Chapter 5
Micro and Nanotechnology

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Abstract Scale measurement is one of the frequently used approaches and tools for classifying micro, nano, and even macro technological application domains, despite the fundamentally significant variations in the chemical and physical mechanisms. Unit scales of macro, micro, and nano are used to understand and interpret better the size of objects in an associated and related manner at different level of scales in order to be able to understand the boundary-evading nature of materials fabricated at different levels for general and specialized fit-for-purpose applications. This book chapter focused on a relatively small portion of the larger and far-reaching field of micro/nanotechnology, which currently encompasses every aspect of science and engineering as well as anything we could possibly dream of or envision.

Keywords Technological advancements · Nanofabrication · Microfabrication · Scale measurement · Biosensing

The History of Micro and Nanotechnologies

Historically, materials always have existed at different dimensional scales, and humans have used different particles and structures since the first ancient civilization. Whether they had been aware or not, the Romans and the Damascans demonstrated one of the most interesting technologies in the ancient world by respectively using nanoparticles to create iridescent glasswares and exceptionally sharp edge swords. Developmental traces of nanoscience in the time of ancient Greek philosophers like Democritus in the fifth century led scientist asked whether matter is a continuum, and therefore, indefinitely divisible into smaller portions, or made up of tiny, indivisible, and indestructible components which today's scientists refer to as atoms [1]. This can only consolidate the belief that archaic artisans were nanotechnologists who had practically used nanoscience to develop historic artefacts [1]. As early as

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the fourth century, Roman artists had discovered that adding gold and silver to glass developed a remarkable effect of colour change with the glass appearing slate green when lit from outside and glowing red when lit from within [2–4]. The ceremonial Lycurgus cup is the most famous surviving example of this technique [1, 2, 4]. While nanoscience intermarries nanotechnology for its practical application, the same goes with the relationship between microtechnology and nanotechnology. Over the course of modern historical evolution of scientific and technological advancements, by scale measurement, micro and nanotechnological materials have progressed hand in hand and used in various application domains. In essence, nowadays, we can buy available precision technological processes workup materials at microscale or work them down to nanoscale, thus, the interwoven nature of both technologies exist at scale boundary line.

In a historical precedence, groundbreaking discoveries and events continue to emerge in an evolutionary timeline fashion resonating the witnessed progress advancement of nanoscience and technology. For instance: Stained glass windows of cathedrals (500–1450 BC) [5], Iridescent/metallic clusters of the Derutta Poetry (1450–1600 BC) [5], colloidal rugby gold nanoparticles synthesis [6], light scattering of nanoparticles (Mie 1908) [7], near field optical microscope [8], cathode ray oscilloscope (CRO) [9], field-ion electron microscope reporting the first surface atom visualization [10], Watson and Crick discovery of DNA [11], electron tunneling [12], etc.; are in a random mix, few of the huge achievements already recorded within the sphere of nanoscience and nanotechnology and has offered highly innovative solutions to various scientific and technological domains tackling human challenges. Table 5.1 gives a more comprehensive overview of the evolutionary trend timeline marking the events that has shaped historical progress in the advancement of nanoscience and nanotechnology to date. This timeline depicts premodern examples of nanotechnology, and in like manner, modern era discoveries so far reached as milestones.

Heralding the era of what today is referred to as modern nanotechnology, American Physicist and nobel laurate Richard Feynman, came up first with ideas and concepts behind nanotechnology in 1959 [1]. At this time and during the annual meeting of the American Physical Society held at California Institute of Technology (Caltech), Feynman presented a lecture titled "There's Plenty of Room at the Bottom" [25]. Though not mentioning the word 'nanotechnology' in his lecture, Feynman posed the question: "why can't we write the entire 24 Encyclopedia Britannica on the head of a pin"?, laying down the possibility of using machines to fabricate and construct smaller machines to molecular level scale [31]. From this point onward, a revolutionary trend in the manipulation of materials at different scale range levels of "micro" and "nano" erupted giving birth to the traverse being witnessed today in the diverse domains of science, engineering and technology for the development of best result outcome materials as a function of size, shape and functions entirely different from their bulk state.

Table 5.1 Evolutionary trend of progress advancement in nanoscience and nanotechnology

Year	Event/discovery & milestone	Brief introduction about finding	References
4th century	The Lycurgus cup (Rome)	An example of a dichroic glass of colloidal gold and silver that makes the glass look opaque green when lit from outside and translucent red when light shines through the inside	[1]
6th–15th centuries	Vibrant stained glass windows (Seen in European cathedrals)	Their rich colours owed to nanoparticles of gold chloride ($AuCl_4$), and other metal oxides and chlorides	[5]
15th–16th centuries	The Italian Renaissance pottery	The Deruta and Gubbio centre became the most famous centre for the production of lustred glazed majolica containing nanoparticle components	[13, 14]
9th–17th centuries	Glowing, glittering "luster" ceramic glazes	Used in Islamic world and later in Europe contains silver or copper or other metallic nanoparticles	[15]
13th–18th centuries	"Damascus" saber blades	Contain carbon nanotube (CNT), and cementite nanowires: an ultra-high carbon-steel formulation that bequeathed them with strength, resilience, ability to hold a well defined edge, and pronounced moiré pattern in the steel from where the blades name originated	[16]
1857	Colloidal "ruby" gold	Michael Faraday demonstrated that nanostructured gold under certain lightening conditions produces different coloured solutions	[6]
1897	Cathode ray oscilloscope (CRO)	Ferdinand Braun developed the CRO for measuring and displaying different forms of electrical signals	[9]
1895	X-ray diffraction (XRD)	Wilhelm Conrad Rontgen stumbled across effects that could create images on fluorescent screens and subsequently on photographic plates at a distance from an optically hidden crooks or similar structured tubes	[17]
1908	Light scattering of nanoparticles	Gustav Mie demonstrated the scattering of nanoparticles by light	[7]

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Table 5.1 (continued)

Year	Event/discovery & milestone	Brief introduction about finding	References
1928	Near field optical microscope	Edward Hutchinson Synge laid out and published an incredibly complete theoretical description of near field microscope: an instrument used in nanotechnology several decades before being experimentally developed	[8]
1928	Raman spectroscopy	Sir C.V. Raman discovered a change that beckoned in the frequency and wavelength of deflected light when passed through a spectrograph	[18]
1931	Transmission electron microscopy (TEM)	Max Knoll and Ernest Ruska invented the technique where beam of electrons is transmitted through a specimen to form an image	[19]
1936	Field electron microscope (FEM)	Erwin Müller while working at Siemens research laboratory invented the field emission microscope that would allow near atomic resolution images of materials	[10]
1937	Scanning electron microscopy (SEM)	Manfred von Ardenne made an invention that utilized electromagnetic lenses to focus scanning electron beam on the target surface and then collect scattered electrons giving back information on the sample topography and structure	[20]
1947	Semiconductor transistor	John Barden, William Shockley, and Walter Brattain at Bells Laboratory made the discovery of semiconductor transistor and expanded greatly the scientific knowledge of semiconductor interfaces, which today has turned out to be the foundation for electronic devices and information age	[9]
1950	Growth process for monodispersed colloidal materials	Victor La Mer & Robert Dinegar developed the theory and process for growing monodispersed colloidal materials which immensely contributed to the ability of controlling and fabricating myriad of materials for diverse industrial applications like specialized papers, paints, thin films, and even for dialysis treatments	[21]

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Table 5.1 (continued)

Year	Event/discovery & milestone	Brief introduction about finding	References
1951	Field Ion microscope (FIM)	Erwin Müller pioneerd the field ion microscope- a means to image the arrangement of atoms at the surface of a sharp tip. He first recorded the image of tungsten atoms	[10, 22]
1953	DNA discovery	James Watson & Francis Crick discovered the molecular structure of Deoxyribose Nucleic Acid (DNA) laying the foundation and paving the way on interdisciplinary research involving scientist from diverse background of physics, chemistry, material science, computer science and medicine in finding solutions to challenges bordering on related issues with this intricate and complex building block of human cells and tissues	[12]
1956	Molecular engineering	Arthur von Hippel introduced many concepts bordering on nanotechnology and coined the term "Molecular Engineering" as applied to dielectrics, ferroelectrics, piezoelectrics, etc.	[23]
1958	Electron tunneling	Leo Esaki first observed and interpreted the negative resistance phenomena in degenerate germanium semiconductor p-n junctions	[12]
1958	Integrated circuit	Jack Kilby of Texas Instruments devised the concept, designed and built the first integrated circuit	[24]
1959	"There is plenty of room at the bottom"	Richard Feynman of the California institute of technology during an American physical society meeting at Caltech delivered what is widely considered to be the first lecture on technology and engineering at atomic scale	[25]
1960	Zeolites and catalysis	Charles Plank and Edward Rosinki developed and patented crystalline zeolite composite for the catalytic cracking of hydrocarbons	[26]

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Table 5.1 (continued)

Year	Event/discovery & milestone	Brief introduction about finding	References
1963	Ferrofluids	Stephen Papell achieved and patented low viscosity magnetic fluid he had obtained by the colloidal suspension of magnetic particles	[27]
1965	Moore's law	Intel's co-founder Gordon E. Moore described in electronics Magazine several trends he foresaw in the field of electronics. One of such trends known today as Moore's law was that the density of transistors on an integrated chip (IC) will double every 12 months (later amended to 2 years). Moore also saw chip sizes and costs shrinking with their growing functionality as they show transformational effect on the way people live and work	[28]
1969	X-ray photoemission spectroscopy (XPS)	A technique for analyzing material's surface chemistry was discovered	[29]
1970	C60 existence as icosahedron	Eiji Osawa was first to have predicted the existence of C60 as icosahedron structure	[30]
1974	First time the term "Nanotechnology" was used	Prof. Norio Taniguchi was the first to coin the term "Nanotechnology" describing the precision of manipulating materials to within atomic scale dimensional limits	[31]
1974	Molecular electronics	Mark A. Ratner & Arieh Avram constructed a rectifier as a simple electronic device based on the use of a simple organic molecule- methylene	[32]
1977	Surface enhanced Raman spectroscopy (SERS)	Richard P. van Dunye and Co-workers verified that by Raman spectroscopy, adsorbed pyridine on a silver surface showed a remarkable sensitivity, which by extension was applicable to other nitrogen heterocycles and amines	[33]
1980	Self assembly monolayers (SAMs)	Jacop Sagip formulated oleophobic mixed layer structures on solid surfaces	[34]

