

Nanotechnology in Herbal Medicine

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Abstract

Herbal medicine has been widely used for centuries as a natural and holistic approach to health care. However, many herbal compounds face challenges, such as low solubility, low bioavailability, instability, and the lack of targeted delivery, which affect their efficacy. The integration of nanotechnology into herbal medicine has emerged as a promising strategy to overcome these challenges and enhance the pharmacological potential of plant-derived compounds. Nanocarriers, such as liposomes, solid lipid nanoparticles, polymeric nanoparticles, nanoemulsions, and metallic nanoparticles, can encapsulate herbal bioactives, protecting them from degradation and facilitating controlled and sustained release at specific sites of action. These nanoformulations not only improve absorption and stability but also reduce the required dosage and minimize side effects. Additionally, nanotechnology enables the development of novel drug delivery systems that combine the advantages of modern science with the therapeutic richness of traditional medicine. Recent studies have demonstrated significant improvements in the efficacy of herbal formulations for treating cancer, diabetes, inflammation, and infectious diseases through nanotechnological approaches. Despite these advancements, issues related to toxicity, standardization, large-scale production, and regulatory approval remain major challenges. Thus, further research and clinical studies are required to ensure the safety, efficacy, and acceptance of nano-herbal formulations. Overall, nanotechnology represents a revolutionary step forward in modernizing herbal medicine, offering innovative pathways for developing more effective, reliable, and scientifically validated natural therapies.

Keywords: Nanotechnology, herbal medicine, drug delivery, bioavailability, nanoformulation

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INTRODUCTION

One of the traditional medical practices in India is Ayurveda. Due to their potential therapeutic benefit and lower side effects when compared to other medications, herbal medicines have gained recognition from both doctors and patients. At the same time, they also boost the medication's bioavailability. Due to processing challenges and a lack of scientific support, herbal medicines were long disregarded for the creation of innovative formulations. The scientific needs of herbal medicines can be met by contemporary phyto-pharmaceutical research in the development of innovative drug delivery methods, including solid dispersions, liposomes, microemulsions, nanoparticles, solid lipid nanoparticles, and matrix systems [1]. Since ancient times, plants have been traditionally used for therapeutic purposes, either in their natural form or through extracted preparations. Because of their many

phytochemicals, low cost, and great nutritional value, plants have been utilized for human health and have gained approval by the broader population. Known as secondary metabolites, phytochemicals are compounds made by plants that are used extensively in traditional medicine. The use of herbs in traditional medicine has a scientific foundation due to their demonstrated biological activity. They exhibit pharmacological properties that can be applied to the treatment of fungal and bacterial infections, as well as chronic degenerative illnesses, including cancer and diabetes [2]. “Nano” is a Greek prefix meaning “dwarf” or “extremely little.” It is critical to distinguish between nanoscience and nanotechnology. The study of molecules in nanoscience is the study of structures and processes at nanoscales (between 1 and 100 nm), whereas nanotechnology is the application of this knowledge to practical devices and other applications. The entire scientific community is interested in the subject of nanotechnology. Nobel Laureate Richard Feynman first presented the idea of nanotechnology in a lecture delivered at the California Institute of Technology in December 1959. Nanotechnology is the processing of material separation, consolidation, and deformation by a single atom or molecule. The relationship between nanotechnologies and plant derivatives can be summed up by two main research areas [3]. The increasing appeal of herbal-based nanoparticles is highlighted by their ability to overcome the drawbacks of conventional drug delivery methods such as the medication’s low solubility, instability, and lack of tissue-specific targeting. When paired with controlled and sustained release mechanisms, these nanoparticles’ ability to distribute drugs precisely guarantees that therapeutic molecules reach particular bodily locations with fewer adverse effects. The goal of this review is to examine different production methods, drug loading and release mechanisms, biocompatibility, and toxicity profiles of nanoparticles based on herbs. By addressing these issues, the review aims to demonstrate how herbal-based nanoparticles can revolutionize contemporary drug delivery systems and contribute to the advancement of personalized medicine [4]. Natural items and herbal medicines have been utilized to treat illnesses since ancient times. In contrast to the popular allopathic approach, herbal medicines contain hundreds of various components that all combat the diseases simultaneously. To improve patient compliance and prevent repetitive administration, phytotherapeutics require a scientific approach to administer the components in a continuous manner. Creating innovative drug delivery systems (NDDSs) for herbal ingredients is one way to accomplish this. By lowering toxicity and raising bioavailability, NDDSs not only lessen the need for repeated administration to overcome non-compliance but also contribute to an increase in therapeutic value. The total function of several active ingredients determines the activity of herbal medications since each component works in concert to improve the therapeutic worth. Every active ingredient has a significant function and is connected to the others. Unfortunately, most medications with an herbal origin are insoluble, which reduces their bioavailability and increases their systemic clearance, necessitating greater doses or repeated administration. As a result, these medications are not good candidates for therapeutic use. There are several benefits for herbal medications from creating nanodispersion forms (polymeric nanoparticles [nanospheres and nanocapsules], liposomes, proliposomes, solid lipid nanoparticles [SLNs], nanoemulsions, etc.) in phyto-formulation research such as improved solubility and bioavailability, and protection from degradation [5]. Some plant or vegetable extracts are limited by factors such as high pH acidity, liver metabolism, etc. Herbal medicine can be delivered by nanoparticles to every organ, improving drug selection, delivery, effectiveness, and safety, which lowers dosage and improves patient compliance. A suitable nanoparticulate system must be tiny enough to enter the target cells and tissues and be able to move through the bloodstream. Many organs, including the brain, lungs, liver, kidneys, the intestinal tract, etc., can benefit from herbal medicines. By 2015, the worldwide market for a product utilizing nanotechnology is projected to grow to \$1 trillion USD. The governments of Australia and India made an offer in 2006 to start the Science Research Funding Program between Australia and India. In 2010 and 2011, the worldwide nanomedicine market was valued at \$63.8 billion and \$72.8 billion, respectively. It is anticipated that the market will reach \$130.9 billion in the 2016 fiscal year. The industry and other organizations that deal with pharmaceutical and Ayurveda items have made testing herbal medicines a fundamental need. Establishing consistent chemical profile, consistent biological work, or even just a quality assurance program to produce pharmaceutical medications requires legislation. Because they are hydrophobic, most herbal treatments do not dissolve well in water. These adverse effects decrease the bioavailability and systemic approval, necessitating higher dosages or repeated administration, which will decrease the therapeutic use of herbal medications. As a result, nanoparticles can be utilized to improve the solubility of herbal medications, help them become more effective locally, and make patient adherence easier

