; assessing efficiency of remediation processes; [16] surfaces and equipment cleaning and disinfection; and development of 'smart packaging' so as to sense and indicate beginning of food spoilage and better control gas diffusion. [17] NTy may improve construction materials for floors, walls, and machines vis-à-vis may result in new devices and techniques in electronics, medicine, wastewater treatment, agriculture and food processing.

In agri-food sector

Engineered NPs based food products and food packaging was commercially available. [5] Considerable amount of fund was invested by industries and governments for finding new applicability of NTy in food packaging, food processing, food safety, and agricultural production. [16, 18, 19]Teeth erosion associated with acids present in soft drinks can be minimized through development of new functional soft drinks using NTy. [16, 20] NTy was used in encapsulation and designing delivery systems for newer food products. [16,21] like infusion of vitamins or other food supplements into the food stuffs in the form of nanoparticles (NPs), development of personalized/customized beverages and foods. [5] Nano-silicon dioxide particles, upon covalent binding to a porcine triacylglycerol lipase, were used for effective hydrolysis of olive oil so as to improve stability, adaptability, and reusability. [22] Packaging disposal problem of traditional packaging materials, mostly produced from fossil fuels, can be minimized through creation of edible and biodegradable films using nanocomposites (NCs), which may help to improve strength, barrier properties, antimicrobial properties, and thermal stability, and reduce packaging waste. [3,16,17,23] NCs based packaging films may boost shelf-life and quality of coated food through impeding diffusion of gases through it; [21,24] while embedding nanosensors (NSs) in packaging will be an indicator for soundness of food products. [23] Polymer-silicate NCs based packaging films have enhanced gas barrier properties, mechanical strength, and stability to heat and cold. [25,26]

NMs based agricultural products were not yet marketed excluding a nano-silver–containing indoor and outdoor spray for plant protection, in Switzerland [27] Still lot of research activity was in progress [28] that was limited to plant protection products. [29] Researches focusing application of NPs in fertilizers was directed on their slow and controlled release using various polymers and clays; [16] with no indications of real applications in the scientific literature, on the Web, and in the feedback from experts or associations. [28]

In cleaning and disinfection

Bactericidal effects of titanium dioxide NPs against *E. coli* was significantly increased by deposition of silver on it [30] while combining it with carbon nanotubes (NTs) had improved its disinfectant properties against *Bacillus cereus* spores. [31] Titanium dioxide NPs upon doping with silver inactivated *B. cereus* spores on polyester and aluminium surfaces [32] and smashed airborne bacteria and moulds upon incorporation into an air filter. [33] Silver NPs, stabilized with sodium dodecyl sulphate or polyvinylpyrrolidone, effectively inhibit growth of *E. coli* and *Staphylococcus aureus*;[33] and prevents growth of pathogen and spoilage bacteria by virtue of its presence on the surfaces of refrigerators and food storage containers.

As nanoensors

Advancement in NTy leaded to development of sensors, as markers for exposal, biological responses, and environmental remediation.[34] NSs/nanobiosensors may be incorporated into packaging to indicate integrity of packaging material through detecting gases present in it, food spoilage or deterioration through identifying released compounds, presence of pathogens or toxins in foods; which may act as an alert for all.[35] For example biosensing of *Staphylococcus* enterotoxin B, in milk, can be done using poly(dimethylsiloxane) chips with a detection limit of 0.5 ng/mL;[36] simultaneous detection of *E. coli* O157:H7, *Salmonella spp*., and *Listeria monocytogenes* with universal G-liposomal nanovesicles, having detection limits of 3.1 x 103, 7.8 x 104, and 7.9 x 105, respectively; [37] electrochemical glucose biosensor, with detection limits of 0.035 and quantification limits of 0.107 mM; [38] liposomal nanovesicles to detect peanut allergenic proteins in chocolate [39] and pathogens ; [40] etc.

In non agri-food sector

Thin films of NMs were used as water repellent, self-cleaning, anti-microbial, anti-fog, anti-reflective, ultraviolet or infrared-resistant, scratch-resistant, or electrically conductive and were nowadays applied on eyeglasses, computer display and cameras to protect or treat the surfaces. [16] Carbon nanotubes (CNTs) potential utility in electronics, optics, architectural fields, and other fields of materials science was exploited. CNTs based membranes were used for water desalination; and NSc titanium dioxide have potentiality to filter and purify water, and neutralize bacteria. [16] CNTs based solar sails and cable for the space elevator, which was light in weight, solves the problem of lifting enough fuel into orbit to power spacecraft during interplanetary missions and reduces the overall cost; CNTs based materials reduces the weight of spaceships while retaining or even increasing the structural strength. NSs and nanorobot were used in spaceships, spacesuits, and the equipment used to explore planets and moons. [41] Incorporation of NSc-transistors/nanoelectronics had improved capabilities of electronic components by reducing power consumption and weight, memory density of chips (memory per square inch), and so on. [42] Integration of NTy systems in the defense resulted in nanorobot development.

