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Nanocrystals: The Building Blocks of Nanotechnology – A Comprehensive Review

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A B S T R A C T

Microsponges are considered as one among the most proficient carrier for the delivery of Active Pharmaceutical Ingredients (API).In the recent past many articles have been published on the microsponges because of its long lasting efficacy. The uses of microsponges are basically focused on the treatments of skin ailments. Cosmeceuticals are cosmetic products with bioactive ingredients purported to have medical benefits where microsponges plays the vital role as drug delivery carrier. In the present article the focus is to highlight the pharmaceutical as well as the economical prospect of the microsponges.

Keywords: Microsponges, NDDS, Cosmetics, Economical, Patents.

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INTRODUCTION:

Prof. Norio Taniguchi of the University of Science of Tokyo coined the term "nanotechnology" to refer to the production of novel materials with nanometer-scale dimensions [1]. Utilizing the unique characteristics and phenomena at that scale in contrast to those linked to single atoms or molecules or bulk behaviour, nanotechnology is the capacity to manipulate and reorganise matter at the atomic and molecular levels in the range of roughly 1–100 nm [2]. The Greek word "nano," referring to "a dwarf," has become the precursor of the prefix "nano." A millionth of a meter can be represented by a nanometre (nm). A large number of biological structures are nano-metres in size. The largest amino acid (tryptophan) is 1.2 nm, whereas a single red blood cell is 2,500 nm, a DNA molecule is 2.5 nm, and a protein molecule is 1–20 nm [3]. As scientists utilise the special qualities of atomic and molecular assemblies constructed at the nanometre scale, nanotechnology has emerged as one of the most important scientific initiatives of the early twenty-first century. Because we can control the physical, chemical, and biological characteristics of these particles, researchers may logically create and employ nanoparticles for drug delivery, image contrast, and diagnostic purposes [4]. It is generally anticipated that the use of nanotechnology in drug delivery will alter the pharmaceutical and biotechnology sectors for the foreseeable future [5]. Observing, measuring, manipulating, assembling, controlling, and manufacturing materials at the nanometre scale is known as nanotechnology [6]. Therapeutics powered by nanotechnology have the ability to alter one or more stages of wound healing by influencing a particular biochemical event within the compromised healing process. Compared to traditional wound care products that are based on dressings, this presents special options. These nano-platforms versatility and tunability are two of its main advantages [7]. As the advantages of nanotechnology become more apparent every day, it has a multifaceted effect on society. Both engineering applications and our daily activities depend heavily on technology. Technology is the branch of knowledge devoted to the development of tools, action processing, and material extraction [8]. Numerous new battery types that are less flammable, faster to charge, more powerful, and lighter are being developed using nanotechnologies, which already have a greater power density and a longer store charge retention period. A novel lithium-ion battery model employs a common, harmless virus in a production method that is environmentally friendly [9]. The topic of nanotechnology has attracted the attention of the whole scientific community. Nobel Laureate Richard Feynman introduced the concept of nanotechnology in a December 1959 lecture at the California Institute of Technology. The field of nanotechnology encompasses the processing of separation, reorganization, and deformation of materials by a single atom or by one molecule [10]. Nanotechnology has been employed considerablyin diurnal life and has revolution mortal civilisation as a whole. Since the USA Ministry of The farming sector published the initial master plan on September 9, 2003, it has been at the mass scale can be transferred to separate unit counters at the nano-scale [11].