[6]. Nanomaterials and nanodevices, the two primary categories of pharmaceutical nanotechnology that are also important in other industries, are divided into these two categories. Nanoparticles originate from the biomaterials used in dental or orthopedic implants as well as scaffolds for tissue-engineered products. Their surface can be altered or coated to improve their biocompatibility with human tissue. These are further divided into two groups: components that are nanostructured and those that are nanocrystalline. In specialized mills, nanocrystals are processed to produce medications that can be administered intravenously as nanosuspensions or inhaled. The surface/volume ratio and bioavailability of nearly insoluble drugs are enhanced by their tiny size. Nanostructured materials are nanomaterials that have been processed to create unique shapes and characteristics. Nanomaterials are commonly used in pharmaceutical delivery because they can enhance solubilization, which results in controlled release and/or drug targeting. They are used in asthma inhalers, hormone administration through the skin, drug delivery through the eye, oral, and vaccine delivery techniques, gene delivery, cancer therapy, and other applications. Nanoparticles are used by several companies to treat cancer. Nanodevices include things like microfluidics (which controls and manipulates fluids in the micro- or nanoliter range), nano- and micro-electromechanical systems (NEMS/MEMS), and microarrays (which perform numerous biological tests including DNA, protein, cell, and antibody analysis). These comprise biological threats, symptoms of disease, airborne infections, biosensors, and detectors that spot minute concentrations of microbes, and some advanced technologies like respirocetes [7].

NANOTECHNOLOGY

Including herbal remedies in the delivery system also contributes to better stability, toxicity prevention, increased solubility, enhanced pharmacological action, enhanced tissue dispersion, ongoing administration, and defense against chemical and physical harm.

Because they are hydrophobic, most herbal treatments do not dissolve well in water. The therapeutic usage of herbal medicines is decreased as a result of these side effects, which decrease bioavailability and increase systemic clearance, necessitating repeated administration or higher dosage. Consequently, the solubility of herbal medications can be improved by using nanoparticles, which can also help the drug function better locally and promote patient adherence. Some plant or vegetable extracts are limited by factors such as high pH acidity, liver metabolism, etc. The brain, lungs, liver, kidneys, intestinal tract, and other organs can all benefit from the use of herbal treatments. Since ancient times, phytomedicines have been utilized more frequently than other treatments because they have more therapeutic activity and fewer side effects than other pharmaceuticals. Because of their natural origin and few side effects, herbal medications are becoming more and more popular in both developed and developing nations. Rapidly developing nanotechnologies have greatly aided in the creation of innovative, one-of-a-kind herbal medicines. Although many nutraceuticals have low bioavailability, they are foods and food additives that provide health benefits over basic nutrition. Applications of nanotechnology have helped to overcome the challenges and technological barriers related to solubility, bioavailability, stability, and transport of bioactives from food [8].