In nanoremediation

Population growth, extended droughts, and numerous competing demands created challenges for meeting an ongoing and increasing demand of clean water and environment for human habitation, agriculture, and industrial processes. Nanoremediation (NR) or pollution abatement involves application of reactive NMs, with properties for chemical reduction and/or catalysis, for transformation and detoxification of concerned pollutants for its mitigation. [43,44] *In situ* NR eliminates pumping out and transportation of ground water for its treatment and disposal [45, 46], while restrict movement of nanoremediant far away from their injection site; [43] maintains their reactivity in soil and water up to 8 weeks, flows with groundwater for more than 20 months, and some results 99% reduction in trichloroethene value in a few days of injection. [47] NSc-zeolites, metal oxides, enzymes, CNTs and fibers, various bimetallic nanoparticles, and titanium dioxide were explored for remediation; while NSc-zero-valent iron (nZVI) was used most extensively.[47,48] nZVI transforms large number of halogenated organic compound based pollutants, commonly contaminants of soil and groundwater; [47,49] and removes Arsenic-V, volatile organic compounds [50], dense non-aqueous-phase liquids, [51] etc. Iron-NPs were very efficient in transforming and detoxifying diversity of familiar environmental pollutants, including Arsenic [52], polychlorinated biphenyls (PCBs), organochlorine pesticides, and chlorinated organic solvents; where as modification of iron-NPs could improve the rapidity and the efficiency of remediation process.[47,53] Noble metals like palladium that catalyze dechlorination and hydrogenation, improves efficiency of the remediation process, [45,54] while silver NPs was advocated to aid clean-up of mercury.[16]

NMs were exploited to adsorb or sequester pollutants and to remove them from water and were considered as novel, improved and efficient methods of water purification, viz. NTy based photocatalytic membranes efficaciously degrading triazine herbicides while composite membranes containing titanium dioxide, tributyl- and triisopropyl vanadate upon exposure to sunlight results in oxidation and destruction of atrazine in water at a concentration of 1 parts per million.[55] NPs loaded with titanium dioxide degrade PCBs and other organic pollutants of water.[56] Nanosorbents were employed for removing certain pollutants while their surface modification through attachment of various chemical groups improves their specificity thereby devising nanosorbents for removing arsenic and chromium from water. Multi-walled CNTs adsorbs three–four times the amount of heavy metals (copper, cadmium, lead, etc.) with respect to powdered or granular activated carbon while chitosan based NPs containing tripolyphosphate adsorb even greater amounts of lead. CNTs and nanoporous activated carbon fibers effectively adsorbs organic pollutants like benzene where as fullerenes adsorbs polycyclic aromatic compounds like naphthalene. [56] NTy reported to enhance effectiveness of ultrafiltration and reverse osmosis, and desalination was achieved with nanofiltration processes. Bacteria and viruses can be effectively removed from water with CNTs based filters while organic pollutants, uranium, arsenic, and nitrates were removed with other nano-structured membranes. NPs of silver compounds and magnesium oxide were used for killing Gram-positive and -negative bacteria. [56] Radionuclides, heavy metals, inorganic ions, and organic solutes forms metal-dendrimer complexes with dendritic polymers (1–20 nm in size), a soluble ligand, which can be subsequently separated from the solution and the adsorbed metals were released by altering the pH thereby reusing the polymers and recovering the metals. A dendritic polymer uses scaffolds for carrying antimicrobial compounds. [56]

In biomedical field

Nanoscience and nanotechnological methods had been urged for the development of more sophisticated diagnostic tools for early stage detection of diseases like cancer, atherosclerosis, etc. [16, 57] and site specific drug delivery system; and performing neurosurgery. In the treatment of wounds, nanocrystalline silver was used as an antimicrobial agent [58] while site specific carbon nanovectors were used for enhancing cancer therapy [59] and leishmaniasis. [60] Application of NMs in biomedical field was expected to improve. [61]

Advantages

NPs aids in increasing stability of drugs/proteins; modulating control release properties, using alternative of matrix polymer; [15,65-67] improving performance through passive and active drug targeting associated with easy manipulability of their size and surface characteristics, upon parenteral administration; altering drug's organ distribution and its subsequent clearance, thereby increasing drug therapeutic efficacy and reduction in side effects; designing a system that can be delivered by oral, nasal, parenteral, intra-ocular, and other routes with high drug loading; improving intracellular uptake with respect to microparticles [68] and availability to a wider range of biological targets [69] associated with their small size an relative mobility; and so on.[70] Encapsulation increases stability, and it allows for controlled release of the ingredients to specific places in the human body.

Disadvantages

Limitations of NPs was associated with their small size and large surface area not also can lead to particle-particle aggregation thereby creating difficulties in their handling (liquid and dry forms) but also results in limited drug loading and burst release [15,65,66]

In diagnosis of disease

Nanotechnological tools were studied to shed light in many normal and pathological physiological processes. Developments of diagnostic tools with NTy were increasing rapidly through combination of specific NPs with NTs, nanowires, nanocantilevers, and microarrays so as to produce automated and integrated detection systems. [62] Paramagnetic NPs of echogenic liposomes, that targets to fibrin and tissue factor proteins associated with atherosclerosis, can be detected by magnetic resonance imaging (MRI) that recognizes an ultrasound signal produced due to the alternation in lipid bi-layers with an aqueous fluid; so as to diagnose atherosclerosis. [63] Superparamagnetic iron oxide loaded NPs were studied to visualize brain tumours using MRI,[57] while iron platinum stealth immunomicelles were evaluated for selective detection of human prostate cancer cells using both fluorescence resonance imaging and MRI.[64]