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Table 5.1 (continued)

Year	Event/discovery & milestone	Brief introduction about finding	References
1981	Scanning tunneling microscope (STM)	Gerd Binning & Heinrich Rohrer discovered the technique that makes possible the imaging of surfaces at atomic scale, and facilitate the creation of atoms and molecules for the creation of structures	[35, 36]
1981	Nanocrystalline quantum dots in a glass matrix	Russian Scientist Alexei Ekimov discovered nanocrystalline semiconducting quantum dots in a glass matrix and conducted pioneering studies of their electrical and optical properties	[37]
1981	Molecular engineering	Eric Drexler developed method equipped with general capabilities for the realization of various manipulated molecules	[38]
1982	DNA concept of nanotechnology	Nadrian Seeman shaded light on the structural junctions and lattices of DNA, paving way for more opportunities and related challenges of DNA nanotechnology	[39, 40]
1983	Colloidal quantum dot	Louis Brus discovered colloidal quantum dots studying the electronic and optical properties of cadmium selenide (CdS)	[41, 42]
1985	Buckminsterfullerene C60 discovery	Harold Kroto, Sean O'Brien, Robert Curl, and Richard Smalley- researchers from Rice university discovered the buckminsterfullerene commonly known as Buckyball: a molecule of the shape of a ball composed entirely of carbon as graphite and diamond	[43]
1986	Atomic force microscopy (AFM) or the scanning force microscope (SFM)	IBM scientists-Gerd Binnig, Calvin Quate, and Christoph Gerber co-invented the first experimental AFM apparatus allowing the use of an atomic size tip to probe the surface of a material, facilitating the creation of a 3D map of the surface to be constructed, down to the scale of individual atoms	[44, 45]

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Table 5.1 (continued)

Year	Event/discovery & milestone	Brief introduction about finding	References
1987	Single-electron tunneling (SET) transistor	Dimitri Averin and Konstantin Likharev developed a macroscopic approach to the theoretical examination of small, current-biased tunnel junctions used to account for the secondary quantization of both the single electron (quasiparticle), and Cooper-pair (Josephson) current components	[46]
1990	Manipulation of the 35 individual Xenon (Xe) atoms to inscribe and spell out the IBM logo	Don Eigler & Erhard Scweizer at IBM's Almaden research center demonstrated the ability to precisely manipulate atoms: a turning point that ushered in the applied use of nanotechnology	[47]
Early '90s	Pioneer nanotechnology companies start to be operational	Nanotechnology companies like Nanophase technologies (1989, Helix energy Solutions group (1990), Zyvex (1991), Nano-Tex (1998), etc.; commenced operations	(Initiative)
1991	Multi-wall carbon nanotube discovery	Though there were early observations of tubular carbon structures, Sumio Iijima of Japanese multinational information technology and electronics corporation (NEC), is credited with the discovery of Carbon Nanotube (CNT): a material like the buckyball but tubular in shape boasting of extraordinary properties of strength, electrical and thermal conductivity amongst other unique features	[48]
1992	Nanostructured catalytic materials MCM-41 & MCM-48	Charles T. Kresge and colleagues at Mobil oil discovered nanostructured catalytic materials: MCM-41 & MCM-48 -mesoporous molecular sieve silica materials that have found wide applications in crude oil refining, drug delivery, water treatment, etc.	[49, 50]
1993	Single-wall carbon nanotube discovery	Sumio Iijma & Donald Bethune grew by cobalt catalyzed reaction; carbon nanotubes with single atomic layer walls and shell of diameter 1 nm	[51, 52]
1993	Method for controlled synthesis of nanocrystals (Quantum dots)	Moungi Bawendi of MIT, and contribution works of other researchers like Louis Brus, and Chris Murray resulted to methods for synthesizing quantum dots for applications ranging from computing to biology to high-efficiency photovoltaics and lighting	[53]
1996	Self assembly molecule (SAM) of DNA + gold colloids	Chad Mirkin & Robert Letsinger developed DNA-based method for the rational manipulation of nanoparticles into macroscopic materials	[54]

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Table 5.1 (continued)

Year	Event/discovery & milestone	Brief introduction about finding	References
1998	Nanotechnology Research Directions: Vision for the Next Decade (1999)	The Interagency working group on nanotechnology was formed under the auspices of the national science and technology council to investigate the state of the art in nanoscale science and technology to forecast possible future developments	[48]
1998	Transistor Creation with Carbon Nanotube	Cees Dekker developed a room temperature operating Carbon nanotube-based transistor	[55]
1999	Invention of Dip-Pen Nanolithography	Chad Mirkin at Northwestern university developed dip-pen nanolithography leading to the manufacturing, and reproducibility of electronic circuits, biomaterial patterning for cell biology, nanoencryption, and other applications	[56]
1999	Molecule Assemblage	Cornell university researchers Wilson Ho and Hyojune Lee investigated the secrets of chemical bonding by assembling iron carbonyl ($Fe(CO)_2$ molecule built from its components of iron (Fe) and carbon (ii) oxide (CO_2) using a scanning tunneling microscope (STM)	[57]
2000	Feedback-Controlled Lithography (FCL)	Mark Hersam & Joseph Lyding developed reliable technique for making individual dangling bond templates on Si(100)-2 × 1:H surface, detecting individual H desorption events while patterning for tip structure variation compensation	[58]
1999–early 2000's	Consumer Products derived by Nanotechnology starts to make Market Entry	consumer products like: light weight nanotechnology -enabled automobile bumpers with denting and scratching resistances, straighter fly golf balls, stiffer tennis rackets, better flex and kick baseball bats, nano-silver antibacterial socks, clear sunscreens, wrinkle and stain resistant clothing, deep-penetrating therapeutic cosmetics, scratch resistant glass coatings, faster-recharging batteries for cordless electric tools, improved TV, cell phones, and digital camera displays etc. made their ways into the market	[48]

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Table 5.1 (continued)

Year	Event/discovery & milestone	Brief introduction about finding	References
2000	United States National Nanotechnology Initiative (US NNI)	President Bill Clinton announced the US NNI for the coordination of the Federal R&D efforts and the positioning of the US competitiveness in nanotechnology	[59]
2001	Molecular Nanomachines: molecular motor (rotor) with nanoscale silicon devices	Carlo Montemagno explored vision of realizing molecular nanomachines through the development of molecular motor powered by nanosilicon components	(CD [60])
2002	DNA functionalized carbon nanotube	Cees Dekker and co-workers conducted the study of unifying single walled carbon nanotube (SW-CNT) by coupling to peptide nucleic acid (PNA)- an uncharged DNA analogue and hybridized the macromolecular wires with complementary DNA thereby unravelling a pathway for achieving versatilized SWCNTs as probes in biological systems	[61]
2003	21st century nanotechnology and development act (P.L. 108–153) enacted by the US congress and officially signed into law	The US congress enacted the 21st century nanotechnology and development Act (P.L. 108–153), providing a statutory foundation for the NNI, established programs, assigned agency responsibilities, authorized funding levels, and promoted research to address key issues and was finally signed into law by United States President, President George W. Bush	[48]
2003	Development of gold nanoshells	Naomi Halas, Jennifer West, and Renata Pasqualin at Rice university developed gold nanoshells tunned in size to absorb near infrared light, serving as integrated discovery, diagnosis, and breast cancer treatment platform with no invasive biopsies, surgery, systemic destructive radiation or chemotherapy	[62, 63]
2004	The EU commission adoption of “towards a European strategy for nanotechnology”	The EU commission adopted the communication ”Towards a European strategy for nanotechnology” COM (2004) 338, with the proposal of intitutionalizing European nanoscience and nanotechnology Research and Developments efforts within an integrated and responsible strategy triggering European action plans and progressive funding for nanotechnology	[48]

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Table 5.1 (continued)

Year	Event/discovery & milestone	Brief introduction about finding	References
2004	Nanoscience and nanotechnology: opportunities and uncertainties published by Britain's royal society and royal society of engineering	In this publication, the Britain's royal society and royal society of engineering advocated the need to address potential health, environmental, social, ethical, and regulatory issues associated with nanotechnology	[48]
2004	College of nanoscale Science and nanotechnology engineering launched	SUNY Albany launched the first college level education programme in Nanotechnology in the US	[48]
2004	Graphene discovery	Adre Geim & Konstantin Novoselov discovered graphene material as atomically thin carbon film	[64]
2004	Fluorescent carbon dot discovery	Xu et al.; discovered single-walled fluorescent carbon dots	[65]
2005	Nanocar on buckyball wheels	James Tour and colleagues at Rice university built nanoscale car turning on buckyball wheel	[66, 67]
2005	DNA -based computation and algorithmic self assembly	Erik Winfree and Paul Rothemund from the California institute of technology (CIT) developed theories for DNA -based computation and algorithmic self assembly in which computations are embedded in the processes of nanocrystal growth	[48]
2006	DNA origami	By his own coined out term @"scaffolded DNA origami, Paul Rothemund was able to assemble six different shapes of DNA strands, e.g., squares, triangles, five-pointed stars etc.	[68]
2007	Type of bacteria lithium ion battery	Angela Belcher and Colleagues at MIT built lithium-ion battery with a common type of bacteria that is unharmful to humans	[48]
2007	Artificial molecular machines	J. Fraser Stoddart developed artificial molecular machines that is like a pH -triggered muscle	[69]

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Table 5.1 (continued)