HISTORY AND DEVELOPMENT

The particle dimension of the nanoscale system is 0.1 μm , or submicrometer. This makes nanotechnology more advanced and extensively researched because it offers numerous benefits in terms of different factors such as the route of administration and enhanced therapeutic effects. Because nano-sized systems can boost activity, lower dosages, and limit negative effects, herbal medicine and nanotechnology have been the subject of numerous studies. The ability to transform less soluble, poorly absorbed, and unstable chemicals into promising pharmaceuticals is one of the many special qualities and enormous potential of herbal medicines that use nanotechnology-based delivery methods. Thus, delivery systems based on nanotechnology offer a promising way to boost herbal activity and get past the problems with herbal medication [2]. The history of nanotechnology dates back to the early days of science; in particular, craftspeople in Mesopotamia first used nanoparticles (NPs) in the ninth century. They were used to give pots' surfaces a dazzling appearance. The uniform dispersion of copper and

silver nanoparticles in the glassy matrix was the cause of the glossy appearance on the ceramic surface. Pottery from the Middle Ages and Renaissance still frequently has a noticeable metallic glitter that is the color of gold or copper. Ag and Cu NPs are evenly distributed throughout the glassy ceramic glaze matrix to create this shine. In those days, the artisans were not familiar with the term NP [9]. People were familiar with and used natural textiles like flax, cotton, wool, and silk thousands of years ago. They were successful in growing them and turning them into goods. These textiles are unique because of their well-developed network of pores, which range in size from 1 to 20 nm. They are typical nanoporous materials. Natural textiles have excellent practical qualities because of their nanoporous structure: they quickly inflate and dry after absorbing perspiration [10]. Interest in the new disciplines of nanoscience and nanotechnology grew at the start of the 21st century. Feynman's reputation and his theory of atomic-level matter manipulation were crucial in determining national science goals in the US. In a speech at Caltech on January 21, 2000, President Bill Clinton urged financing for study on this new technology. The study of possible harmful health effects of nanoparticles is known as nanotoxicology. Nanomedicine was created to investigate the advantages and hazards of using nanomaterials in medicine and medical devices. It encompasses subsectors such as tissue engineering, biomaterials, biosensors, and bioimaging. Improved medication distribution, antimicrobial coatings for medical equipment, less inflammation, and enhanced surgical techniques are a few possible advantages of medical nanomaterials, tissue repair, and identification of cancer cells in circulation [11].

TECHNIQUES

High-Pressure Homogenization Method

Solid lipid nano-dispersions were first produced using the high-pressure homogenization process. Both approaches are widely used and simple to use. However, the presence of microorganisms frequently degrades the quality of dispersion fragments. Melt emulsification is used to create SLNs using a high-speed homogenization technique [12]. This approach is most frequently utilized for nanosuspension formulation since it is simple to apply and works with most of drugs that are water-insoluble. There are three steps in this procedure. Pre-milling is the process of homogenizing the drug powder pre-suspension at both lower and higher pressures after it has been prepared in the first phase. Until the necessary particle size is achieved, 10 to 25 cycles at greater pressure are carried out in the last stage [13].

Complex Coacervation Method

When two oppositely charged polyelectrolytes combine in an aqueous solution, they interact and cause a spontaneous phase separation of the two liquid phases in colloidal systems [14]. Complex coacervation, co-precipitation, salting-out, nanoprecipitation, solvent emulsification–diffusion, supercritical fluid, and high-strain homogenization procedures. These tactics have offered natural products a strong boost against deterioration, which has increased medicine safety and pharmacological enjoyment. The optimal amount of the medication will be delivered to the site of action by nanocarriers using natural remedies, overcoming all restrictions, such as the stomach's acidic pH and the liver's metabolism, due to its nanodispersity [15].

Co-Precipitation Method

A variant of the intensive coacervation technique for producing core-shell nanoparticles is the co-precipitation method. This method, which provides superior dispersion stability, has apparently replaced the weakly water-soluble drugs [16]. These techniques are regarded as environmentally advantageous since the stabilizing and reducing agents used in the synthesis of biosynthetic nanoparticles are either bacteria, fungi, yeasts, or plants or their active ingredients. Over the past ten years, several plant species and plant-derived materials have been identified for the environmentally friendly manufacturing of various nanoparticles.

Alkaloids, phenols, flavonoids, ascorbic acid, citric acid, polyphenols, terpenes, reductase, and other physiologically active compounds are found in many plants and serve as reducing agents for metal salts [17].

Salting-Out Method

Butanol, pentanol, and butanone are examples of polar micromolecules that can form two-phase systems with water, respectively. Butanol's partial solubility in water results in the formation of two-phase systems in its aqueous solution. Butanol and water form a two-phase system that can be used to extract 2,3-butanediol from fermentation broth [18]. The emulsification/solvent diffusion method is modified by the salting-out process.

The medication and polymer are first dissolved in a solvent. Toxic solvents are not employed in this process. Acetone is typically utilized since it is easily removed and miscible with water. The aforementioned mixture is then emulsified into an aqueous gel that contains a colloidal stabilizer (polyvinyl pyrrolidone or hydroxyethylcellulose) and salting-out agents like electrolytes, magnesium chloride, calcium chloride, and magnesium acetate, or non-electrolytes like sucrose.