In drug targeting

NMs and NPs were tried for aiding in delivery of drugs directly to tissue targets. Smooth muscle cells specific NPs, loaded with paclitaxel or fumagillin, for inhibiting plaque development on artery walls [63] and poly(lactide)-tocopheryl polyethylene glycol succinate NPs for efficient delivery of anticancer drug, paclitaxel.[71] Stealth-NPs that circumvent the blood-brain barrier (BBB) were designed for delivering drugs to treat brain tumours.[57] NPs loaded with small interfering RNA and folate was studied for treating nasopharyngeal carcinoma.[72] NPs loaded with quaternary ammonium polyethylenimine after being incorporated in composite resins were used in dentistry for replacing hard tissues, while the resins exert antibacterial effects, for one month or more, against *Streptococcus mutans* without diminishing its structural integrity.[73] Nanocrystals containing hydroxyapatite-aspartic acid (or –glutamic acid) interact with osteoblasts and enhance their activity in mineralization reactions, and may be utilized in treating osteoporosis and other bone diseases.[74] Peptide amphiphile loaded nanofibers had been employed for constructing scaffold having ability to attach mesenchymal stem cells and enhancing their proliferation and differentiation, having utility in tissue repair.[74] Self-assembling peptide nanofiber scaffolds were used to repair a severed optic nerve tract in hamsters employing 'nano neuro knitting' technique. Nanoscience will advance our perceptive of basic science and will potentially escort to useful interventions. [75] Defining nanotopography of substrates may assist in development of prosthetic devices and in tissue engineering. [76]

In tumour targeting

Enhanced permeability and retention effect or active target-ability of NPs through ligand attachment, on its surface, results in its ability to deliver a concentrate dose of drug in the locality of the tumour targets vis-à-vis its ability to reduce exposure of drug to healthy tissues, by limiting drug distribution to target organ, advocates its rationale use in tumour targeting.[15] Doxorubicin loaded poly(isohexyl cyanoacrylate) nanopsheres manifested higher concentrations of doxorubicin in the liver, spleen and lungs of mice with respect to mice treated with free doxorubicin.[77] Bio-distribution studies of RGD-doxorubicin-NPs, in tumour-bearing mice, indicates decreasing drug concentrations over time in the heart, the lung, the kidney and the plasma while accumulating drug concentrations in the liver, the spleen and the tumour resulting improved therapeutic efficacy.[78] This improved therapeutic efficacy of NPs formulation was due to prolonged diffusion of free doxorubicin from accumulated NPs in the lysosomal vesicles of Kupffer cells within healthy tissue that acts as drug reservoir to the malignant tissues.[79] NPs biodistribution mechanism was explicit but was rapid and lies within ½ hour to 3 hours, and was likely mediated through mononuclear phagocytic system (MPS) in liver and spleen, [80] and targeting MPS-rich organs that localizes outside tumours will be desirous for a successful drug delivery system.[81] Endocytosis/phagocytosis propensity of NPs, by MPS, can be exploited to effectively deliver chemotherapeutic agents to MPS-rich organs/tissues localized tumours like hepatocarcinoma, gynaecological cancers, brochopulmonary tumours, primitive tumours and metastasis, small cell tumours, mycelia and leukaemia. NPs bearing folate ligand may be used to target ovarian carcinoma while specific peptides or carbohydrates may be used to target integrins and selectins [82] and coating with folate ligand facilitates tumour cell internalization and retention of Gold-NPs in the tumour tissue.[83] Development of resistance mechanisms in the cancer cells leading to multi-drug resistance (MDR) limits efficacy of anticancer drugs against numerous solid tumour types which occurs mainly owing to the over expression of plasma membrane pglycoprotein (Pgp) possessing capability of extruding diverse positively charged xenobiotics as well as some anticancer drugs, out of cells.[84] Colloidal carriers were used for restoring the tumoral cells sensitivity to anticancer drugs through circumvention of Pgp-mediated MDR, as Pgp probably recognizes and effluxes the drug out of the tumoral cells during endocytosis, only when drug was present in the plasma membrane, and not when it was located in the cytoplasm or lysosomes.[85]

As long-circulating nanomaterials

With an objective of keeping NPs in the circulation for a longer period of time and to prevent their localization in the MPS-rich organs 'stealth' particles or PEGylated/long-circulating NPs that were invisible to macrophages or phagocytes, were developed.[86] Hydrophilic polymers like polyethylene glycol, poloxamines, poloxamers, and polysaccharides were used to efficiently coat surface of conventional NPs thereby preventing their uptake by the MPS [86,87] as dynamic-cloud of hydrophilic and neutral chains at the particle surface, resulting from coating, repel plasma proteins thereby NPs become invisible to MPS. [88] Introduction of hydrophilic polymers at the surface of NPs can be achieved either by use of block or branched copolymers for their production or by adsorption of surfactants.[81,86] PEGylated NPs possess prolonged half-life in the blood compartment and were able to target the pathological sites (inflamed or tumours regions having leaky vasculature) and the tumours located outside MPS-rich regions, [81] while their surface characteristics and size determines their biological fate like size less than 100 nm and hydrophilic surface were prerequisite for reducing opsonization reactions and subsequent clearance. [81]