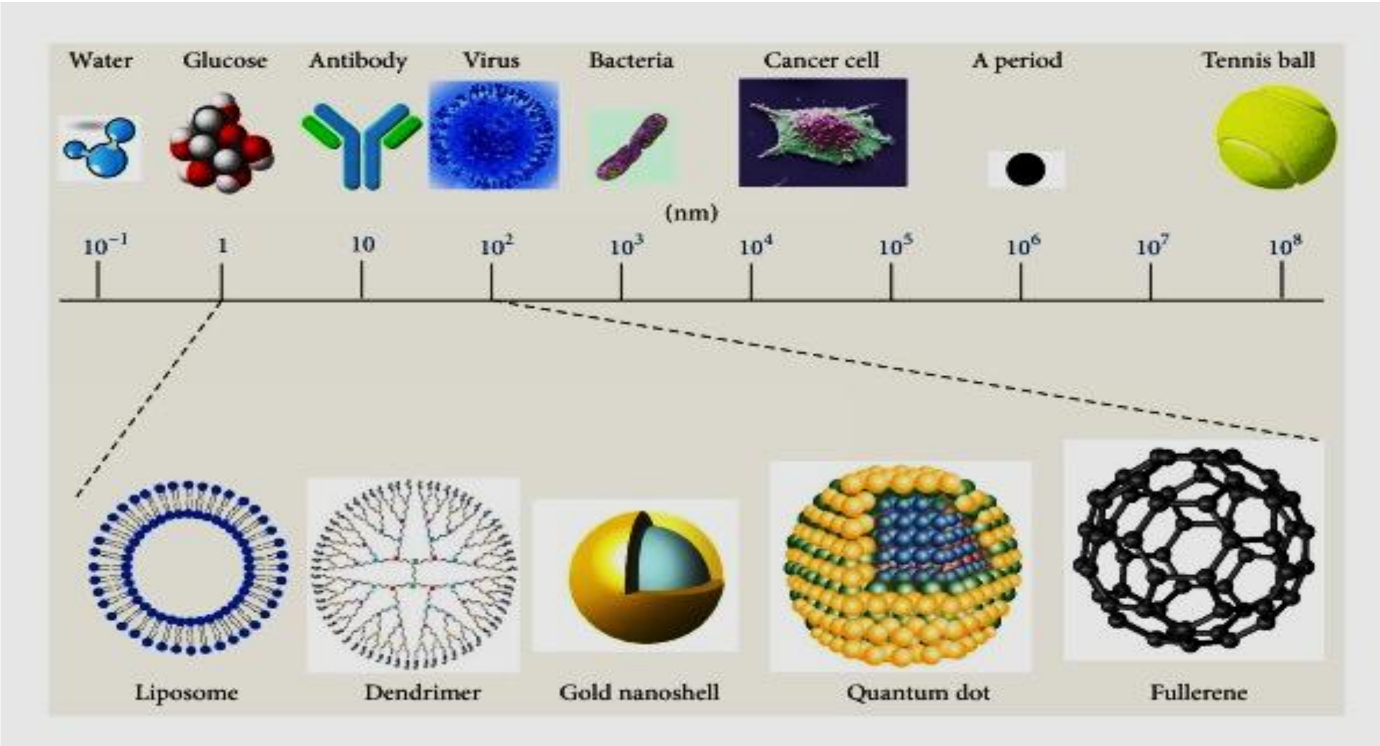

Figure1: Relative size of nanoparticles compared with familiar items [4].

History of nanotechnology:

Interest in the new disciplines of nano-science and nanotechnology grew at the start of the twenty-first century. Feynman's reputation and his theory of atomic-level matter manipulation were crucial in determining national research goals in the US [12]. In addition to the well-established fields of biotechnology and information technology, nanotechnology is acknowledged as a new enabling technology for the twenty-first century. This is due to the scientific convergence of nano-scale engineering, physics, chemistry, biology, and materials, as well as the significance of nano-scale matter control for nearly all technologies [13]. The fields of nano-science and nanotechnology saw a surge in attention around the start of the twenty-first century. Feynman's theory of the atomic-level manipulation of matter was crucial in determining national research objectives in the US. On January 21, 2000, President Bill Clinton spoke at Caltech and spoke in favour of financing nanotechnology research [6].

Origin of Nanotechnology

Scientists are looking to nanotechnology for creative answers to this problem. Antibacterial resistance can be combated by the use of nanotechnology, which involves altering and designing materials at the nanoscale (1 to 100 nanometers) [14]. Nanotechnology provides concepts and solutions for a wide range of industries, including agriculture, industry, information, and communication [15].

Uses of Nanotechnology in treatment of various disease:

Nanotechnologies for treatment of cardiovascular disease: One area of nanomedicine, for instance, is on controlling and modifying bio macromolecular and supramolecular components that are essential for human health, such as DNA, RNA, cell membranes, and lipid bilayers. Over the past 20 years, a wide variety of nanotechnologies with specific advantages as well as features have been created for biomedicine. These are composed of dendrimers, liposomes, nanoparticles, micelles, and the utilisation of nano-coating [16].

A. **Liposomes:** Pharmaceutical delivery has showed promise with the liposome, a novel delivery method [17]. Liposomes are phospholipid molecules in a circular sac. Specifically, it encloses a water droplet that is artificially formed to transport the medicine into the tissue membrane. Liposomes are 100 nm-sized nanoparticles. The phosphatidylcholine molecule was dispersed in water by Bangham in 1961, and during this accidental discovery, he discovered that the molecule was forming a closed bilayer shape with an aqueous segment that was entrapped by a lipid bilayer [18].

B. **Nanoparticles:** MRI imaging of the cardiovascular system uses superparamagnetic iron oxide nanoparticles or ultrasmall SPIONs. By detecting cellular inflammation where SPION-loaded leukocytes congregate, their uptake by inflammatory cells also yields extra biological and functional information. USPIONs are stabilised by the hydrophilic polymer dextran and have particle sizes between 10 and 30 nm. They can avoid opsonisation, avoid being recognised by the reticuloendothelial system right away and stay in the bloodstream longer than larger particles because of their small size [19].

C. **Dendrimers:** The Greek word "dendron," which means tree, is the source of the phrase "dendrimer," which appropriately describes the structure of these frequently branching molecules. Dendrimers are special because of their three-dimensional, multibranched structure, low polydispersity, and excellent functioning [16].

D. **Niosomes:** Despite their negative effects, conventional dose forms are still used because of their excellent patient compliance. Niosomes are lipid-bilayer-containing nanosystems that can be used to encapsulate both hydrophilic and hydrophobic medications. Lipid additions, such as cholesterol, are typically used to stabilise niosomes [20].

E. **Micelles:** Micelles are amphiphilic structures made of lipid or polymer-based amphiphilic molecules that have distinctive hydrophilic shells and hydrophobic centres. They develop spontaneously as a result of a decrease in free energy brought on by the aggregation of the hydrophobic parts of the aqueous environment and the formation of a micelle core stabilised by water-exposed hydrophilic fragments [16].