To promote the diffusion of acetone into the aqueous phase and induce the creation of nanospheres, the oil/water emulsion is diluted with an adequate volume of water or an aqueous solution [19].

Nanoprecipitation Method

Two miscible solvents are needed for this technique, which is also known as the solvent displacement method (Figure 1). A polymer dissolved in a miscible organic solvent, like acetone or acetonitrile, makes up the internal phase.

They are easily eliminated by evaporation due to their immiscibility in water. This method's basic idea is the interfacial deposition of a polymer following the organic solvent's displacement from a lipophilic solution to the aqueous phase [20].

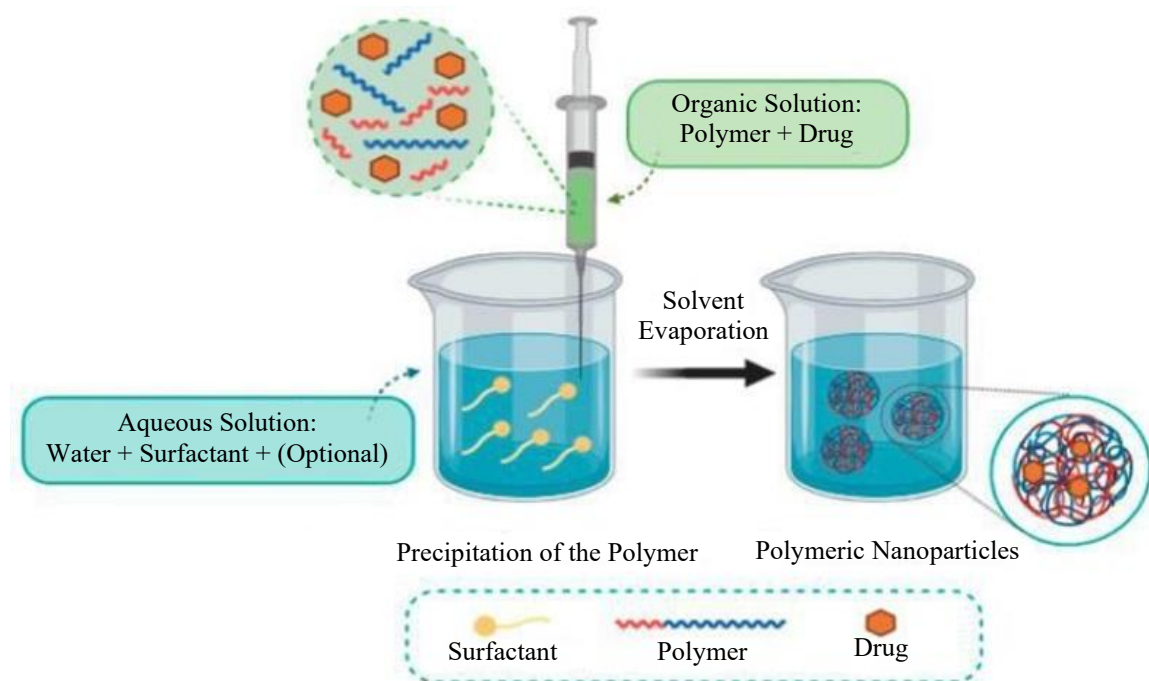


Figure 1. Nanoprecipitation method.

Solvent Emulsification–Diffusion Method

One of the most widely used techniques for encapsulating drugs in water-insoluble polymers is this one. It entails creating an emulsion with a distinct exterior phase based on the type of polymer and medication being encapsulated, then evaporating the solvent to produce the microspheres or nanospheres (Figure 2) [21].