As ligand attached nanomaterials

NPs attached with small ligands were easier to handle and manufacture, and targeting; and could be advantageous in active targeting of long-circulating NPs with likelihood of maximizing success. Active targeting of NPs can be achieved with molecular recognition processes such as ligand-receptor or antigen-antibody interaction. Folate receptors that were over expressed on the surface of some human malignant can be targeted with folate, and cells and the cell adhesion molecules such as selectins and integrins that were involved in metastatic events with specific peptides or carbohydrates [82]. Attachment of lectins (ligands) like bean and tomato lectin, on NPs, had been exploited for enhanced oral peptide adsorption. [89, 90]

In oral delivery of peptides and proteins

Either paracellular route or endocytic pathway was generally involved in the gastrointestinal (GI) absorption of macromolecules and particulate materials. Endocytic pathway was initiated by an unspecific physical adsorption of material to the cell surface by electrostatic forces such as hydrogen bonding or hydrophobic interactions [91] for absorption of NPs either through receptor-mediated endocytosis (ligand mediated) or through adsorptive endocytosis (not requiring ligands). The size and the surface charge and hydrophilicity of the material play major role in the affinity towards adsorptive endocytosis as demonstrated with poly-styrene NPs and when it was carboxylated.[92] NPs based on chitosan [93] or starch [94] or poly(acrylate) [95] improves the paracellular permeability of macromolecules so as to improve their GI absorption.

Advancement in biotechnology and biochemistry resulted in discovery of peptides and proteins based bioactive molecules and vaccines with limited bioavailability associated with epithelial barriers (i.e. mucus layer and epithelial cell lining) of the GI-tract and their susceptibility to degradation by proteolytic enzymes of the gut lumen (viz. pepsin, trypsin and chymotrypsin) and at the brush border membrane (endopeptidases), and bacterial gut flora in the GI-tract. [96] Encapsulation of these bioactive molecules within NPs protects them from enzymatic and hydrolytic degradation. Insulin-loaded NPs preserves insulin activity and results in blood glucose reduction of diabetic rats for up to 14 days, upon their oral administration [97] while colloidal carrier system in the form of NPs overcomes the GI-barrier. Covalent coupling of vitamin B-12 to particles had been exploited to increase oral bioavailability of various peptides like granulocyte colony stimulating factor, erythropoietin, etc. [98, 99] via receptor-mediated endocytosis.

In gene delivery

Plasmid DNA loaded NPs were exploited as sustained release gene delivery system, associated with their rapid escape from the degradative endolysosomal compartment to the cytoplasmic compartment [100] that could release DNA at a sustained rate, following their intracellular uptake and endolysosomal escape, resulting in sustained gene expression. [101] Polyethyleneimine nanocomplexes [102], CNTs [103], poly (D, L-lactide-co-glycolide) (PLGA) NPs loaded with therapeutic genes, like bone morphogenic protein, were under investigation to facilitate bone healing.

In drug delivery into the brain

Polysorbate 80 or low density lipoproteins, transferrin receptor binding antibody (such as OX26), lactoferrin, cell-penetrating peptides and melanotransferrin had exhibited capability for delivery of a self non transportable drug into the brain through chimeric construct that could undergo receptor-mediated transcytosis. [104-108] Reported success of polysorbate 80 coated NPs, was rare while desorption of polysorbate coating, and rapid NPs degradation and toxicity associated with high concentration of polysorbate 80 were the shortcomings. [87,109] Poly(butylcyanoacrylate) NPs possessing ability for delivering hexapeptide dalargin, doxorubicin and other agents that face difficulty in crossing the BBB. [104] BBB penetration of lipsosomes can be enhanced with BBB targeting antibody like OX26, anti-transferrin receptor monoclonal antibodies.[110] Lactoferrin, an iron-binding glycoprotein belonging to the transferrin family demonstrates two fold *in vivo* brain uptakes with respect to OX26 and transferrin can be exploited for BBB targeting. [105] BBB specific molecules for targeting NPs to the brain were extensively studied and will be outcome of the future. [111-113]

Effect of nanomaterial's characteristics on drug delivery

Particle size and surface properties

Particle size and size distribution as well as surface characteristics and hydrophobicity [114] of NPs and NMs were the most important characteristics, which determine its *in vivo* distribution, biological fate, toxicity and the targetability vis-à-vis influences the drug loading, drug release and stability. Drug release profile was dependant on particle size, like fast drug release with smaller particles associated with its larger surface area and sustained release with larger particles associated with higher amount of drug loading followed by slow diffusion.[115] Dispersion of smaller particles had lower stability owing to their greater potentiality towards aggregation during storage and transportation. Effect of particle size on polymer degradation rate was controversial like increase in particle size increases polymer degradation of PLGA particles [116] while absence of substantial difference in *in vitro* polymer degradation rates of PLGA particles with different size particles was also observed.[117] Some cell lines efficiently can take up, only submicron NPs while unable to take up microparticles.[118] Attaching/coating surface of NPs with specific ligands like folate were used for targeting ovarian carcinoma [83] while specific peptides or carbohydrates for integrins and selectins.[82] Particle size less than 100 nm and a hydrophilic surface were indispensable for achieving decrease in opsonization reactions and subsequent clearance by macrophages [86,114] The surface charge property of NPs that was characterized with zeta potential, was utilized to determine whether a charged active material was encapsulated within the core of the NPs or NMs or adsorbed onto its surface, and a zeta potential value above (+/-) 30 mV indicates stability of suspension by preventing aggregation of particles [119].