Year	Event/discovery & milestone	Brief introduction about finding	References
2008	Development of green fluorescent protein (GFP) won a nobel	Osamu Shimomura, Martin Chalfie, and Roger Y. Tsien were awarded Nobel prize in Chemistry for their collaboration on the development of green fluorescent protein (GFP)	[70]
2008	NNI strategy for nanotechnology-related environmental, health, and safety (EHS) research published	The NNI strategy for Nanotechnology related EHS was published after 2-year process of NNI-sponsored investigations and public dialogs. The strategy was further updated in 2011 after series of workshops and public review	[48]
2009–2010	DNA-like robotic nanoscle assembly devices	Nadrian Seeman and colleagues at New York University developed several DNA-like robotic nanoscale assembly device, and also created DNA assembly line for which he shared the prestigious Kavli Prize in Nanoscience 2010	[71]
2010	Development of an ultra-fast lithography to create 3D nanoscale textured surface	IBM developed the method of creating nanoscale patterns and structures as small as 15 nm at a reduced cost and complexity opening new prospects in the field of electronics, optoelectronics, and medicine	[72]
2011	Electro-mechano properties of individual molecules and the polymer chains	Leonhard Grill used scanning tunneling microscope (STM) for the description of electrical, and mechanical properties of individual molecules and polymer chain	[73]
2011	Updating of the NNI strategic plan and NNI environmental, health, and safety research strategy	The nanoscale science, engineering and technology -NSET subcommittee of the NNI updated the NNI strategic plan and the EHS strategy drawing extensive input from public workshops, and online dialog with stakeholders from Government, academia, NGOs, the public, and others	[48]
2012	Launching of two more nanotechnology signature initiatives (NSIs)	The NNI launched nanosensors, and the nanotechnology knowledge infrastructure (NKI)	[48]

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Table 5.1 (continued)

Year	Event/discovery & milestone	Brief introduction about finding	References
2013	NNI strategic planning	NNI starts next round of strategic planning commencing with stakeholder workshop	[48]
2013	Carbon nanotube computer	Standford researchers developed first carbon nanotube computer	[48]
2014	Release of updated strategic planning	NNI releases the updated 2014 strategic plan, progress review on the coordinated implementation of the NNI 2011 EHS research startegy	[48]
2016	Nobel for design and synthesis of molecular machines	Jean-Pierre Sauvage, Sir J. Fraser Stoddart, and Bernard L. Feringa won the 2016 nobel prize in chemistry for their work on design and synthesis of molecular machines	[74]
2017	Nobel for gravitational waves	Nobel prize in physics for work on gravitational waves	[31]
2018	World smallest game board with DNA	World smallest tic-tac-toe game board was developed with DNA	[75]
2018	Object shrinkage	Object shrinkage to nanoscale was demonstrated	[76]

Definition of Microtechnology

Micro and nanotechnologies are roughly related on scale basis; however do have significant differences underlying their physical and chemical mechanisms [77–79]. However, no hardline differences between these technologies, scientific and technology communities regimentally approach them differently [77–81]. Hence, the challenge of arriving to an all-inclusive and sufficient definition of these concepts transcending multiple disciplinary frontiers with no fit-in-one category exists. As particularly pervasive as they are, microtechnology extends into nanotechnology. Just as science and technology have always being heavily intertwined, impossible to discuss and indeed advance independently, such connection exists between micro and nanotechnology. In essence, both micro and nanotechnologies are about miniaturizing and scaling materials down to produce other material products. Majority of material manufacturing processes which earlier were classified as microtechnological processes have now further being scaled down and falling within the scope of nanotechnology. Microtechnology is the application of technological processes in the manufacture of miniaturized objects or systems at microscale [77–79]. Matter manipulation at this scale is within the range of 1micron (μm) or 10^{-6} m (in the equivalent of meter) or 10^{-3} mm (in the equivalent of millimeter) or even 10^{3} nm (in the equivalent of nanometer scale).

Definition of Nanotechnology

Fifteen years later following the exploration of Feyman, the word "Nanotechnology" was first used and defined as "a process comprising mainly of separation, consolidation, and deformation of materials by one atom or one molecule" by Norio Tanuguchi, a Japanese scientist [31]. In recognition of his inspiring contributions, Richard Feynman was credited and widely regarded today as the father of modern nanotechnology [1]. Following the discovery and insight into this new research field, scientists and researchers were highly illuminated with a trigger of huge interest, focus and concerted efforts. Such scientific research community approach has advanced findings with tremendous impact translating nanoscience capability of manipulating materials at nano and molecular scales to observing, measuring, manipulating, assembling, controlling and manufacturing matter at the nanometer scale [80]. In the light of the huge potential prompting the declaration of nanotechnology as one of the most promising technologies of the twenty-first century, the National Nanotechnology Initiative (NNI) in the United States of America (USA) defined nanotechnology as the science, engineering, and technology of manipulating materials at the nanoscale range of (1–100 nm) size, making it possible to leverage on their exhibited outstanding properties of sizes and shapes at this scale; for extensive novel application to variety of fields ranging from chemistry, physics, and biology to medicine/life sciences, engineering, and electronics [48]. Enshrined in the NNI

definition of nanotechnology are the structural manipulation of materials based on sizes and shapes at nanoscale, and the inherent novelty taking advantage of materials manipulation at this scale where unique physical, chemical, and biological properties not obtainable at either smaller scales like atoms nor larger scales of millimeters/inches frequently used in everyday life emerge [48].

Increased information capabilities, system miniaturization, new material science development with increased functionality and autonomy are some of natural consequences in the advances of micro and nanotechnologies resultant effect of scaling to small size [77–81]. The definition of microtechnology do not completely border on categorized microscale dimension materials but could however also be classified based on manufacturing composition for instance microelectrionic material devices originally fabricated with microscale development processes [77, 81]. The transitional means in fabrication of micro and nanotechnologies offers material workability at both scales to meet need for specific applications. This interplay has led to revolutioned material advancement with robust and ultimate properties emerging at nanoscale [81]. Typically, apparent trends in microelectronics with component miniaturization, increased capability as per information density, reduced cost function, increased reliability and ruggedness etc., are improved features at the micro-nanotechnologies interface [77, 81].

In absolute sense, the two particularly pervasive themes of microtechnology with extension into nanotechnology lie interfacially at the convergence of science disciplines of chemistry, biology, physics, and material science and subsequently lay foundation for nanoscience. While nanoscience interwove with these principal core science disciplines, the technological application of the knowledge emerging from the involved nanoscience interconnectivity delivers the capability of measurement observation, manipulation, assemblage, control, and matter manufacturing at the scale of nanometer and micrometer. In accounting for a more regulated and laid out definition of micro and nanotechnologies, several organizations and regulatory bodies and agencies have provided explanation to scientific terms associated with research areas focusing on the understanding and manipulation of matter at atomic and molecular scales. The associative defined terms as relayed in Table 5.2, complements the capacity for the observation, measurement, manipulation, production and manufacturing of materials at nano scale to facilitate their integration and incorporation into miniaturized microsystems, components and subcomponents fit for variety of applications.

Differences Between Macro, Micro and Nano Scale

Despite the underlying significant differences in the chemical and physical mechanisms of micro, nano, and even macrotechnological application domains, one of the widely used approach and means for their classification is scale measurement [96]. In order to be able to come to terms with across the boundary evading nature of materials fabricated at different levels for general and specialized fit –for-purpose applications;

Table 5.2 Nanotechnology and related terms definition by international regulatory bodies

Regulatory body/ committee/organization	Term	Definition	References
British Standards Institution (BSI)	Nanoscale	Nanometer size measurement of range ~1 to 100 nm	[82]
British Standards Institution (BSI)	Nanoscience	Study of the understanding of size and structure dependent features of nano-scaled matter and their comparison for related differences with individual atoms, molecules or bulk materials	[82]
Technical committee of the international standard organization- ISO/TC 229: Nanotechnologies	Nanotechnology	Available scientific data/ information for the manipulation and control of nano-matter (100 nm) needed for the harnessing of its size- and specific structural properties different from its individually existing atoms/molecules, or bulk materials	[83]
European Patent Office (EPO)	Nanotechnology	Description of entities controlled at geometrical sizes of < 100 nm displayed by atleast one functional component of one or more dimensional exhibition with resultant effect to size-dependent physical, chemical, and biological responses	[84]
American National Standard Institute (ANSI)- Nanotechnology standards panel	Nanotechnology	Manipulation and control of matter in nanoscale (~1 to 100 nm), at which point new properties emerge of materials and for new applications. A composition of nanoscale science, engineering and technology, in which nanomaterials are observed and imaged, measured, modelled and simulated, and manipulated	[85]

(continued)

Table 5.2 (continued)

Regulatory body/ committee/organization	Term	Definition	References
European Commission-EC	Nanomaterials	Natural, incidental, or manufactured material including unbound, aggregated, or agglomerated particles with ≥ 50% of those population present in the 1–100 nm size range. The ≥ 50% threshold maybe replaced exactly at 1–50% by the reason of specified related environmental, health, safety concerns, or issues of competition with such materials. Fullerenes, graphene flakes, and single-walled carbon nanotubes (SWCNT) with one or even more external dimensions < 1 nm are by the EC regulations classified as nanomaterials	[86]
European commission for novel foods (Amending regulation regulation No 258/97 (under harmonization)	Nanomaterials	Intensionally produced material within the dimension range (≥1– ≤ 100 nm), or made up of distinct functional parts at the internal or surface of the material, many of which are of ≥ 1 nm to ≤ 100 nm in dimension. Aggregate or agglomerate structures of size > 100 nm but with nanoscale level specific properties are also included	[86]
European Commission -EC: cosmetic product regulation	Nanomaterials	Intensionally produced insoluble or bio-persistent material with one or more external dimension or internal structure at the nanoscale size range of 1–100 nm	[87, 88]

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Table 5.2 (continued)