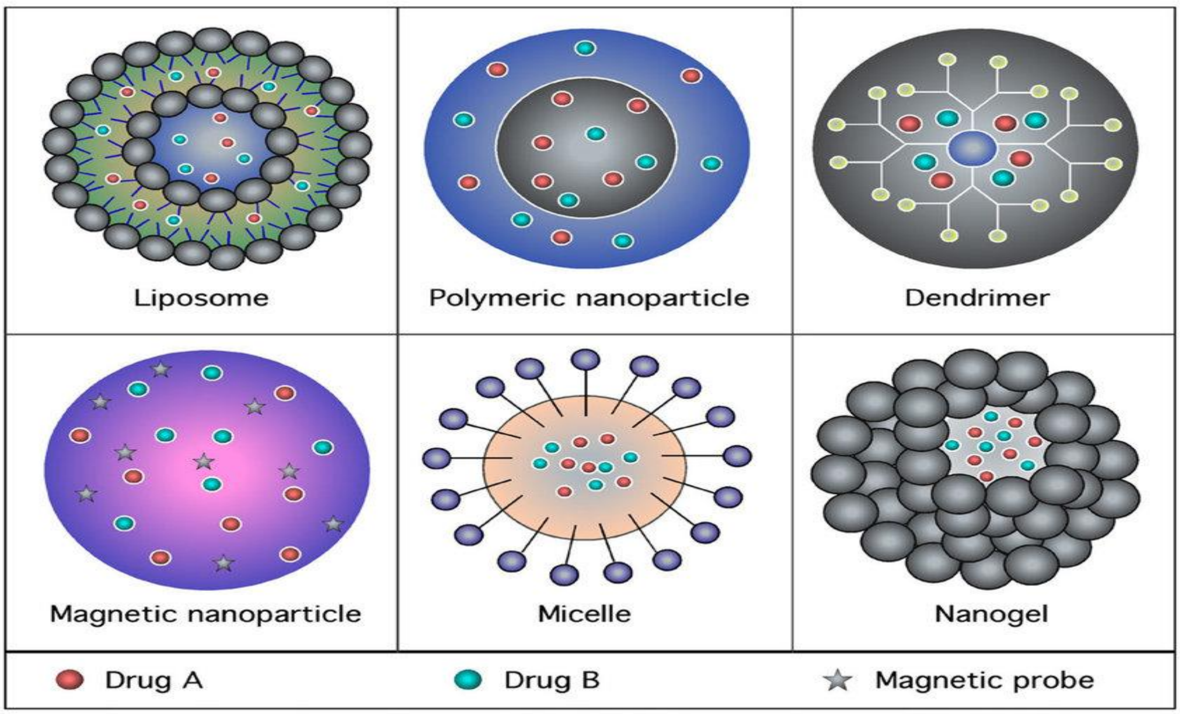

Figure2: Schematic diagram representing the various types of nanoparticle use to develop MTIs. Liposome, Polymeric nanoparticle, Dendrimer, Magnetic nanoparticle, Micelle, Nanogel [21].

- Nanotechnology for neurological disorders: Current treatments for neurological disorders include topical, oral, intravascular and intrathecal pharmaceutical administration; surgeries; vaccinations; deep brain stimulations; emotional, cognitive, physical, and occupational therapies; radiotherapy and angio graphic procedures; rehabilitation and retroviral therapy [22].
- Nanotechnology for the treatment of infectious diseases: A number of therapeutic approaches have recently been discovered to treat viral and bacterial illnesses that were thought to be challenging to overcome. However, full recovery from infection can be challenging and new technologies to detect, treat, and potentially prevent infection are highly desired methods for treating the three well-known infectious diseases Hepatitis C Virus, HIV and Mycobacterium tuberculosis [23].
- Nanotechnology for wound healing: Damage to normal tissue is referred to as a wound or injury. The process of repairing damaged skin or bodily tissues is a dynamic and intricate phenomenon known as wound healing. To prevent the production of excess heat at the wound, a well-designed dressing should keep the area moist. It should also allow for normal debridement, allow gaseous and fluid exchange, prevent bacterial infection, absorb wound odour, be non-adherent to the wound and removable without trauma, be non-toxic, non-allergic, non-sensitizing, sterile, non-scarring, biocompatible and biodegradable [24].
- Nanotechnology for neuromodulation: Any intervention that is submicron in scope is included in the field of nanotechnology for neuromodulation. Both fixed and circulating nanodevices are examples of such treatments. Various nanoparticles, including magnetic nanoparticles, dendrimers, polymeric micelles and quantum dots are used in the latter treatments. The following are some uses for these circulating nanodevices:

1. Iron oxide nanoparticles that are employed as MRI contrast agents to improve the detection of tumours in the malignant neurological system.
2. Using quantum dots to target particular cell types (like tumour cells) or label particular features of cells (like receptors) [25].