Drug loading

Nanoparticulate system will be successful if the same possesses high drug-loading capacity thereby reduces quantity of matrix materials and matrix associated toxicity; and was very much dependant on the solid-state drug solubility in matrix material or polymer that was related to the polymer composition, the molecular weight, the drug polymer interaction and the presence of end-functional groups like ester or carboxyl group.[120,121]. Drug loading was affected by polyethylene glycol moiety to very negligible extent [121] while macromolecule or protein has highest loading efficiency, when loaded at or near its isoelectric point associated with its minimum solubility and maximum adsorption [122]. Ionic interaction between the drug and matrix materials reported to be very efficient way for increasing drug loading of small molecules [123,124].

Drug release

Drug release and polymer biodegradation were important factor that requires consideration for developing a successful nanoparticulate system. Solubility and method of incorporation of drug into the matrix, diffusion of drug through the NPs matrix and biodegradation of the matrix materials govern drug release process. Weakly bound or adsorbed drug to the surface of NPs attributes to rapid initial release or burst-effect. [125]. Loading of the drug by incorporation method results in better-sustained release characteristics; [126] coating of NPs with polymer, that acts as a barrier and determining factor to drug release, controls release of drug by its diffusion from the core through the polymeric membrane; and ionic interaction between the drug and addition of auxiliary ingredients governs drug release, like drug interaction with auxiliary ingredients forming less water-soluble complex results in very slow release with almost no burst-release-effect [123] and addition of di-block co-polymer of ethylene oxide or propylene oxide (PEO-PPO) to chitosan reduces interaction of bovine serum albumin with the matrix material through competitive electrostatic interaction of PEO-PPO with chitosan results in an increase of drug release [127]. *In vitro* drug release can be studied with various methods like: side-by-side diffusion cells with artificial or biological membranes; agitation followed by ultra centrifugation/centrifugation; ultra-filtration or centrifugal ultra-filtration techniques; dialysis bag diffusion technique; reverse dialysis bag technique; and so on. Controlled agitation followed by centrifugation technique was usually followed, which was time-consuming and leads to technical difficulties during separation of NPs from release media, advocating for preferential use of dialysis technique.

PRODUCTION OF NANOMATERIALS

Various techniques were utilized to fabricate different NMs or NPs. [15] Ultra-fine grinders, lasers, and vaporization followed by cooling techniques were used to get NPs from larger structures while complex NPs were generally synthesize by a bottom-up approach through arranging molecules to figure complex structures with new and valuable properties. However, supercritical fluid technology method [128] and particle replication in non-wetting templates method [129] were also used. These techniques can be used in various ways as described below. Medicinal NPs were prepared using materials like proteins, polysaccharides and synthetic polymers following frequently used methods, including dispersion of preformed polymers, polymerization of monomers, and ionic gelation or coacervation of hydrophilic polymers. Factors like desired size of NPs; aqueous solubility and stability of drug; surface characteristics like charge and permeability; degree of biodegradability, biocompatibility and toxicity; desired drug release profile; and antigenicity of the final product determines selection of matrix materials. [3]

Dispersion of preformed polymers

Commonly, dispersion of preformed polymers technique was used to prepare biodegradable nanoparticles from poly (lactic acid), poly (D,L-glycolide), PLGA, and poly (cyanoacrylate).[67, 130]

Solvent evaporation/extraction method

This method, was suitable for hydrophobic or hydrophilic drugs, uses organic solvent like dichloromethane or chloroform or ethyl acetate, involves dissolving polymer and hydrophobic drugs (if any), followed by its emulsification with an aqueous solution (a solvent for aqueous soluble drug) containing a surfactant or emulsifying agent to form an oil-in-water emulsion followed by sonication of stabilized emulsion, evaporation of organic solvent by continuous stirring or reducing the pressure, filtration, and freeze-drying [71]. Hydrophilic drug necessitates formation of multiple water-in-oil-in-water (w/o/w) emulsion in which the drug was dissolved in internal aqueous phase. Type and concentrations of stabilizer, homogenizer speed and polymer concentration influences particle size [131] and high-speed homogenization or ultrasonication results in small size particles. [132]

Spontaneous emulsification or solvent diffusion method

It is a modified solvent evaporation method in which the water-miscible solvent along with a small amount of the water immiscible organic solvent was used as an oil phase [133] and was suitable for hydrophobic or hydrophilic drugs. For hydrophilic drug a multiple w/o/w emulsion had to be formed by dissolving the drug in the internal aqueous phase. Here spontaneous diffusion of solvents creates an interfacial turbulence between the two phases thereby forms small particles. An increase in the concentration of water miscible solvent results in decrease of particle size.

Polymerization method

In this technique monomers were polymerized to form NPs in an aqueous solution while the drug was incorporated, *in situ*, during polymerization process or by adsorbing onto the NPs after polymerization; followed by purification of NPs suspension by ultracentrifugation to remove employed stabilizers and surfactants and re-suspending the particles in an isotonic surfactant-free medium. [134] This method had been used for preparing poly(butylcyanoacrylate) or poly(alkyl cyanoacrylate) NPs in which formation and particle size of NPs depends on the concentration of the surfactants and the stabilizers. [135]

Coacervation or ionic gelation method

This method was designed for preparation of NPs using biodegradable hydrophilic polymers like chitosan, gelatin and sodium alginate [122,127,136] and involves admixture of two aqueous phases containing polymer chitosan and PEO-PPO in one phase and other contains polyanion sodium tripolyphosphate. Ionic interaction between positively charged amino group of chitosan and negative charged tripolyphosphate leads to transition of polymer in liquid phase to gel phase, at room temperature, results in formation of coacervates with particle size in nanometers.