Regulatory body/ committee/organization	Term	Definition	References
European Union scientific committee on consumers products	Nanomaterials	Nanoscale materials of one or more external dimension or internal structure within the ~1 to 100 nm nanoscale size range with possible exhibition of newly acquired novel properties upon manipulation different from the same material not at the nanoscale	[89]
American chemistry council	Engineered nanomaterials	Intentionally produced materials with possible existence at 1, 2, or 3 dimensions (1D, 2D, or 3D) lying within 1–100 nm size range. However, such materials might- (i) not exhibit any acquired new or novel properties compared to bulk materials, (ii) be soluble in water or relevant biological solvent media at the molecular size level, but with the exception of micelles and single-polymer compounds	[90]
British Standards Institution (BSI)	Nanostructured materials	Internal or surface nanostructured exhibiting materials	[91]
British Standards Institution (BSI)	Nanostructures	Materials with interconnected structural constituent parts within the nanoscale region	[92]
British Standards Institution (BSI)	Nanocomposites	Multiphase materials with atleast one phase within the nanoscale region	[93]
British Standards Institution (BSI)	Nanofibres	Nanomaterials with similar exterior nanoscale dimension different from the third dimension which is larger	[94]

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Table 5.2 (continued)

Regulatory body/ committee/organization	Term	Definition	References
British Standards Institution (BSI)	Nanoparticles	Nano-objects with 3 different external nanoscale dimensions. Terms like nanorods, nanoplates, nanosheets are used to describe such nanoparticles with different dimensional lengths of the longest and shortest axis	[95]
British Standards Institution (BSI)	Nano-objects	Materials with atleast one or more external parts displaying nanoscale dimensions	[96]

unit scales of macro, micro and nano are used to understand and interpret better size of objects in associated and related manner at different level of scales [77, 81]. The connection between size and scale in the understanding of the differences between macro, micro, and nano terminologies of size and scale can for a better insight be comparatively illustrated. Therefore, to draw a clear-cut line and make differences between objects within the macro, micro, and nano range, scale and size needs to be associated by correlation. While sizes of objects can be comparatively illustrated in a scale, scale itself defines the relationship of what object is being compared and how that relationship can be represented either numerically or visually. While objects within the macro, micro, and nano brackets can be numerically defined by scale, visual control has the restriction function of what the human naked eye can see, and objects at both the nano and to a point micro scale can only be visualized by machine-aided visual devices. As a classic example, the human bone tissue for instance, is an open material constituent of different components that exist at different scale of measurement and sizes for its components [97].

Figure 5.1 shows the macro, micro, and nano scale measurements and the corresponding sizes within those three scale levels where the cortical and cancellous bone, osteons with Haversian systems, lamellae, the collagen fibrous assemblages of collagen fibrils, bone mineral crystals (HA), collagen molecules, and non-collageneous protein layers lie [98]. Figure 5.1 example is a demonstration of translational manipulation of different sizes and at different scales by nature of the human bone tissue material composed of five-level hierarchical structures at the macro (10 mm to several cm), micro (10–500 μm), sub-nano (1–10 μm), and nano (<1 μm) scales [99, 100]. In a practical approach of the application of micro and nanotechnologies for instance in Biomedical/Tissue Engineering related deployments, bone tissue therapies effortlessy adopt this kind of scale-size related bone architecture to fabricate bone-mimicking scaffolds in the development of bone

support materials. For a more generalized example, Fig. 5.2, depicts a comparative scale and size chart of various materials from minute objects at femto level to pico level to nano to micro, millimeter and to meter level at which point macro scale materials reside. By a conversion factor of X1000, the next scale level is obtained from the preceding one for scale region material size assignment (Fig. 5.2).

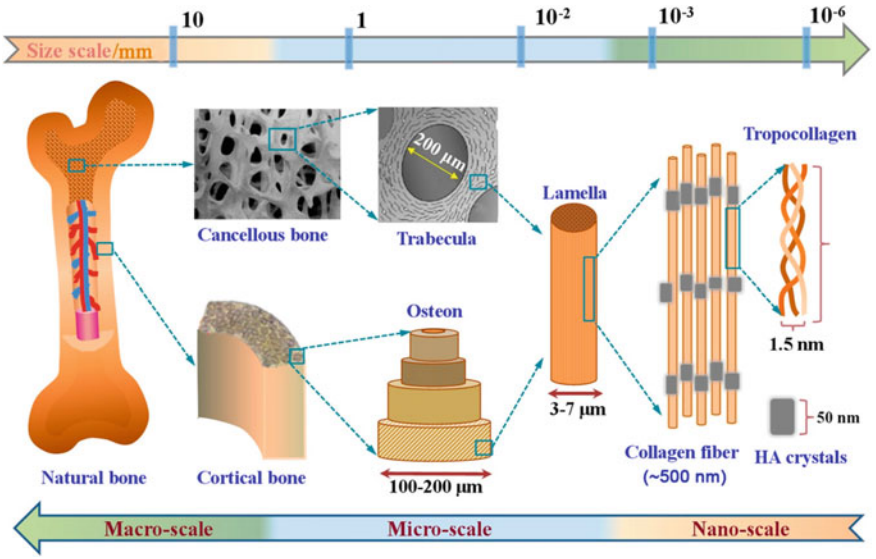

Fig. 5.1 Hierachical Bone Tissue Structure Components showing: cortical and cancellous bone, osteons with Haversian systems, Lamellae, the collagen fibrous assemblages of collagen fibrils, bone mineral crystals (HA), collagen molecules, and non-collageneous protein layers at their different scale measurement residences and sizes [98]

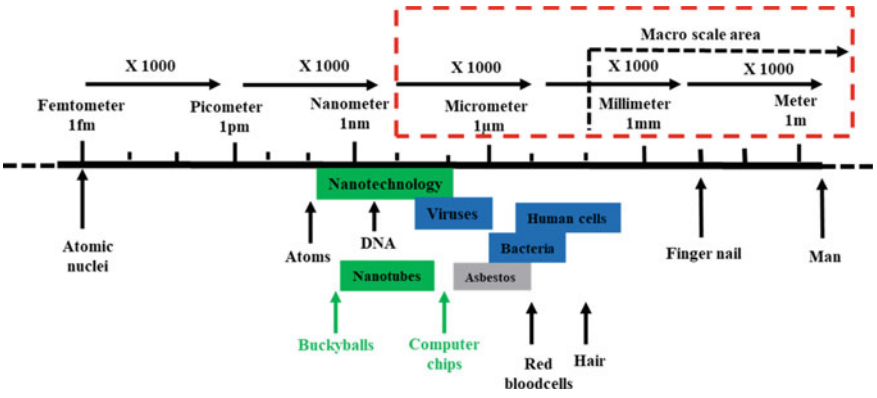

Fig. 5.2 Comparative size chart of materials from femtometer to meter scale range

The exploration of the existing borderlines as a matter of differences between materials in the macro, micro, and nano scale and size measurements of materials will continue to find a balance in the combined application of micro and nanotechnologies for the now and future perspective. The miniaturization of things in effect of application of micro and nanotechnologies has for instance led to transistors going from macroscopic (~1-mm) junction length-devices to, (~90-nanometeter) gates in the recent commercial chips and to ~10-nm gates in laboratory devices in a linear fashion and will continue to reduce approaching the size of an atom ~ (0.2 nm) [96]. On the other hand, volumetric approach had equally resulted to new materials with reliance on different computing strategies allowing for the advancement of increased capabilities and function of electronic and storage devices at weight/volume/power of electronics. In scale progression, there is the appreciation of the challenge in the control of the applicative technological tolerances at different levels. Scales at macro, micro and nano levels by virtue of material sizes have differences in application. Comparatively, macroscopic devices are smaller, lighter, more energy efficient, and fabricated with fewer materials than microscopic devices while by equivalence of application micro devices have edge over macro devices in terms of reliability, efficiency, selectivity, response time and energy consumption [77, 78, 81, 96]. Applicatively, micro scale exist in microtechnology and in the production of microsystems and microsystem components. Microsystems are miniaturized integrated systems in a small package or more specifically, micro sized components functioning together as a unit system and assembled into a package that fits on a pinhead [81, 96]. They are referred to as microsystems (MST) in Europe or microelectromechanical systems (MEMS) in the US and have been interchangeably used. Microsystems are microscopic scale level, integrated, self-aware, stand-alone products with sensory, thoughts, communication and action capabilities and have found application in areas of accelerometers, micro fluidic pumps, pressure sensor, spatial light modulators, lab on a chip, radio frequency (RF), mass storage devices etc. [77–81, 96]. The downscaling of microsystems where as they get smaller and smaller, their components correspondingly does eventually creates a meeting point between microtechnology and nanotechnology. Despite the transient tiny line difference that exist between macro, micro, and nano scale, their fabrication is another parameter that can be used to separate them. While microtechnology generally uses "top down" method type of fabrication, nanotechnology more often uses what is referred to as "bottom up approach" method of fabrication [20].

Micro and Nanotechnology: Size and Properties

The manipulation of materials at the micro and or nano level of scale measurement have led to the creation and the use of structures, devices, and systems that have novel properties and functions because of their small and or intermediate size. Classically, dimensions as well as composition and structure impact material properties in micro and nano scale. The decrease in the dimension of an object from the macroscopic to

micrometric scale properties is not the same. For instance, at the microscale and at the surface of a liquid, an insect is able to stay afloat as gravitational influence becomes negligible relative to surface tension. Scaling law dependence properties can also be seen in microfluidics where transition from laminar to turbulent flow given by the Reynolds number (R_e) for the prediction of flow patterns, depend on the size of the tubing [101]. Low R_e numbers favour flows dominated by laminar flow, while at high R_e values turbulent flows dominate. However, due to their size in microfluidic systems, turbulence flow dominance disappears as flow properties become particular. The gecko's ability to stand on a wall is due to micro and nano structuration of its leg. This micro and nano scale level structuration is a scale dependence property of the material found in the gecko's leg which facilitates it's locomotry function as friction and adhesion forces become prominent over gravity [102]. Properties and functions of micro and nanotechnological systems have not only being regulated by scale sizes but shape as well relatively. Enhanced surface to volume ratio as seen in materials for example tiny nanoparticles of single crystal structure have exhibited drastically different shape- and size dependent features (e.g.; thermal decomposition, melting, electrical/thermal conductivity, magnetism, optical behaviour, and catalytic and bioactivity properties, sensing and plasmonic features, steric features etc.) [103–105]. The size and shape control of materials have offered the needed leverage in the identification of critical sizes below which target properties of interest differs from the bulk material to be able to achieve simple, cost-effective, environmentally begin, and easily scalable production methods and processes [97]. Various synthesis methods and procedures have been used to adjust the properties of nanomaterials as per their target application of interest [97]. While Fig. 5.3 show size property dependence of micro/nano scale level systems structural function reliance, Fig. 5.4 depicts combination of size/shape dependence for target application functions.