- Nanotechnology for patch-clamps: Through the impalement or attachment of a glass micro pipette with a micron size diameter to the membrane, a patch-clamp system can clamp the membrane voltage using the same electrical principles as a voltage-clamp [26].
- Nanotechnology for treatment of gastrointestinal cancer: Colorectal, gastric, pancreatic, and hepatic malignancies are among the many solid tumours of the gastrointestinal system that can be treated with nanotechnology. Additionally, they consist of gastrointestinal stromal tumours, which are sarcomas of the digestive system that originate from interstitial cells and can be located anywhere between the anus and the oesophagus. New medications with strong anticancer efficacy are constrained by their poor specificity or brief plasma half-life. An amino-bisphosphonate with anti-angiogenic properties that prevents bone metastases and was recently linked to liposome is zoledronic acid [27].
- Nanotechnology for treatment of Cancer: Although there is obviously need for improvement, nanotechnology has revolutionised the medical industry by creating potential pathways in diagnosis and treatment. The degree of hypoxia or the expression of particular enzymes necessary for medication release may vary at different metastatic sites due to tumour heterogeneity, which could make drug release unpredictable. Dual stimuli responsive triggers are one potential way to improve tumour specificity [28]. An current and constantly growing nanotechnology toolkit, which includes surface changes, encapsulation and controlled release techniques, and engineering and modification of physical properties, has made it possible for the development of nanotechnologies across several generations [29].
- Nanotechnology for treatment of Alzheimer's disease: The most prevalent habitual progressive neurodegenerative disease in older adults, particularly those over 65, is typified by irreversible cognitive dysfunction, behavioural impairment, and, as symptoms worsen, insanity. A person with announcement eventually dies from announcement because of severe neuronal death, after experiencing increasing memory loss, cognitive function impairment, and language degeneration. The idea that brain and supplementary blood announcement are in balance with one another is the foundation of a therapeutically useful conception in announcement [30].
- Nanotechnology treatment of Skin: Nanoparticles in cosmetic compositions enhance the look, coverage, and skin-adherence of cosmeceuticals without altering their characteristics. In order to enhance a number of characteristics, including UV protection, skin penetration, colour, scent release, finish quality, and anti-aging effect, cosmetic producers utilise nanosized components. By regulating the active ingredient administration, generating site-specificity, boosting drug-loading capacity or improving biocompatibility, they extend the duration of action [31].
- Nanotechnology for nail health: Like the claws of other mammals, the nail is a vital part of the human body. It is a protrusion that conceals the leading edges of the fingers and toes. It enhances the enjoyment of discriminative touch and makes it easier to pick up and move objects. In addition, the nail serves as a tool for beauty and maintenance, and it can sometimes be used to convey social status [32]. The fungal disease of the nail, onychomycosis is the single most prevalent disturbance of the nail. It is characterized by discoloration, brittleness and thickening of the infected nail and is caused predominantly by dermatophytes but also by non-dermatophyte molds and yeast [33].

Application of Nanotechnology:

- Nanotechnology Applications in Various Industries: Numerous industries where nanotechnology is generating impressive applications have been examined, evaluated, and chosen to be included in this review following extensive and meticulous investigations. It should be noted that in order to further explain the extensive uses of nanotechnology across various industries, several subcategories of industrial connections may be covered under a single category [34]. Compared to other industries like medicine and pharmaceuticals, the use of nanotechnology in agriculture is relatively new. The first studies on the topic were published by the US Department of Agriculture in 2003, marking the beginning of nano science's presence in the agricultural sector [1].
- Nanotechnology Applications in Agriculture: Agriculture has been dealing with a number of issues in the current situation, such as the unpredictability of climate change, soil contamination from various harmful environmental pollutants like pesticides and fertilisers, and, most importantly, rising food demands due to a growing world population [35]. Nanoscales act as transporters and offer onboard chemical sensing and self-regulation decision-making capabilities. These intelligent devices provide the necessary amounts of medications, nutrition, or other agrochemicals [36]. Productive and sustainable agricultural system is essential to the existence of humanity. Although current agricultural practices can produce enough food for nearly eight billion people, they cannot continue to do so sustainably without technological intervention [37].
- Nanotechnology Applications in the Food Sector: Food packaging, food preservation, and additives are just a few of the areas of consumer goods where food nanotechnology has crept in. The acceptance of this new technology has improved food safety through advancements in food processing and storage. It has also been discovered that many common compounds used as food additives or packaging materials partially exist at the nanoscale. For instance, it has recently been discovered that up to 40% of food-grade TiO_2 NPs are in the nanometre range [38].

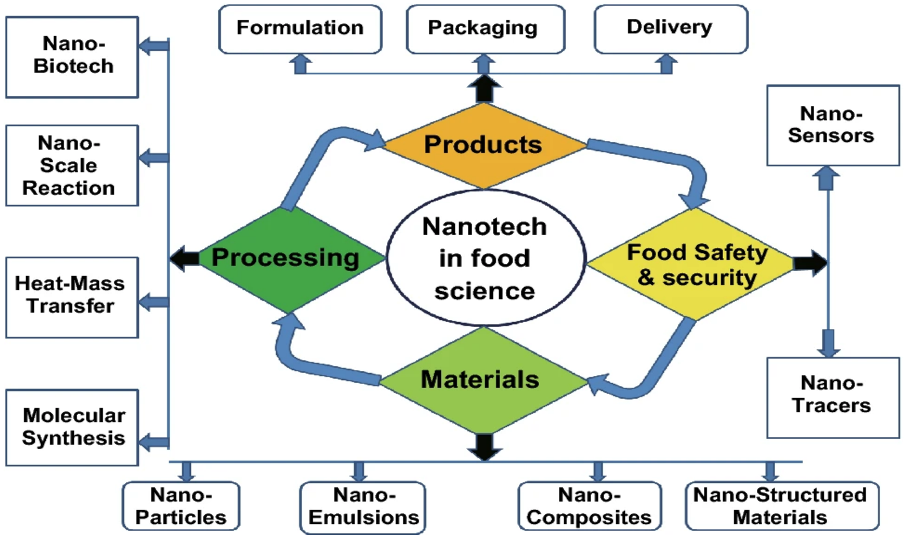

Figure 3: Nanotechnology in food science and technology [39].