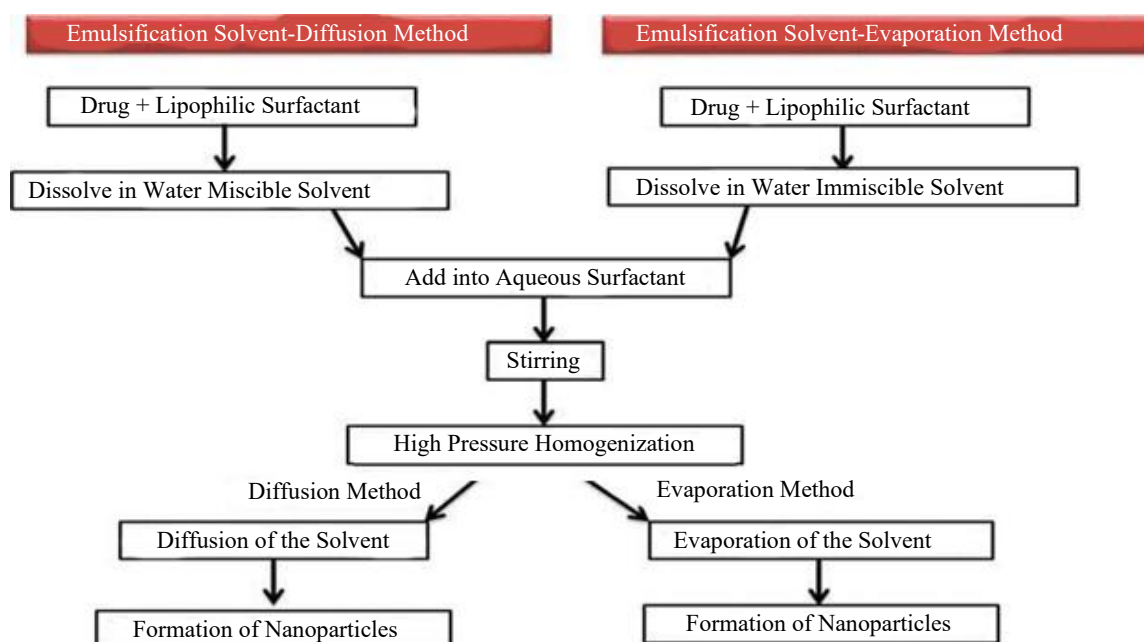


Figure 2. Synthesis of nanoparticles by the emulsification solvent–diffusion method and the emulsification–solvent evaporation method.

Supercritical Fluid Method

Depending on how SCF-CO₂ is used, SCF technology can be divided into three main categories: Using SCF-CO₂ as a solvent for active substances and their excipients (RESS, PGSS, RESOLV, RESAS, DELOS); using SCF-CO₂ as an antisolvent to precipitate active substances and their excipients in organic solvents (GAS, ASES, PCA, SAS, AS AIS, SEDS); and using SCF-CO₂ to assist spray drying or aerosolization-based techniques (CAN-BD, SAA) [22]. Many different applications, including chromatography, reaction, and extraction, have made extensive use of supercritical fluid technologies, as well as material processing. The most notable aspect of particle generation from supercritical fluid technology is the creation of microparticles or nanoparticles with distinct morphologies [23].

Self-Assembly Method

When molecules or other system components come together and organize into a regular shape without the aid of outside forces, this process is known as self-assembly. Since self-assembled structures are oriented toward the lowest energy of isolated monomers, they have lower entropy than the disordered state. Usually, the system is changed from a disordered to an ordered state through the self-assembly process, which can function on various scales. As in the case of surfactant molecules self-assembling into micelles, the molecules initially assemble into nanoscale supramolecular clusters [24]. In nanoscience, self-assembly holds a unique position. Although top–down fabrication techniques allow for the creation of designs, they are expensive, two-dimensional, and have a limited supply of materials [25].

TYPE OF NANOPHARMACEUTICALS

Liposomes

The first kind of nanomaterial used in medicine delivery was liposomes, sometimes referred to as lipid vesicles, which were initially identified in 1976. Liposomal vesicles, consisting of amphiphilic phospholipids and cholesterol, self-assemble into bilayers to encircle an aqueous core. While keeping in touch with the aquatic environment through the hydrophilic head group, the amphiphilic phospholipid molecules create a tight bilayer sphere to protect their hydrophobic core. The aqueous solution inside a liposome is surrounded by a hydrophobic barrier that prevents hydrophilic solutes from passing through the lipids [7].

Lipid film hydration, extrusion, sonication, the French pressure cell method, and freeze–thaw are examples of mechanical dispersion techniques shown in Figure 3. To manufacture liposomes, the solvent dispersion method uses supercritical fluids such as ethanol injection and reverse-phase evaporation. The two most popular mechanical dispersion techniques for creating liposomes are sonication and lipid film hydration [26].