The size and property phenomenon in the functionality of micro/nanoscale materials is as well predominant in the development processes of fabricating microelectronics, and microscale devices, which are not only classified based on dimensional

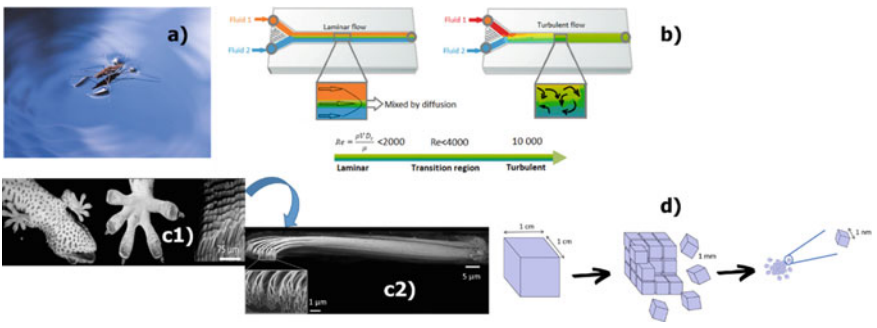

Fig. 5.3 Image representation of size-dependent properties and features of micro/nano objects: **a** microscale effect on an afloat water insect, **b** laminar and turbulent flow restrictions in microfluidics system [101], **c1, c2** micro and nano structuration of gecko's leg [102], **d** a demonstration of surface interface display for enhanced surface/volume ratio

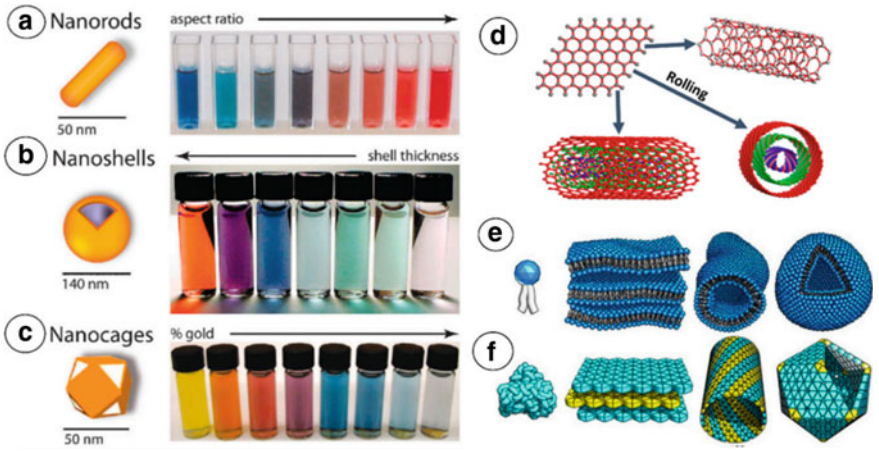

Fig. 5.4 Size- and shape dependent properties of nanomaterials: (a–c) Changes in optical properties (colour) [106], (d) Integration by rolling graphite layer into single-walled and multi-walled carbon nanotubes [107], Self-assemblage of (e) and (f) proteins into complex nanostructures [108]

scale, but also their composition and manufacturer. The two distinct yet overlapping fields of microelectromechanical systems (MEMS) and nanosystems or nanotechnology share a common set of engineering design considerations unique from other more typical engineering systems distinguishing their existence, effectiveness, and development like in the area of micro-scale and nanoscale transducers from those of conventional scale [81, 96]. To achieve application target of these systems, physics of scaling and the suitability of manufacturing techniques and processes largely convey their function-based link of size property dependence. Just as molecular machines involve macrobiolgical molecules (e.g. Proteins, DNA etc.,), nanotechnology has equally played considerable role in the down sizing of these micro-scale devices for biomedical applications down to assembly of individual molecules to fabricate molecular machines. Nanoscale and its implication on medicine has equally showed that biological molecules are in size range of nanomaterials. Once again, the size property related function is at play here as representation of comparison existing between particularly the involved biological molecule and nanoparticle for a particular target application functionalization achieved via size property based interaction (Fig. 5.5) [109].

Preparation of Micro-nano Objects

Unlike natural nanomaterials, micro and nano material objects are designed, fabricated, and or processed in the laboratory/industry. During the manipulation and engineering of these objects, their size, morphology and composition are controlled

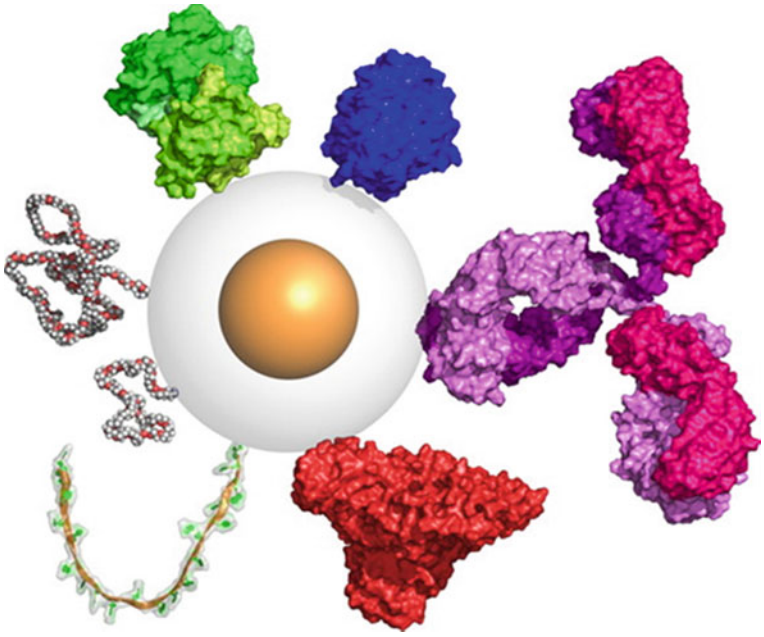

Fig. 5.5 Relative size of nanoparticles and biomolecules, drawn to scale. Schematic representation of a nanoparticle with 5 nm core diameter, 10 nm shell diameter, with PEG molecules of 2000 and 5000 g mol^{-1} (on the left, light grey), streptavidin (green), transferrin (blue), antibody (IgG, purple), albumin (red), single-stranded DNA (20mer, cartoon and space filling). Proteins are crystal structures taken from the Protein Data Bank (http://www.rcsb.org) and displayed as surfaces; PEG and DNA have been modelled from their chemical structure and space filling. Reused with permission of Sperling and Parak [109]

with high level of precision. The complexity involved in the fabrication of micro/nano scale level devices, have led to the progress sophistication of the processes and procedures used in the realization of micro and nano material objects. Notwithstanding, nanomanufacturing/nanofabrication still adopt chemical processes that have been around for centuries as variety of archived nanomaterials under microscopic observation have shown their micro and or nano scale manifestation for expected or unexpected reasons of production at that time [110, 111]. Several techniques for the fabrication of nanomaterials in general have been reported, however the two main strategies used irrespective of the origin of the nanoparticle are "Bottom up and Top down approaches" [112, 113].

Bottom Up Method

This method fabricates materials building blocks through the assembling of individual atoms or molecules [112]. It involves the manipulation of atoms, ions,

molecules, or engage the unique property of nanoparticles self-assembly ability, their physico-chemical interactions (e.g. hydrogen and ionic bonds, van der Waals forces, and water-media generated hydrogen bond) to assemble fundamental building blocks into macroscopic structures [112, 114]. Theoretically, it ensures the perfect control over the production of nanomaterials with well defined size, shape and highly homogeneous size dispersion. As a chemical synthesis route, liquid synthesis (also known as wet synthesis) widely used for the preparation of inorganic nanoparticles is a typical example of bottom up approach [115]. This methodology also used in the industry nevertheless often suffer from a poor scalability. Several techniques can be employed in liquid synthesis depending on the precursors, the reactants and the nature of the expected end nanomaterial. The most common liquid syntheses abundantly described in the literature are chemical precipitation synthesis [116], solvothermal synthesis [117], and sol–gel synthesis [118]. However, the mechanisms of the nano-object formation are widely studied such as the nucleation and growth mechanism described by Lamer [119]. The main challenges of these syntheses is the inability to effectively control the growth of the nanocrystals and afford a stable and homogeneous suspension in solution, and lack of the needed tools to effectively handle the seed atoms and molecules [1].

Top Down Method

The top down procedure primarily involves the breaking down of bulk materials to get down to nanoparticles or the solid compartmentalization of uniformly distributed materials into smaller fractions for the formation of nanoparticles [1, 97]. Techniques like advanced industry precision engineering and lithography, etching, etc.; are some of the reported suitable approaches of top down method for the production of nanostructures [1, 97]. Others are ball milling, flame synthesis, laser ablation methods, and plasma technology. The superiority of application of top down method in the fabrication of electronic circuitry for their effect of integration and network interconnectivity has been highly recommended and thus, widely used in microelectronic industry [113, 120]. Thin film synthesis and nanoparticles creation of size > 100 nm with unique properties acquisition relative to their bulk parent material analogues, are good credits endorsement for top down approach [1, 97]. Though the precision engineering support of top down approach has made it an established preferred fabrication choice technique for the creation of nanomaterials within the electronic industry, limitation in resolution remains a big challenge to overcome [121]. In tackling this challenge, the strategy of combining both the bottom up and top down fabrication methods have been adopted for improved product outcome. This combinative approach of bottom up and top down fabrication method has led to a third type of fabrication approach known as ‘hybrid approach’ developed and optimized to weather off bottom up and top down challenges and deliver fabrication improvements [1, 97].