- Nanotechnology Applications in Food Processing: Nano-food is food produced by applying nanotechnology to food production, processing, packaging, and security. Nanotechnology holds great promise for food processing after harvest. In addition to altering the particle size, size distribution, potential cluster formation, and surface charge, it improves the flavour, texture, consistency, and bioavailability of food or masks an unpleasant taste or odour [39]. Food processing is the process of transforming food into a consumable state using a variety of procedures and processes. These methods are made to retain the food's flavour and quality while simultaneously shielding it from microorganisms [40]. The fields of biology, chemistry, material science, and most recently, food science, have all made substantial use of atomic force microscopy [41]. Alternative methods of food processing have been made possible by nanotechnology, which has improved physicochemical properties and increased nutrient storage and bioavailability [42].

- Nanotechnology and Bio-processing Industries: Extensive scientific and engineering research is being done to connect the disciplines of nanotechnology and bioprocessing. The application of the fundamentals of nanomaterials to the bio-material quality of interest to researchers [34].

- Environmental Protection Through Nanotechnology: In recent decades, very dangerous chemical substances have release to the atmosphere for long-term direct or indirect use. Among these components include pesticides, poly-chlorinated bi-phenyl, and polycyclic aromatic hydrocarbons. Certain mixed chemical compounds actively resist biodegradation by native flora, in contrast to organic molecules that can degrade rapidly when added to the environment [9].

- Nanotechnology for Food Packaging: The packaging sector plays a significant role in the global economy in the United States, food and beverage packaging accounted for between 55 and 65 percent of $130 billion. Meat and muscle products are packaged to prevent spoiling, avoid contamination, improve softness by promoting enzymatic activity, prevent weight loss and preserve the cherry red colour of red meats [39].

- In Vivo Imaging using Nanotechnology: In animal models and human clinical trials, a range of nano-scale particles have previously shown promise in imaging tumours and the surrounding environment. Dextran-coated, ultra-small super paramagnetic iron oxide nanoparticles are used in some of the most cutting-edge research in this field to imaging lymph nodes in prostate cancer patients that have micro-metastases. Other research has imaged lymphatic micro-metastasesmouse mode RL of breast cancer using paramagnetic, gadolinium-labeled, nano-particulate dendrimer [4].

- The Fruit and Vegetable Industry and Nanotechnology: Under this scenario, the fruit and vegetable, agricultural and medical sectors cannot stay unaffected. To meet the dietary demands of an expanding population, scientists are working to extend the shelf life of fresh organic products. Nanotechnology is essential to the production and safety of fruits and vegetables, from horticulture to food processing, packaging, and disease detection technology [34].

- The Medical Industry and Nanotechnology in Healthcare: In the larger context of nano-biotechnology, nanotechnology is already surpassing expectations. Successful uses of nanotechnology in medicine have consistently raised human life quality, leading to the emergence of a whole new field called nano-medicine. This has enabled researchers to develop improved methods for disease prevention, screening, treatment, diagnosis, and proactive healthcare measures. With developments in tissue engineering, gene therapy, and nano-based genomics, these procedures may also include drug design, conjugation, manufacture, and effective delivery methods [34].

- Nanotechnology in Medicine: Work on biodegradable and biocompatible comb-like polymers was presented by Dr. Davide Moscatelli of the Politecnico di Milano. Polyesters are appealing for drug delivery because of their biocompatibility and biodegradability. The talk concentrated on biocompatible and biodegradable nanoparticles made using innovative CLB that had adjustable hydrophobicity and biodegradation kinetics [43].

- Plant disease management with nanotechnology: The use of pesticides, including insecticides, fungicides, and herbicides, is a major component of pest management in contemporary farming methods. It is essential to produce high-performing, reasonably priced pesticides that are less damaging to the environment. Pesticides may benefit from innovative ideas like nanotechnology, which can decrease toxicity, extend shelf life, and make poorly water-soluble pesticides more soluble. These benefits could all have a good effect on the environment [44].

Figure 4: Nanotechnology applications in medical industry. Nanotechnology has a broad range of applications in various diagnostics and treatments using nano-robotics and drug delivery systems [34]

Nanocrystal:

Pure drug particles having dimensions that vary between 10 to 1000 nm have been termed as drug nano biologicals, and they can be maintained by polymeric or surfactant stabilisation agents. This idea of increased solubility has been supported by a number of theories, including the Noyes-Whitney equation, Kelvin, and Ostwald-Freundlich [45]. Coming up with pharmaceuticals as nano-crystals is a reasonably straightforward method for improving their solubility and dissolving characteristics. Drug nanocrystals, also known as solid micelles, are solid nano-sized drug particles encapsulated in a stabilisation layer. Depending on the reason for being, they are consistently approximately 200 and 800 nm in size [46]. Nanocrystals have drawn a lot of interest in recent decades as one of the effective formulation techniques for enhancing the bioavailability of natural products and insoluble medications [47]. The original purpose of nanocrystals was to increJit1lthe oral bioavailability of medications that were not very soluble in water. This is due to the fact that nanosizing increases specific surface and curvature, which improves solubility and dissolving. The need for dissolution enhancement has led to an explosion of activity in this field [48]. An established technique for resolving issues with oral bioavailability of medications that are poorly soluble in water is nanocrystal [49]. One of the factors limiting the rate of medication absorption is poor water solubility. Additionally, the lungs' restricted fluid capacity slows down the rate of disintegration and, thus, absorption [50].