Supercritical fluid technology based method

To eliminate use of organic solvents having hazardous effect on the environment and the physiological systems; the supercritical fluid (SCF) technology has been investigated as an alternate for preparing biodegradable NPs, as was environmentally safe. [137] Supercritical CO2 (SCC) was the most extensively used SCF associated with its mild critical conditions (critical temperature of 31.1 °C and critical pressure of 73.8 bars), non-toxicity, non-flammability, and cheapness. Supercritical anti-solvent (SAS) and rapid expansion of critical solution (RESS) were common processing techniques involved in the SCF technology. SAS employs a SCF miscible liquid solvent (e.g. methanol), to dissolve the solute to be micronized. During processing admixture of the SCF miscible liquid solvent and the SCF leads to extraction of the liquid solvent by SCF resulting instantaneous precipitation of the solute in the form of NPs associated with the insolubility of the solute in the SCF. [128] In RESS the solute was dissolved in a SCF (e.g. supercritical methanol) followed by rapid expansion of the solution through a small nozzle into a region of lower pressure thereby results in dramatically decrease in solvent power of SCF leading to eventual precipitation of solute [137] and was used for preparing NPs of hydrophilic drug (e.g. dexamethasone phosphate).[138] RESS and its modified process had been employed for preparing polymeric NPs.[139] An environmentally friendly technique yields solvent free precipitate, have suitability for mass production but requires specially designed equipment and was expensive.[3]

Crystallization method

In the presence of solutions containing different amounts of amino acids, hydroxyapatite-aspartic/glutamic acid nanocrystals were synthesized, with this method.[74]

Self-assembly vesicles

Fibrous nanostructures were induced from self-assembly of molecules through manipulation of physical and chemical conditions like pH, temperature, and solute concentrations;[74] and slow evaporation of an organic solvent form self assembled vesicles, polymersomes.[140]

Layer-by-layer deposition method

Layering of sodium silicate and poly(allylamine hydrochloride) on gold followed by calcinations in a furnace was used for fabrication nano-system, to detect specific proteins.[141]

Biosynthesis or green production

Biosynthesis a green approach of NPs synthesis using biological entities had been exploited with great interest over other physico-chemical methods that were laden with several disadvantages.

Microbial synthesis

Silver NPs produced extracellularly by harnessing the living cells.[142] *Aspergillus fumigatus* [143] and other fungi, and a number of bacterial species were exploited for producing gold and silver NPs.[144,145]

Biomass reactions

Plant-mediated synthesis of silver and gold NPs was exploited for their wider applications [146]. Incubating dead oat stalks with an acidic aqueous solution of gold ions (AuIII) produces gold-nanorods and NPs having other shapes [147] while living plants having ability to take up and sequester heavy metals can also be used in green biosynthesizing NPs of metals.[144] and gold and silver.[148] Plants like *Avena sativa,* [147] *Helianthus annus*, *Basella alba*, *Cinnamomum camphora,*[149], *Capsicum annuum,*[150], *Medicago sativa,*[151] *Parathenium,* [152] *Aloe vera,* [153] *Coriandrum sativum,* [154] *Gliricidia sepium,* [155] *Arachis hypogaea* L., *[156] Azardirachta indica*, *Pelargonium graveolens,* and so on were the exploited biomasses for green biosynthesis of NMs.

MEASUREMENT, CHARACTERIZATION, AND MANIPULATION OF NANOMATERIALS

Images of nanostructures, obtained with high resolution electron microscopy and scanning probe microscopy, were used to manipulate NMs. Information on nanostructures was also obtained with the scanning tunnelling microscopy, magnetic force spectroscopy, and magnetic resonance microscopy. Cantilever probes and optical tweezers were designed for manipulating NPs. Varieties of computer programs have been developed for simulating and modeling formation and interactions of NMs.[126,130, 157]

PUBLIC PERCEPTION OF NANOTECHNOLOGY

Public consciousness of NTy was low and knowledge about NTy was limited at best [158-164] while lay people differently perceive various applications of NTy [165] and overall acceptance seem to be some parallels to gene technology which was less for food products with respect to medical products and packaging technology [166-171] NTy packaging was perceived as being more beneficial and safe with respect to NTy foods [170,171] and individually modifiable feed and forage as most risky. Mostly people were searching in internet related to the future, health, and applications of NTy. [172]

OCCURRENCE AND LIFE-CYCLE OF ENGINEERED NANOMATERIALS IN THE ENVIRONMENT

Information related to the type and the quantity of industrially used/manufactured NPs, and the economic impact of NTy was lacking; [173] were major reason of inability to quantify the level of exposure for consumers and the environment. Initial survey of Swiss industry reveals that the highest proportions of NPs were used in producing cosmetics, food, paints, and powders. [174]. NPs can get released into the environment and subsequently into the food cycle, throughout all the stages of product life-cycle while the amount gets released was dependant on the content of NPs in it, the method of their incorporation, and its life-time and actual use/usage, [175] necessitate for accessing/accounting the possible exposures to NPs throughout the phases of product life-cycle [176-178]. All NPs used with imaginable application may enter the environment through critical stage of product life-cycle, including production and shipment, the most vulnerable phase for release into environment; production of final product; use; and recycling or disposal by their dumping into landfills or burning in waste incineration plants.[175] Short life-time, low usage and strong fixation of NPs, retards likelihood for their release till disposed up, [18,179] into the environment and also from the products that were used up during use. Nano-titanium dioxide/silver from sunscreens [180] and nano-silver from antimicrobial agent [181] enter water systems during their washing off while NPs in sanitizing contaminates groundwater and soil. Ionic form of silver (in from NPs) was released from plastics and textiles.[182] Silver from NPs was found to contribute only 0.5 – 15% to the total silver flow into the environment.