In the hybrid fabrication administration, there is the concurrent application of bottom up and top down methods where representative particles from these two methods can complement their fabrication process material outcome either as desired nanomaterial process result outcome or precursor fragment fit as a new source raw material for bottom up creation [97]. Lithographic methods e.g. photolithography, electron beam lithography, focused ion beam, soft lithography, neutral atomic beam lithography, nanoimprint lithography etc.; that can be used to realize 1D or 2D nanostructures, microtechnological materials etc.; is considered a hybrid fabrication process when combined with etching as the complementary top down technique, or with ion growth layering as the bottom up complementary method [122, 123]. Other improvement approach geared towards better created product outcome include the use of advanced nanostructured diamond or boron nitride-based sensors capable of controlling size, coupled with numerical control and advanced servo-drive technologies [1]. Though the introduction of the hybrid system has dealt with fabricated product outcome resolution; cost and the use of non-environmentally friendly chemicals, is still a setback and needs addressing.

Figure 5.6, displays the fundamental concepts involved in the bottom up and top down fabrication methods for micro and or nanotechnological material development.

Objects in the Micro and Nano Scales

Long before 1959 when the concept of nanotechnology was introduced by Richard Fenyman (Table 5.1, [25], and subsequently its definition in 1974 [31], variety of materials of either organic or inorganic origin and source that can be characterized by the concept terminology of nanotechnology were already in existence. The nano scale (nm) unit measurement of materials placed such a restriction in the sense that on the premise of a material size falling within 1–100 nm, it can only be classified a nanomaterial, otherwise it cannot. By this narrow definition, several biological materials of organic components fits within this nano scale range and have a long established history of medical benefits. For instance, the development and application Cowpox virus developed by Edwar Jenner in 1798 that helped with the saving of millions of lives from small pox and facilitate the eradication of such a deadly disease, underlines the impact nanotechnologies have already had in the history of the world [124]. Outside the walls of nanotechnology, the range of these biomedical materials and components is huge. As the concepts related to them continue to widen, the definition of nanotechnology in this area has been ceiled further a top and in the range of +100 nm to accommodate them. Therefore, from the viewpoint of biomedical applications and platforms, advances in nanomedicine including the emerging field of biologics where cellular size consideration in the range of (1–25 + μm) exist, ropes in the entire biomedical platforms and promote their inclusivity within the advancing micro-and nanotechnology.

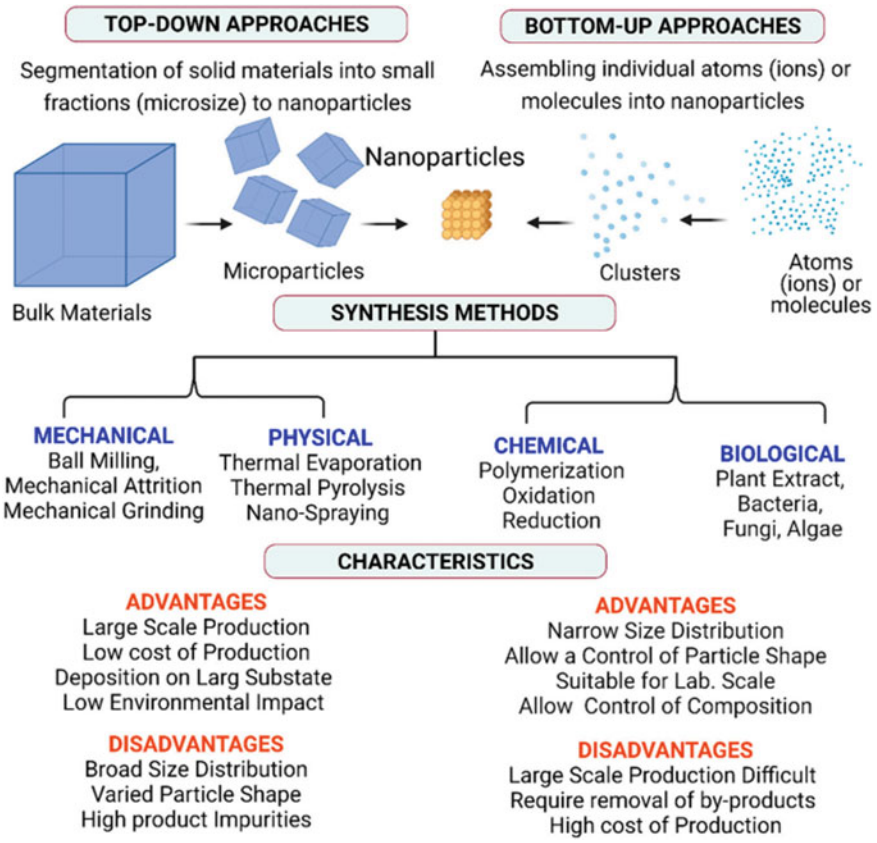

Fig. 5.6 Schematic illustration of top down and bottom up approaches applied in the fabrication of materials showing their synthesis methods and pros and cons [97]

Nanomedicine

The development of nanotechnology gave rise to the nanomedicine concept where nanomaterials having new properties owing to their nanosize are able to be used in several medical science related domains. Micro and nanomaterial unique properties of increased surface to volume ratio, charge density, surface chemistry etc.; are among the various acquired new properties that facilitate desired interaction between the cell environment and the administered micro and nanotechnology platforms [125]. For example, nobel metal plasmonic properties can be used for sensors or phototherapy. Superparamagnetism obtained of several metal oxides at the nanoscale can be used for magnetic resonance imaging (MRI) or even developed as therapeutic tools for magnetic hyperthermia. There has been evaluation of vast majority of nanomaterials for drug delivery and vaccine with several of such systems already present, for instance COVID vaccines. Micro and nano objects application within the veils of

nanomedicine are expanding into the micro and nano biomedical platform and are familiar to areas of imaging, drug delivery and vaccine therapy, biosensing etc. [126].

- Imaging

Medical imaging has become a fundamental component in the field of biomedical research, clinical practise and diagnosis. Advancement made in medical imaging techniques have led to important breakthrough researches in clinical anatomy and forensic pathology. The emergence of new medical imaging technologies have served well and instrumentally too healthcare professionals with proper vision and understanding of the anatomy of the human body from different perspectives. Following the discovery of X-ray radiography in the nineteenth century, several progress advancement in diverse imaging modalities have been achieved. Prominent amongst the most advanced medical imaging modalities are magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), fluorescence, ultrasound imaging (sonography), etc. Spatial resolution, sensitivity, field strength, pulse sequence speed, absence of ionizing radiation, etc.; are among the various imaging capabilities used in the specification of the functional efficiency of these modalities and which can by combination present bundled features to leverage high performance level imaging applications. In order to obtain accurate imaging information that is representative of analysed cell tissue, contrast agents are utilized, to facilitate and make easy during imaging test the recognition by difference of a healthy cell tissue from a pathogenic one. Generally, contrast agents are small molecules or organometallic complexes, which by their presence manifest high toxicity, short life span blood circulation, and poor biodistribution.

Nanomaterial acquisition of new and novel properties upon manipulation at nanoscale have presented huge opportunity for enhanced performance contrast agents for medical imaging lately [127]. Contrast agents of nanoparticulate nature as a benefit; deliver various advantages that can enhance their application as imaging media. Ability to manipulate and control the size features via synthesis parameteric variations ensure and guarantee uniformity in biodistribution. Additionally, blood circulation enhancement through size conjugation by enhanced permeability and retention (EPR) effect promotes passive targeting [128]. The possibility in regulating the surface of the nanomaterials permits its tuning for the addition of new properties and features designed for improved functionalities of the contrast agents. The practicality in active targeting is effected by the addition of targeting molecules for increased spatial localization of pathologic tissue or the targeting of a specific type of cell with receptor suppression. Strategic modification of the chemical nature of the surface by charge alteration, covalent polymeric attachment with organic compounds like polyethylene glycol (PEG) possibly effects biodistribution, retention, and clearance or blood-circulation half-life modification for a balanced stealth and echogenic

contrast agent. Summarized introduction and mode of operation of the key medical imaging techniques as already mentioned will be focused in the below section.

- Magnetic Image Resonance (MRI)

Magnetic Resonance Imaging (MRI) is a nonivasive modality that supports the observation of anatomic structures, physiological functions and molecular tissue compositions. It functions based on Nuclear Magnetic Resonance (NMR) with production of multiplanar and true 3D invivo subject datasets, excellent soft tissue contrast of high spatial image resolution, and with no harmful ionizing radiation effect. It is commonly used for stroke and cancer pathology diagnosis. MRI are of two different modalities and the contrast agents are categorized into T1 or T2 contrast agents in relation to the time of relaxation of the water proton. Bright contrast paramagnetic gadolinium (Gd^{3+}) chelates belongs to T1 contrast agents and in the modern MRI used as the gold standard. However, concerns of low sensitivity and perception of toxicity has widen search for options. Iron oxide nanoparticle as an alternative with superparamagnetic behaviour and as a T2 black contrast agent have attracted an overwhelming interest towards the end of the last century [129]. Majority of such contrast agents approved by Food and Drug Administration (FDA) have already had market entry and administered for years. Market available ones with trademark names: Feridex®, Resovist®, Combidex®, Lumiren® are however, trailing with limitation issues of signal intensity identified with T1 contrast agents [130]. Considerably, manganese oxide nanoparticles are feasibly T1 contrast agent alternatives [131], as well as gadolinium oxide nanoparticles that boast a dual T1/T2 modality. Recent advancement in size control, aqueous media stability, composition, and coating thickness permitted iron oxide nanoparticle as a MRI T1 contrast agent [132].