Advantages of nanocrystals

- Enhanced dissolution velocity and saturation solubility lead to increased bioavailability [51].
- Increased bioavailability in the eyes, Enhanced safety for the eyes [45].
- Especially compared to micronised particles, nanocrystals demonstrate a slight rise in saturation solubility plus an elevated rate of dissolution resulting from the substantial surface enlargement circulation [52].
- Better biological performance of medications in different ways of delivery, regardless of how they are administered [53].
- A decrease in the necessary dose and an improvement in dose proportionality [4].
- Minimise or eradicate the impact of diet on bioavailability [16].

Properties of Nanocrystals:

Drug nanocrystals are solid drug particles encased in a layer of one or more stabilisers; they are also referred to as solid micelles. Because the nanocrystals are unstable due to their small particle size, stabilisers are required to stop the individual nano-sized particles from aggregating. Different types of polymers, such as cellulose derivatives, PVP, poloxamers, vitamin E TPGS, or amphiphilic surfactants like polysorbates and SDS, are common stabilisers. They can also increase solubility through improved wetting and solubilising properties [54]. Particle size and shape, interaction properties and the linked solid-state features should all be taken into account when characterising nanocrystals [46].

- Solid State Properties: The apparent solubility and, consequently, the rate of dissolution are influenced by the solid-state form. Determining these characteristics in nanocrystals is therefore essential. To reduce the possibility of solid-state transitions during administration and storage, the thermodynamically most stable crystalline form is usually used. It is feasible to create nanocrystals in a metastable crystalline form or even their amorphous equivalent in order to improve their solubility and bioavailability, but this is uncommon.
- Particle Size and Surface Properties: Effective stabilisation of nano-suspensions is correlated with the size, shape, and variety of nano crystals. Particles have a higher surface energy when they are smaller, which

encourages aggregation. Therefore, choosing stabilisers carefully is essential while creating nanocrystals. Although stabilising the produced nanoparticles is the primary function of stabilisers in nano-crystallization, the majority of stabilisers also improve permeation to some extent or have other effects on active transport systems. As a result, with proper formulation, the stabilisers in the nanocrystal-based formulation may actively improve both the dissolving and the permeation.

- Dissolution of Nanocrystals: The most stable crystalline form of a drug's solubility in a particular medium at a specific temperature and pressure is known as thermodynamic solubility. Drug particles that are nano-sized, metastable polymorphic, or have higher energy amorphous forms, for instance may have solubility that is momentarily greater than thermodynamic solubility. Different words have been used to characterise this increased solubility, including kinetic and apparent solubility. The dissolution of nanocrystalline material is likely to result in a supersaturated solution, commonly referred to as the "spring effect" [46].

Method for preparation of drug nanocrystals:

Depending on the type of production process used, a drug's degree of crystallinity or amorphous nature changes in nanocrystal technology [55].

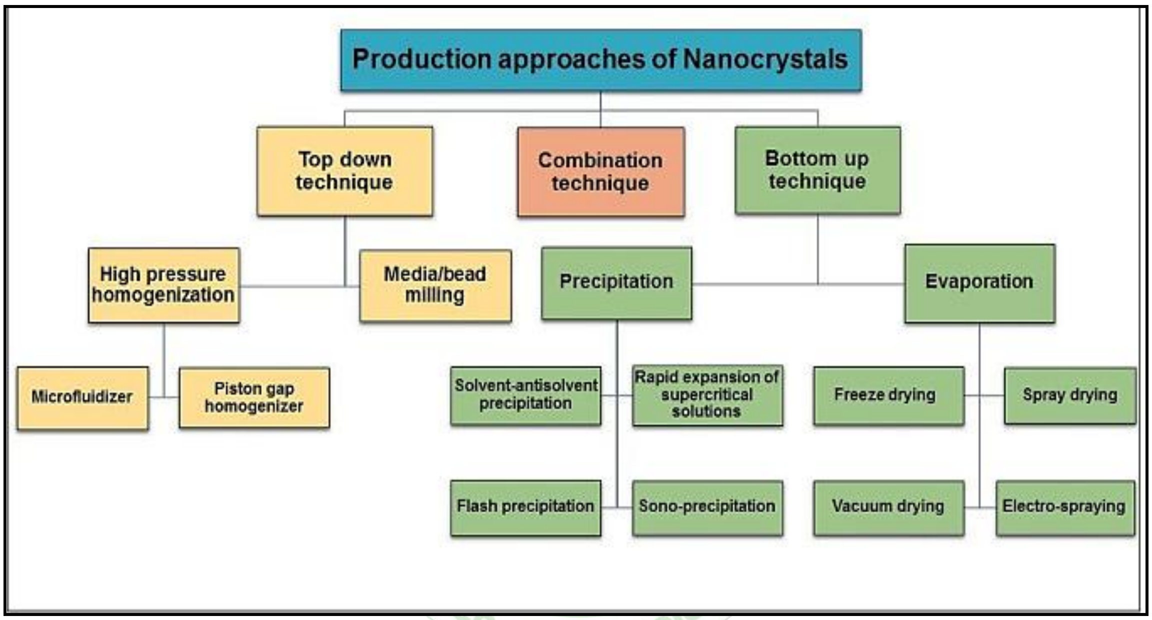

Figure 5: Classification of production approaches of nanocrystals [55].