BEHAVIOUR OF ENGINEERED NANOMATERIALS IN THE ENVIRONMENT

It had been suggested, manufactured NMs may act differently with respect to natural NMs as manufactured NMs were designed with specific surface properties and chemistries that were not likely to be observable with natural particles.[183] Determination of environmental fate of NPs comprises study of their tendency for aggregation – segregation and adsorption – desorption through interaction among themselves and with other natural NPs or macroparticles. [184-186] Their aggregation in natural systems was studied considering their physical processes like Brownian diffusion, fluid motion, and gravity; and was dependent on particle size thereby resulting in efficient removal of small particles from environmental systems.[187] The surface charge plays a dominant role in the adsorption processes of NPs [188,189] that consequently modifies its nature [190] and their mobility was modified with coating[191]and environmental conditions like composition of groundwater and the hydrologic conditions [192-194], and was responsible for facilitation or inhibition of contaminant transport;[195]thereby increasing/decreasing toxicity associated with transported contaminants. Size-dependent adsorption reactivity of crystalline iron-oxide NPs [196] was responsible for carrying adsorbed pollutants like copper, mercury, and silver eliciting toxicity on algae, flowering plants, fungi, and phytoplankton.[197]

ECOTOXICOLOGY OF NANOSCIENCE AND ENGINEERED NANONATERIALS

Manufactured NPs, designed with specific surface properties and chemistries, enhance novel physicochemical and possibly ecotoxicological properties with respect to natural particles, as they may act differently.[183] Reports related to ecotoxicological effects of manufactured NMs were available.[198] Lab-scale report relating to take up of some manufactured NPs by fish, *Daphnia magna,* [199] copepods, and other organisms [200-202] were available while concerns had been raised that high reactivity of NPs might have impact on plants, animals, micro-organisms, and ecosystems.[203]

NPs enter human body through the GI-tract, the skin or the lungs [204] and concern on their safety was rising associated with its similar properties associated with pathogenic particles. [203,205] Engineered NPs differs with respect to material, size, surface, and shape; therefore general claims cannot be made regarding associated health and other risks and consequently suggestions had been made to assess their risk and toxicity on case-by-case basis. [206] Evidence exhibiting NPs uptake and internalization by a wide variety of mammalian cell types, and their ability to cross the cell membrane were available.[207-209] Concentration, size or surface area, surface energy, surface morphology, aggregation, and properties of dissolution media and adsorbing species that influences dissolution potential of NPs; the characteristics of exposed environment, and the biochemical, physiological, and behavioural traits of the exposed organism; determines their biological fate and effects. [210, 211] Size dependency for uptake, [212,213] increased concentration and exposure time, [214] and large surface area associated with small particle size [9] play major roles in the toxicity of NPs. Probably NPs were more likely to penetrate the skin and presently it was impossible to predict its skin permeability to significant extent.[215] Inhalation of higher concentrations of NPs may cause inflammatory reactions in the lungs and adverse effects in the nervous and cardiovascular systems while data related to their translocation to other parts of the body was not available and rodents have demonstrated some toxic effects with CNTs.[215] NPs cause oxidative stress in the liver, harm the brain associated with higher BBB permeability, and activate blood platelets leading to clot formation.[215] Ferric oxide NPs upon exposure through inhalation may taken up by cells, resulting oxidative stress response at much higher dosages.[216] while same may internalized by cells leading to cell death and may persist in biological systems thereby could potentially lead to long-term effects linking mutagenic influence on organisms [217] through DNA damage, lipid peroxidation, and oxidative protein damage *in vivo* mediated through abundance of free chelating iron [218], and dispersion of C60 fullerenes. [219] Fullerenes results morphological changes in the vascular endothelial cells while at higher concentrations could induce cytotoxic and lethal effects. [220] Potential GI-tract effects of NPs were chiefly unknown. [221] Transport of particles across the epithelium of GI-tract occurs by paracellular or transcellular route [222] while transcytosis process was involved in the transcellular uptake of NPs that was dependant on the physicochemical properties of the particles, the physiology of the GI-tract, and the animal model used for study.[222] Some aspects of the GI environment and abrupt change in pH from the stomach to the intestine, diseases of the gut and many other macromolecules in food may affect uptake of NMs or possible toxicity.[215]

Reports highlighting the toxicology, the gaps in research, and possible testing strategies for NPs were published. [12,176,214,223,224] Several government and non-government organizations (NGOs) had identified health risks and potential environmental consequences, and the importance for assessing same; so as to determine hazardous effects like toxicity, fate and transport, and bioaccumulation of released NMs and NTy. [16, 205,223,225-228] Without a demonstration on the potential benefits outweigh the potential risks, use of free NMs that had not been fixed in the matrix for remediation was strongly opposed by The Royal Society, in their report [229, 230] The U.S. EPA has raised concern on the biomagnifications of NPs without any reported data regarding approval and dismissal of this hypothesis [227, 231] Respiratory symptoms after use had pulled out a nanotechnology-based spray for ceramic sealant to repel dirt, Magic Nano, from Europe in March 2006 [232] and several other reported complicacies, advocating for commencing their ecotoxicology/safety assessment.