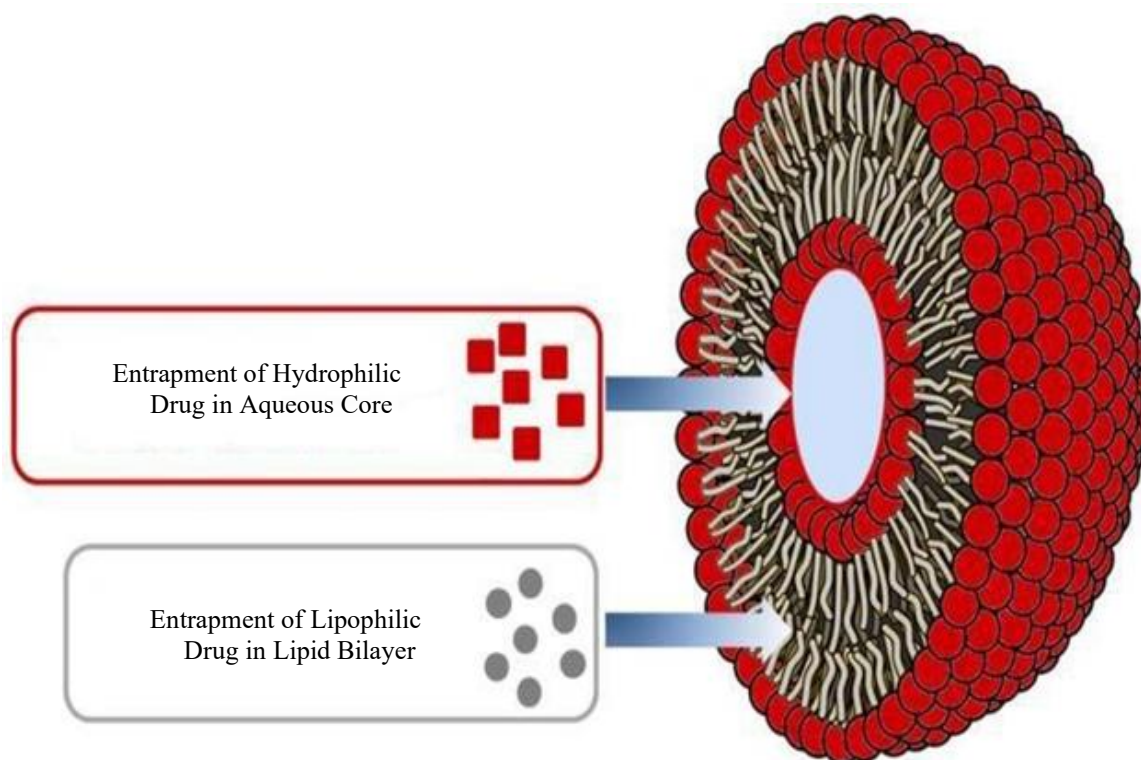


Figure 3. Liposomes.

Carbon Nanotubes

Nanotechnology is based on carbon nanotubes (CNTs). In nanotechnology, carbon, which has an atomic number of six, is essential. Iijima made the discovery of them. Made of carbon, carbon nanotubes are a tube-shaped substance with a relatively small diameter as determined by nanoscale measurements. Carbon nanotubes are created when graphenes are folded up into cylinders. Nanotubes have a diameter that is roughly 10,000 times smaller than that of human hair (Figure 4) [27].

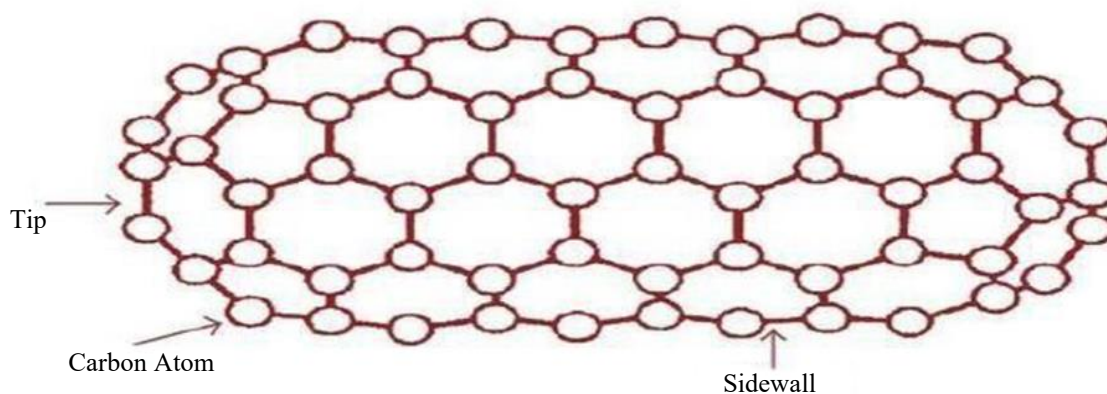


Figure 4. Structure of a carbon nanotube.

There are numerous unusual fullerene structures, including typical spheres, cones, tubes, and more intricate and peculiar forms. A few of the most well-known and significant structures are outlined here. Long wrapped graphene sheets are one way to think of single-walled nanotubes (SWNT). Since nanotubes typically have a length-to-diameter ratio of roughly 1000, they can be regarded as structures that are almost one-dimensional [28].

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) represent a promising advancement in drug delivery systems, particularly in oral solid dosage forms and lipid-based formulations. Their incorporation into pellets and minitablets enhances the solubility and stability of drugs, like indomethacin, facilitating more effective therapies for conditions such as inflammation and cancer [6]. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers further exemplify the potential of these systems by improving bioavailability and enabling targeted drug delivery while minimizing side effects (Figure 5) [29].