- **Bottom-uptechnology:** A traditional precipitation technique that applies the fundamentals of precipitation is the bottom-up approach. The medication precipitates after being dissolved in a solvent and then added to a non-solvent. The size of the crystals and the crystallinity of the particles produced are crucial specifications for this technology. Because amorphous nanocrystals are more soluble than their crystalline counterparts, it becomes vital to regulate the crystalline nature of developing particles. Sono-crystallization, liquid jet precipitation, high gravity-controlled precipitation, multi-inlet vortex mixing, rapid expansion of supercritical solution, supercritical anti-solvent, and evaporative precipitation into aqueous solution are examples of bottom-up technology variations [51].

- **Top-down technology:** This method uses high shear forces to reduce the size of big medication particles. This technology can be further separated into media milling and high-pressurehomogenization based on how shear force is applied [3]. The top-down method comminutes coarse particles by mechanical attrition, usually through media milling or high-pressure homogenisation. In contrast, the top-down approach is more flexible and adaptive for larger production scales [56].

- **Media milling:** A mill with a milling chamber, milling motor, milling pearls, and a recirculation chamber is used to carry out the milling operation. Glass, polystyrene beads, and zirconium oxide are utilising as milling media. The milling chamber is charged with drug, water, surfactant, and milling media. The fast rotation speed of the milling media generates tremendous energy and shear, which breaks down the drug particles. Using this technique, a drug suspension is aggressively pushed through a 25 μm homogenisation gap, resulting in cavitation, particle collisions, and high shear force that causes size [45].

- **Combination technology:** For the efficient synthesis of nano crystals, the combination technique uses both top-down and bottom-up approaches. Its main goal is to generate uniform, small-sized drug nano crystals at reduced cycles that are easily scalable. It aids in overcoming the shortcomings of the aforementioned technologies, including equipment blockage and extended processing times. It basically consists of a pre-treatment stage that comprises a bottom-up strategy that involves precipitating the drug solution, followed by a secondary step that involves high energy mixing from the top down, such as ultrasonic energy or high-pressurehomogenization [55].

Administration Routes of Primary Nanocrystals:

- Oral delivery: As previously stated, a medicine that is extremely permeable and poorly water soluble can be categorise as a BCS class II drug. Because of its poor oral bioavailability, the medicine has a lower blood concentration, which reduces the likelihood that it will reach the target tissue or organ. If the medication is not dissolved, it can be difficult to absorb in the gastrointestinal tract, specifically through the gastrointestinal epithelium. Nano crystal formulation has advantageous effects on oral medication administration, such as imparting the same bio equivalence regarding the fed or fasted condition, to address this problem. Improved saturation solubility and dissolving rate characteristics account for the effectiveness of nano crystal compositions. medication delivery in the form of nanocrystals increases medication bioavailability in the bloodstream by creating a notable drug concentration gradient between the GIT and systemic circulation [57].
- Parenteral delivery: When a medicine suffers extremely high first pass metabolism or is unstable in the gastric fluid, parenteral delivery is typically the better option than oral administration. Furthermore, it has a quick beginning of action and a high bioavailability when compared to other routes; nonetheless, it is frequently linked to allergic reactions, patient noncompliance, restricted excipient use, and macrophage uptake. While certain methods, such as liposomes and emulsions, improve solubility to some degree but have poor drug loading, other methods, such as pH modulation and salt creation, result in injection site responses. The performance of poorly soluble medications administered parenterally is improved using nanocrystal technology. It uses aqueous-based solvents instead of organic ones, improves drug loading, dissolves drugs more quickly and prevents macrophage absorption, all of which lower dosage volume [53].
- Intravenous drug delivery: The in vivo fate of injected nanocrystals is contingent upon the pace at which the nanocrystals dissolve in the bloodstream, much like the fate of oral administration. Cells have the ability to absorb circulating nanocrystals. Crystalline materials were discovered in the spleen after intravenous injection, despite the paucity of data supporting the uptake and transportation of nanocrystals [10]. Nanocrystals can be discharged intact and with a size and shape comparable to the original nanocrystals after undergoing endocytic recycling as opposed to destruction in macrophages. Apart from macrophages, cancer cells like KB cells can also absorb integral nanocrystals [58].
- Ocular drug delivery: Several researchers are investigating the use of nanocrystals for ocular medication delivery in addition to their potential advantages in oral drug delivery. There isn't a single product on the market that uses nanocrystals to treat eye conditions. This might be as a result of patents on production methods used in nanocrystal development. The benefits of using nanocrystals in ocular drug delivery have been demonstrated by research, raising hopes for the treatment of a number of ocular conditions and the creation of superior substitute formulations for medications that are poorly soluble.
- Pulmonary drug delivery: For pulmonary uses, aerosolised nanocrystals are perfect vehicles for poorly soluble medications. Although the destiny of inhaled nanocrystals is poorly understood, improved bioavailability is typically a result of improved solubility and extended retention. Possible processes include phagocytosis, transfer into cells, blood, and lymph, muco-ciliary clearance, and dissolution [58].
- Topical drug delivery: It is described as transporting particular medications into and through the skin. Because topical drugs penetrate the epidermal barrier, they present a difficulty. The two primary product categories for topical drugs are internal and exterior. Topical drugs are applied to the affected area by spraying, sprinkling, or other means onto the skin tissue. A semi-solid preparation of large and small molecules scattered over aqueous liquid carriers is called a gel. Gels are semi-solid systems where colloidal particles interact with a liquid carrier either physically or covalently. Increased patient compliance, constant medication delivery, and fewer side effects are just a few benefits of the topical route over other drug administration methods [59].