- Computed Tomography (CT)

Computed tomography also referred to as computerized tomography or computed axial tomography (CAT) is a non-invasive medical examination or procedure that relies on specialized X-ray equipment to generate cross-sectional images of the body for variety of reasons ranging from diagnosis, treatment, screening, and interventional purposes for outpatient procedures. It is credited for its low cost of operation, fast result delivery and high image resolution. High x-ray attenuation need for contrast agents used in CT analysis have placed huge interest of consideration on some metallic nanoparticles like gold, tantalum or zirconium oxide [133]. The interest over gold (Au) nanoparticles hinges back on its ease of production and functionalization that facilitates targeting and enhanced biocompatibility. Commercialzed Au nanoparticle radiosensitizer for instance AuroVist™ though with no market entry yet, is potentially for invivo research. Though with long track record in clinical imaging, iodine based contrast agents with diverse limitation issues of lack of fast clearance, renal toxicity potential, blood pool distribution nonspecificity, and adverse effects/anaphylaxis documentations has been upgraded by the complementary vector

platform support of nanoparticles, and therefore, continue to be administered for biomedical imaging applications.

- Positron Emission Tomography (PET)/Single Photon Emission Computed Tomography (SPECT)

Positron emission tomography (PET) is a nuclear medicine technology overly used and credited with high tissue penetration, high-sensitivity, and real-time quantitative imaging analysis. Single photon emission computed tomography (SPECT), similarly, is another imaging tool of nuclear medicine technology for the detection of abnormal biochemical functions prior to body anatomical alterations. Despite limitations of high cost, radioactive exposure, and less image resolution in comparison to MRI, PET/SPECT continue to find application in molecular and early diagnostic imaging with the use of target specific radionuclide nanomaterials. Common radionuclides like ^{68}Ga, ^{64}Cu, for PET, and ^{67}Ga, ^{99m}Tc for SPECT have been applied for the advantages of reasonably having longer half-life over the likes of Flourine-18 with a half-life of about 109.8 min [133]. Direct introduction of radionuclides during nanoparticle preparations and incorporation of radionuclide tracers post synthetically are such methodologies adopted to circumvent short half-life issues during preparation and thus, for the improvement of cellular tissue material uptake for rapid diagnosis [134].

- Fluorescence

Nanoparticle fluorescence imaging has been applied in research and the monitoring of real time therapeutic effects including gene detection, protein analysis, enzyme activity evaluation, element tracing/cell tracking, early stage disease diagnosis etc. Equipped with near-infrared fluorescence capability, fluorescence imaging technology offer highest spatial resolution for disease diagnosis on macroscopic level taking advantages of its near-infrared responsiveness for deeper tissue penetration, and less non-specific tissue auto-fluorescence in comparison to visible light operation mode [133]. Notwithstanding, low penetration depth, and auto-fluorescence with related scattering properties in some cellular tissues continues to hamper its outright clinical utility [135]. In this aspect, nanoparticles properties have been seen useful to subdue the limiting challenges of fluorescence imaging. The use of large number of dye molecules loaded onto nanoparticles for extra signal provision, structural modifications for counter potential quenching of near-infrared (NIR) when necessary, nanoparticle concentration lesion increase via active/passive protocols, upgraded circulation time for uptake enhancement in lesion regions, and lower energy to high energy conversion design for blink and photobleaching reduction effects, etc.; are some of the strategies directed towards the development of fluorescent material-based nanoparticle [136–138]. Noteworthy still is the possibility in the combination of different imaging techniques for the execution of a hyphenated multimodal imaging agents beckoned on the versatility of nanomaterials to leverage coupled techniques (e.g.; PET/CT, PET/MRI, PET/US, CT/MRI, etc.;) for enhanced imaging therapeutic capabilities. Therapeutic capabilities of drug delivery systems (DDS), typified intrinsic physical property like photothermal therapy display of Au

nanoparticles or magnetic hyperthermia of iron oxide nanoparticles, etc., are amongst the many accessible benefits of nanomaterials in such coupled/hyphenated medical imaging systems and have already received attention for potential dual exploitation of therapeutics and diagnosis in the recent emerging field of theragnostics [139].

- Ultrasound Imaging (Sonography)

Ultrasound imaging is a well-established imaging technique for clinical analysis. Its mode of operation is based on the detection of reflected sound waves in the range of 2–12 MHz frequency. The degree of reflection largely depends of the material nature whereby molecules in the gas phase return higher image contrast than the ones residing in the biological tissue media. For a long time, gas core microbubbles and lipids, protein or polymer shell have continuously been deployed as contrast agents for disease diagnosis in the vascular space. Limitation in the extravasation of these microbubble contrast agents due to inherent issues of size (1–3 μm), and instability has hindered their extended use as contrast agents for diagnostic ultrasound imaging applications, and in particular for vascular anatomy and gastrointestinal tract (GIT) [140]. Nanosized formulations of hollow silica nanoparticles, carbon nanotubes (CNT), nanobubbles based natural polymers or lipids, and gas vesicles of microbial origin has been studied as potential alternatives for ultrasound contrast agent fit for biomedical applications [141]. Dose-dependent ultrasound demonstration outcome so far has revealed microbial originated gas vesicles ability to diffuse into extracellular and intracellular environments due to their small size and waterproof-like gas-permeable protein shells. This biocompatibility feature, through their gene-coded form has given them a huge exploitable potential as ultrasound gene reporters in the same manner fluorescent proteins have served as optical reporters [141].

- Biosensing

Biosensors are analytical devices operating on biological recognition element with the capability of generating short time interval quantitative or semi-quantitative information through the transduction of chemical reactions into quantifiable physical response. Categorically, they fall into two groups of: biological recognition elements such as DNA, enzymes, antibodies, microorganisms, tissues, cell receptors, etc.; and transduction principle system group such as optical, electrochemical and mass-based biosensors. There is high specificity and sensitivity in the mechanism of biosensors of the category of biologically recognized elements as macromolecules are for instance used to match antibody-antigen or enzyme substrate pairs. Biosensor development is overached by physiological modifications in biological fluids or the apparition of pathogenic molecules as early signal indicators for the detection and subsequent follow up on various disease outcomes. High costs, and long signal data treatment time are amongst some of the noticeable drawbacks limiting wider application of biosensors in majority of fields. Thus, the incorporation of nanomaterials into biosensors has led to the emergence of bionanosensors delivering the possibility of new physico-chemical properties at nanoscale and increasing the possibility of surface coupling of biomolecules to nanomaterials [142]. Notwithstanding, the fabrication of

diverse restructured material composites including nanomaterials open up the development of wider spectrum window of medical health and services including point of personal care medicine and other improvement such as for example wearable electronic devices for healthcare monitoring [143].

Majority of nanomaterials based biosensing devices; compose of gold nanoparticles [144]. As has been earlier stated, at the nanoscale, materials inherit new properties that are unique and different from its bulk material state. There is the exhibition of plasmonic effect by gold (Au) nanoparticle as a consequence of its small size acquisition at nanoscale, and that is completely absent with Au material at macroscopic level. This phenomenon is referred to as localized surface plasmon resonance (LSPR): an effect generated due to the collective oscillations of particle's free electron at the surface of the metal nanoparticles. The enhancement of the near surface electromagnetic field by the surface plasmon resonance (SPR) of the plasmonic metal nanoparticle improves the detection capabilities of deployed bionanosensor and have been extended to detection application techniques such as surface enhanced Raman spectroscopy (SERS). Optical extinction display at maximum absorption wavelength of the plasmon resonance frequency is also a registered effect linked to the size, form or agglomeration state of the nanoparticles [145]. These properties are consequential effects of nanoscale material manipulation underlining the functional mode of operation in gold and other plasmonic metal biosensor nanomaterials. Many nanomaterial biosensing applications have also been witnessed in the area of colorimetrics, Qdot tagged fluorescence, Förster resonance energy transfer (FRET), etc. [146, 147]. Comparatively, surface enhanced Raman scattering (SERS) spectroscopy have recently gained more attention as one of the most effective detection techniques particularly due to its capability of single molecule detection.

SERS is an analytical technique that functions based on plasmonic metallic colloids like Au, Ag, Pd, Pt etc., and using their surface roughness to detect target analyte samples. Plasmonic phenomenon properties and charge transfer between particle and the analyte generate Raman signal intensification signal of up to 10^6 response in sensitivity value. Interest on SERS application has grown over the detection of small molecules, proteins, DNA [148], or even viruses [149], giving it a competitive advantage over other detection/sensing method protocols like dynamic light scattering and hyper-Rayleigh scattering-based sensing, Two-photon photoluminescence (TPPL)-based sensing, chiroplasmonic activity-based sensing etc. [150].

Property features applications in biosensor operations have equally found their way into the lateral flow Immunoassay strips test, which has been clinically, tested for different detection measurements [151, 152]. Amongst those test, human chorionic gonadotrophin (HCG) pregnancy test is well documented. The pink appearing colour for the pregnancy positivity test assurance is often due to the presence of gold nanoparticle in the sensor material. Lateral flow immunoassay based gold nanoparticles kit analyzers have also been utilized for HIV detection and lately COVID tests. As a basic functioning principle, these tests are generally employing a detection strategy derived from the most used clinical technique for biomarker sample presence evaluation: enzyme-linked immunosorbent assay (ELISA). Usually, ELISA

strips are coated with antibodies for the selected antigen with the incubation of the analyte performed with other antibodies bound to Horse Radish peroxidase (HRP) for the oxidization of the colour changing substrates, thereby helping to facilitate the manifestation. Nanomaterial-based architectural instruments have been used to enhance the detection capabilities of ELISA. Antibodies decorated nanoparticles are utilized for the elaboration of surface binding sites, which in turn allows improved selectivity for the detection of analyte. Catalytic properties of the nanoparticles can leverage visualization in combination with colour changing substrates. However, nanoparticles can also be directly used as the detected object owing to their plasmonic properties for example gold nanoparticle or even due to their magnetic properties, and for example in the case of iron oxide-based immunoassays [153]. In the later scenario, such developed dedicated detector have been reported of high sensitivity possession [154]. Displayed in Fig. 5.7 is the timeline evolution indicating first reported instances of micro and nanotechnology nanomedical therapeutic, vaccine, and imaging applications but to mention a few.