Knowledge indicating potential impact of NMs in the environment and on human health was still limited.[177,198] Ecotoxicological risk assessment data on NMs was sparse[177] excluding some recent reports on ongoing projects [233] while their unique physicochemical property complicates risk assessment. [234, 235] It had been suggested that toxicity studies should not be limited to human and wildlife but also to be extended to benthic and soil flora and fauna, as they make up the basis of food chains [202] and biological systems did not grow alongside the NPs that were presently manufactured and released [236] Assessing the risks associated with use of NMs needs development of preliminary framework/strategies regarding need and type of research, methodology of integration, generation of data related to toxic effects after their entry in to the body upon exposure to and/or uptake of, and analyzing the information for making decisions about safety. [177, 201, 234-238] Assessment and quantification of potential risks of manufactured NPs needs deep study related to their mobility, bioavailability, toxicity, fate processes, and persistence of environmental health perspectives, [239] while fate processes and toxicity depend on the particle coating, surface treatments, surface excitation by ultraviolet radiation, and aggregation potential along with the characteristics of environmental system [9,198] Environmental stability of NPs can be quantified by studying stability of their suspensions and their tendency to aggregate and interact with other particles.[185]

DEALING WITH THE UNCERTAINTY ASSOCIATED WITH NANOSCIENCE AND NANOTECHNOLOOGY

However, advocated promising beneficial properties of NTy based engineered NMs (sufficiently powerful products), could hostile governments or angry individual and damage humans and environment thereby leading to wreak havoc [203, 240,241]and become a hot topic presently.[242] Unavailability of data related to toxicity, exposure, and life-cycle of NTy applications, regulatory decisions were in a state of ambiguity with level of uncertainty; may result in either forgoing the benefits of NTy associated with too much regulation or damages associated with too relaxed regulation. [243] Perceptions on regulatory policy issues in the field of NMs [206] and delayed government regulations for engineered NPs [244] conferring expressions on importance for implementation of voluntary standards of care, while several have called for cessation on the use of NMs, the further commercial release of food products and food packaging/contact materials associated with infancy risk governance strategies for these products [14,245], and agrochemicals; until NTy-specific safety laws was established along with public involvement in decision making. [177, 246] Lack of scientific evidence indicating harmful/hazardous effect of NMs eliminates need to regulate this area by regulatory bodies and industry while NGOs were advocating for more proactive risk management strategies leading to different opinions.[177,247] High degree of scientific uncertainty related to the risks of NTy leading to argument that policy-making cannot be kept on hold until risk assessments were complete.[245] Unrestricted/irresponsible NTy-based manufacturing without proper administration and care may well outweigh their benefits leading to black markets, immense destruction through unstable arms races, and possibly a release of grey goo [230,240, 247] To overcome the apparent weaknesses of earlier approaches; diverse integrative risk management frameworks having common elements like integration of hazard assessment, exposure assessment, risk management, and risk communication; for NMs had been developed, recently [248-251]

Governmental investment along with careful redressal of health and the environmental consequences was necessary for receiving benefit from nanotechnological commercial products and public acceptance.[3] NTy will provide opportunities for integrating science and technology with social science and humanities while scientists and engineers can be updated with societal effects of new technologies by well developed educational mechanisms through intelligent database, accordingly an undergraduate course on nanotechnology has been designed.[3,252]

SCIENTISTS AND INDUSTRIAL PERSPECTIVE FOR NANOTECHNOLOOGY

Scientists working in the field of NTy were generally more optimistic regarding potential benefits of this technology while less concerned about risks with respect to public [165,253] Experts expect that NTy may provide novelty in the treatment of human diseases and the pollution abatement [253] where as several scientists were more concerned regarding NTy associated higher pollution and environmental contamination, and new health problems. Lay people and experts assess the NTy associated risk, differently [165, 169] and lay people perceive higher risks than experts [253] while discussions of previous section reveals higher concern of experts than lay people, in this regard. Doubts related to proper redressal of possible risks associated with NTy, industry of Switzerland and Germany was rising gradually [173] and non- redressal of the issues with respect to public expectation may lead to a social amplification process [3, 166, 254] NTy applications in the area of food or health were associated with a high level of terror and suspect [165, 169] and were likely to turn into controversial topics.

CONCLUSION

Nanotechnology had higher opportunities to integrate science and technology with social science and humanities but requires proper redressal of environmental and societal issues/effects so as to receive public acceptance and decrease hostilely attitude of public. Scientists and engineers working in the field should be updated with related issues/effects with well developed educational mechanisms through intelligent database. General public and intellectuals should be convinced with proper scientific data so as to eliminate associated terror and suspect, and eliminate controversies related to the topic. The sphere should be advanced and regulated judiciously so that the benefit of this science and technology could be best weeded to the society eliminating ecotoxicological effects thereby protecting environment and humanities.

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