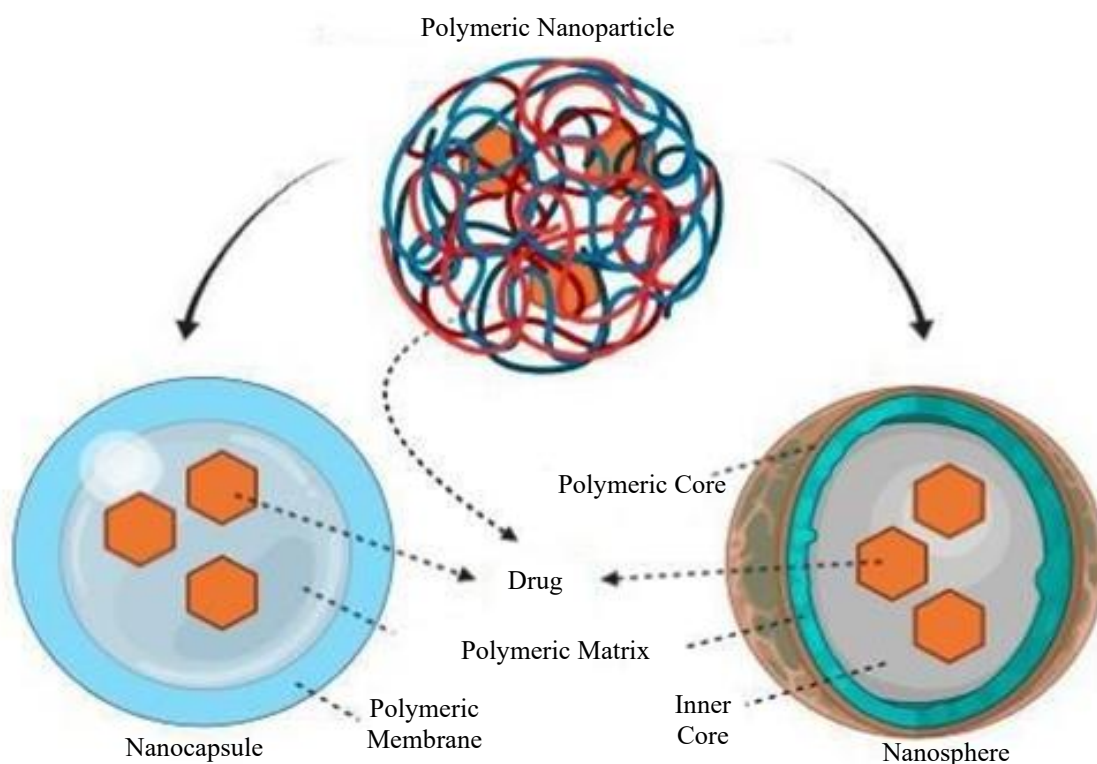


Figure 5. Schematic representation of the structure of nanocapsules and nanospheres (arrow stands for the presence of drug/bioactive within the nanoparticles).

Dendrimers

Dendrimers are hyperbranched, three-dimensional, monodisperse structures with a central core encircled by peripheral groups. Their biological and physicochemical characteristics depend on these elements. Typically, dendrimers consist of three architectural elements: a core, terminal groups connected to the branches, and branches, an internal layer composed of repeating units tied to the core. The dendritic polymer structure's internal chambers enable the medication to be deposited, improving its stability and solubility [30]. Because of their special qualities, dendrimers have several benefits over other cutting-edge drug delivery methods. They have a distinct, compact, spherical three-dimensional architecture with precise controllable surface functionality and size. This makes it possible to modify dendrimers to deliver particular medications and target particular bodily areas or cells. Dendrimers have a high drug-loading capacity because they can either attach drug molecules to their surfaces or encapsulate them inside. Additionally, surface groups can be altered to increase solubility, boost cellular absorption, or slow down the body's quick removal, all of which increase the bioavailability and effectiveness of drugs [31].

Quantum Dots

A quantum dot is a zero-dimensional substance. Every dimension falls inside the nanoscale, which is 100 nm. Their density is more acute. The range of particle sizes is 2–10 nm. The size of the quantum dot has an inverse relationship with the band gap energy. Band gap energy $\propto 1/\text{Quantum dot size}$. The band gap is larger when the quantum dot is smaller, and vice versa. Both aqueous and organic preparations are available.

When exposed to ultraviolet light, quantum dots exhibit a color glow. The emission color will exhibit a red spectral shift as quantum dots get bigger and a blue color as they get smaller. The band gap and quantum dot size determine color irradiation [32].

Metallic Nanoparticles

Nanoparticles with high surface energy combine to form thermodynamically favored bulk particles. In the absence of repulsive forces, two metallic nanoparticles will coagulate. Therefore, stabilizing the metallic nanoparticles is crucial for their spatial confinement on the nanoscale. Therefore, either steric exclusion or electrostatic stabilization utilizing a capping agent, such as a surfactant, polymer, solid support, or ligand with appropriate functional groups, can accomplish this stabilization [33]. Phytochemicals included in plant extracts reduce metal ions during the creation of metallic nanoparticles. Polysaccharides, vitamins, proteins, amino acids, saponins, alkaloids, terpenes, and phenolics are examples of phytochemicals that play a part in this synthesis. Green biogenesis of metal nanoparticles often entails combining a metal salt solution with a plant or microbial extract that contains reducing agents. As a result, metal ions are reduced to atoms and nucleated to create the first nanoparticles [34].