Nanocrystals based Formulation:

- **Suspension:** A pharmaceutical suspension is a coarse dispersion consisting of an internal phase uniformly dispersed throughout the exterior phase. The insoluble solid particles that make up the interior phase are suspended by one or more suspending agents. The external phase, which is typically aqueous, can also be an organic or greasy liquid for non-oral use. Individual particles range in size from 0.5 to 5.0, and they usually consist of a finely divided solid suspended in a liquid or semi-solid media that forms the continuous phase [60].
- **Tablet:** Immediate-release, delayed-release, extended-release, and fast-melt tablets might all use nanocrystal technology. It is typically a powdered mixture of the active agent and excipients that has been compressed or compacted into a predetermined dosage. There should be no functional or visual deformities on the perfect tablet. During manufacture, an artificial druggist typically runs into a variety of issues. A lengthy list of potential problems, including fluctuating weight, sticking, blackening, locking, lamination, changeable hardness, and more, is included in the strict criteria for tablets [61].
- **Emulsion:** When a parenteral product is sought, emulsions are also recommended as an IV formulation in addition to suspensions. In order to create an emulsion, the medicine is first dissolved in an organic solvent that contains lecithin, then the mixture is utilised to create an emulsion in which the drug molecules are integrated into the emulsion's interfacial layer [53].

- **Syrup:** Aqueous solutions that include sucrose at 66.7% sugar content are called syrups. They also contain flavourings and medications. A solution is the most basic kind of pharmacological preparation that has a quick onset and fast absorption of medications. A pair of substances have been combined in order to produce a solution that is the solvent and the solute [62].
- **Powder of Inhalation:** One of the alternatives to deep lung delivery for systemic or local effects or preferential pulmonary delivery of medications for the treatment of conditions like asthma is nanocrystals. Techniques like high-pressure homogenisation and milling, which typically produce nano-suspensions, might easily produce drug particles in the nano-sized range. These nanocrystal dispersions are spray-dried to create powders that can be administered via the lungs [53].
- **Pellets:** One advantage of matrix pellets over coated ones is their straightforward manufacturing process, which is based on the melt pelletisation technique. Using a high shear mixer, a mixture of microcrystalline waxes, starches, and the nanocrystalline medication is homogenised in this method. When wax melts, a dough-like substance is created that is constantly stirred at a high speed (3000 rpm) at 50° C. After cooling, the resultant pellets are sieved to separate them [53].

Targeted Delivery for Cancer Therapy [57]

Reaching the target site without increasing nonspecific toxicity is a major problem with nanocrystal drug delivery. It is simple to comprehend how drug accumulation is not ideal at the target site, leading to undesired bio-distribution to healthy tissues, given that the body is made up of sequential barriers.

Passive delivery: Since the liver, lungs, spleen, and kidneys absorb non-functionalized nanoparticles, it has been shown that these particles are quickly eliminated from the bloodstream. Nanoparticles cannot reach healthy tissues because the vascular endothelium's intercellular connections are tightly packed. On the other hand, an inflammatory response that is marked by an increase in vascular permeability takes place as tumour tissues form. Because of this endothelial dilatation, nanoparticles can diffuse through and enter cancerous tissues. The enhanced permeability and retention (EPR) effect, another name for this passive targeting effect, was first put forth by Maeda and colleagues in 2000.

Active delivery: These days, active targeting is incorporated into new nanoparticle formulations to improve specificity for a particular spot. This method entails functionalising the surface of the nanoparticle with substances that cancer cell receptors may particularly recognise, such as polymers, proteins, peptides, etc. Park et al. examined the efficacy of PTX-coated nanocrystals and a traditional albumin-based PTX formulation in treating B16F10 melanoma in mice in order to comprehend the significance of such functionalised nanocrystals.

Figure 6: Targeted therapy [63]

CONCLUSION:

The multidisciplinary scientific discipline of nanotechnology examines and works with matter at the molecular level. It has benefited numerous industries, including as food, medicine, and energy, and it is anticipated to have even more sophisticated uses in the future. It's possible that nanotechnology will soon become a basic technology. Nanocrystal formulations have become a particularly intriguing method for increasing the bioavailability of medications that are poorly soluble in recent decades. A crystalline particle that ranges in size from 1 to 1000 nanometres is called a nanocrystal. Because of their special physical characteristics, nanocrystals differ from glasses and traditional polycrystals. Drugs that are poorly soluble can have their bioavailability increased by using nanocrystal formulations. Numerous techniques, including as top-down, bottom-up, and combination technologies, can be used to create nanocrystals. There are numerous applications for nanocrystal formulations, such as tablets, pellets, emulsions, powders, etc.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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