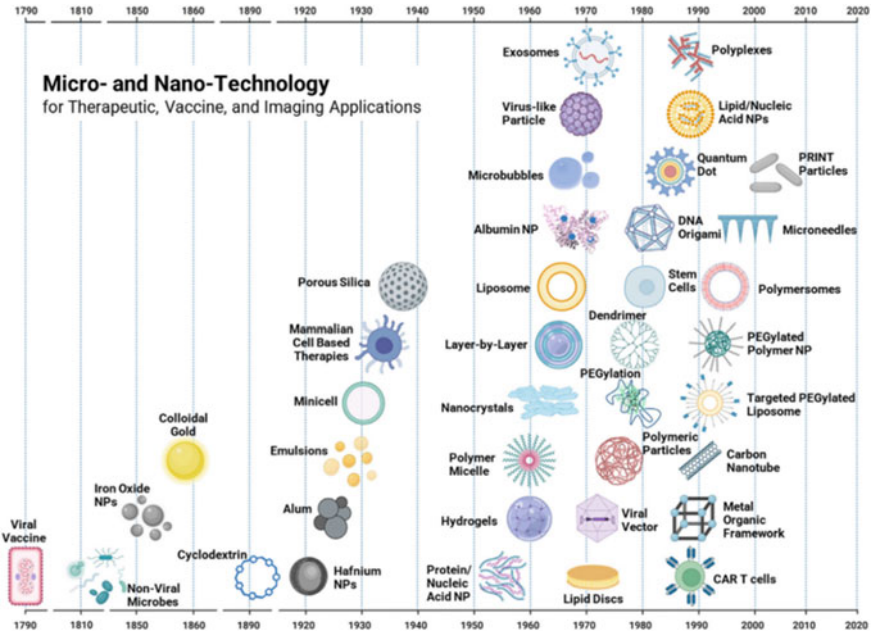

Fig. 5.7 First report timeline of micro and nanotechnology used for therapeutic, vaccine and imaging applications [155]. *CAR T cells: chimeric antigen receptor T cells; NP: nanoparticle; PEG: polyethylene glycol; PEGlyation/PEGlyated: PEG covalently bound; PRINT: particle replication in non wetting templates

Micro-nano Technology and 3D Printing

The development of micro-electro-mechanical systems (MEMS): thanks to the cross-border overlapping technological advancement at nano and micro scale of material and devices; have now unleashed the huge potential of this technology in the area of life science (biology and medicine) for diverse of applications. Interest on the extension and application of MEMS to applied biological domain has created a link and built a bridge across two words of biology or biomedical sciences and micro-electronic and mechanical systems to set us up with what is now referred to as "BioMEMS". The huge potential embodiment of BioMEMS is unrivalled starting all the way from the two areas of biomedical and life sciences, stretching and encompassing diagnostics, therapeutics, drug delivery, biosensors, as well as tissue engineering [156]. The transformation witnessed now in those two areas of biology and medicine of the life sciences has drastically changed the way one is able to see and detect substances in the biological world [101, 157]. This tremendous contribution has been registered in bioassay and instrumentation through micro and nanotechnology, and thus, bringing such an overwhelming development to the domain of biomedical sciences. This revolution of biological assays and instrumentation is made possible by the miniaturization of the current biological tests by combining different microtechnological tools like microfluidics, microactuators, and other micromachine processes [101]. These novel and advanced biomedical devices, now guarantee high performance throughput methodologies by running on robust and efficient biomedical device platforms like microarrays, organ-on-a-chip, etc. [101, 157]. With all the outstanding progress achievements recorded so far in the wide domain world of science, engineering, and medicine through breakthrough advancements in micro and nanotechnology; the contribution of additive manufacturing cannot but be commended. The many capabilities of additive manufacturing processes e.g. design alteration, rapid manufacturing, industry scale up cost effectiveness, ease of material integration, structure and functions, which are readily amenable to diverse technology processes are its uncommon blessing that has left it positioned in such a central indispensable role within the ever-dynamic micro and nanotechnology fabrication processes world (Grandviewresearch n.d.). 3D Printers (3DPs) are continuously evolving in terms of their capabilities and specification as the extrusion of multiple material is now possible with wide range printable materials due to diverse presence of specialized printers, and material science evolution. By the advances made in printing processes, scale of precision has been minimized to nano and micro scale level which relatively have effect on the material properties as well the application that can be targeted with such materials [158]. On this premise, precision fabrication type of micro/nano scale printing to achieve range of biomedical and electronic devices have diffused. Stereolithography printing, Two Photon Polymerization (TPP), Dip-Pen Nanolithography (DPN), Inkjet printing, Piezoelectric Inkjet Printing, Thermal Inkject Printing, Electrohydrodynamic (EHD) printing are all diverse kinds of 3D printing processes of different control/process parameters and other capabilities adopted for the micro/nano fabrication of various material target

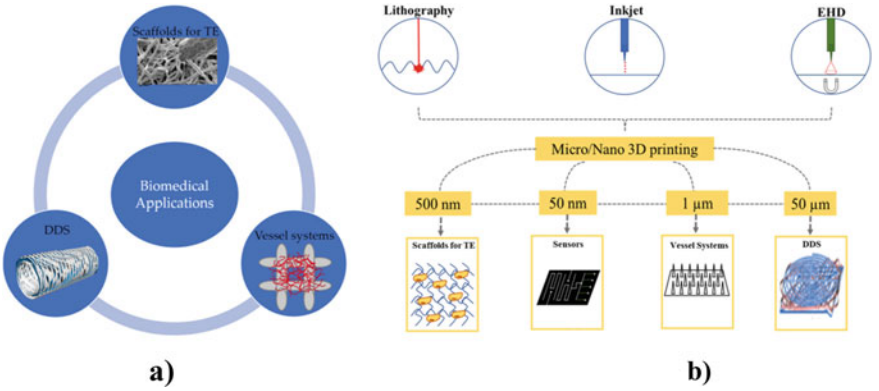

Fig. 5.8 A representative outlook of the many evolving printable materials for biomedical application (**a**) [163, 164], and a narrow spectrum of the most deployed 3D printing process for the realization of different biomedical application materials at micro/nano level (**b**) [160]

application purposes from biomedical, to electronics, to environmental, etc. [159, 160]. Differently from the conventional 3D printing processes, lithography printing, ink-jet printing, and electrohydrodynamic (EHD) printing processes are specifically deployed for printing operations where precision is highly needed. They are suitable for biomedical and electronic device printing application where they transfer their capabilities of offering physical and chemical properties to printed materials, introduce with ease micro/nano structures, which remain unattainable with conventional fabrication processes [158, 161, 162]. Figure 5.8 shows the possibility of arriving to micro/nano level by 3D printing processes to execute materials fit for different biomedical/other applications from tissue engineering, sensor, cell vessels to biomaterial for drug delivery system (DDS) [159].

Conclusion

In this book chapter, we have covered five different sections of- the history of micro and nanotechnology where we looked at the definitions of both worlds and x-rayed their closely knitted differences. This section laid the foundation of this book chapter by looking at the dynamics and ever evolving world of micro and nanotechnology, while at the same time traced back to historic times, the origin of what today is driving innovation in science and engineering and that will continue to dominate in the coming years. In doing this, we spurred the curiosity, in the mind of the reader to ask questions of how emerging nanotechnology and ofcourse the microtechnology counterpart is; as historic evidence of fabricated archived premedivial, materials show nanometric proofs. The line difference between scale levels of materials is thin and transient. In differentiating nanomaterials or materials at nano and micro level, it

should not only be a question of what the present scale is as per the materials in view at a point in time, but rather a holistic understanding of the material composition, target of application in mind before the fabrication and the manufacturer of such a material. As it is possible for a nanomaterial to exist at microscale theoretically, it is practical to build a micro matter from nano scale components like in micro-electronics and mechanical systems (MEMS) devices. The pervasive world of micro and nanotechnology leaves no clear-cut line along the scale for instance where a certain device constituting of nano building unit in a micro content resides. In this case, various modalities in the conveyance of the function of the material and its composition gives the best insight into its level classification by scale.

Section 5.2: Looked at the new acquired properties of materials due to their scale size level and established in a narrowed down fashion of what is a broad spectrum of diverse field of applications, a connection between different sizes and shapes of materials for particular and target material functions.

Section 5.3: was about the two main fabrication protocols of micro and nanomaterials and the meaning of those approaches. For a more specialized material function, a combination of the bottom up and top down approach could result to improved material property for specialized function.

Section 5.4: drew insight about the application of micro and nanotechnology in medical science, an overached field, presently designated as nanomedicine. In this chapter, we took a random look of the application of nanomedicine using micro and nano technological prowess to drive several medical diagnosis and treatments.

Finally, Sect. 5.5 focused on the connection between micro and nanotechnology and 3D printing (3DPs). We looked at the best available technology (BAT) practices in printing fabrication processes to realize materials, which serve purpose in several application domains of biomedicine and electronics.

Micro and nanotechnology is a huge and diversified field within nanoscience and nanotechnological application. The intricacies of both areas yet one for the sake of their service of purpose lies in their overlapping interlocking nature especially in systems where materials of differences in scale level occupy the same suit to serve target-particularized functions.

This book chapter explored just about a narrow overlay of the wider and far-reaching world of micro/nanotechnology which now occupies everything and anything that we could ever think or imagine possible within science and engineering enclave.

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