Polymeric Micelles

Amphiphilic polymers self-assemble at the CMC to produce micelles. A polymeric micelle is the self-assembly of an amphiphilic polymer with a hydrophilic head and a hydrophobic tail.

Micelles can have a variety of morphologies, such as spheres, tubules, inverse micelles, bottle-brush forms, and more, depending on the hydrophobic and hydrophilic segments and solvent conditions (Figure 6). Dilution, lyophilization, solvent evaporation, dialysis, and oil-in-water emulsion are some of the techniques used to create micelles. Grafted polymers, random block copolymers, and block copolymers all self-assemble into micelles [35].

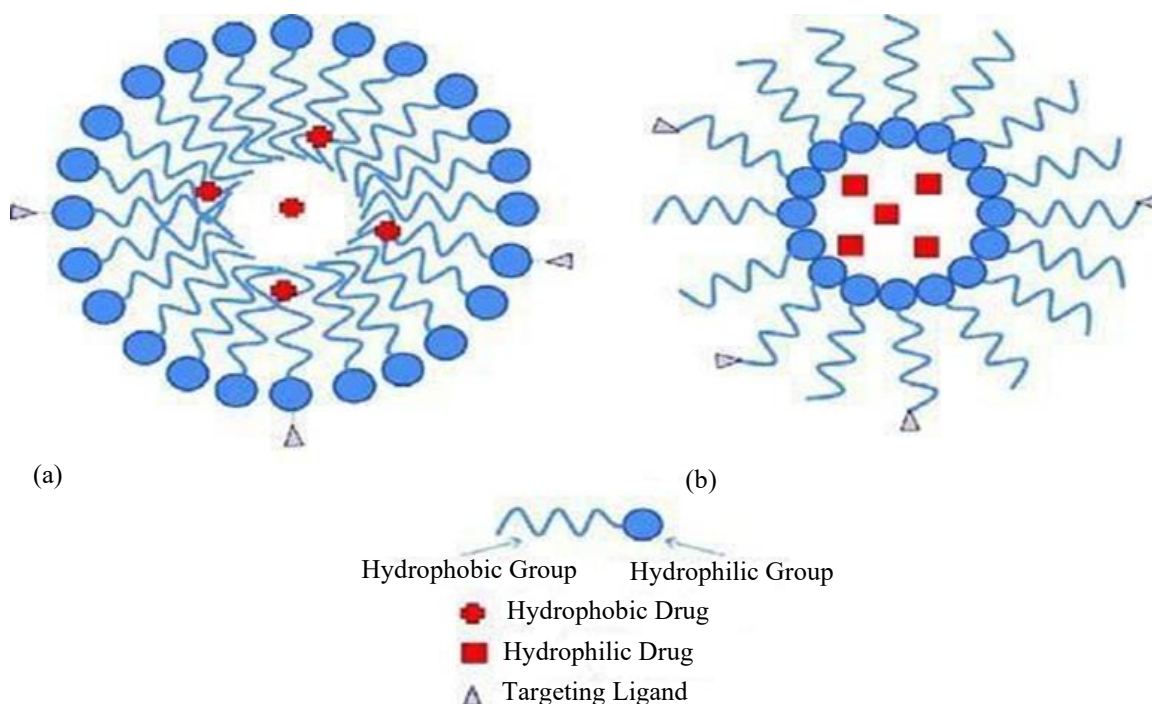


Figure 6. Polymeric micelles.

APPROACHES OF NANOTECHNOLOGY

Nanotechnology Approaches to Enhance the Bioavailability of Curcumin

Any substance's lower bioavailability within the body might be caused by low intrinsic activity, poor absorption, a high rate of metabolism, inactivity of metabolic products, and/or rapid excretion and clearance from the body. Studies have demonstrated the strong intrinsic activity of curcumin, which makes it a useful therapeutic treatment for several diseases. However, over the past thirty years, studies on curcumin's absorption, distribution, metabolism, and excretion have shown that it is poorly absorbed and quickly metabolized, significantly reducing its bioavailability [36].

Numerous curcumin nanoformulations have been created in recent years. Most of them concentrate on enhancing curcumin's solubility and bioavailability, as well as protecting it from hydrolysis inactivation. While reminders have concentrated on cellular delivery and intracellular release mechanisms, some formulations aim for long-term circulation and retention in the body. Numerous curcumin nanoformulations have had a significant impact on pharmaceutical applications and been helpful in the diagnosis of numerous human ailments. Here, they are described and discussed [37].

Nanotechnology Approaches to Enhance the Bioavailability of Berberine Hydrochloride

One of the main obstacles to BBR's market acceptance is its limited oral bioavailability. Unfortunately, investigations on BBR's absorption, biodistribution, metabolism, and elimination have revealed that the main causes of its low bioavailability are poor absorption, fast metabolism, and removal. Effective control of the P-gp-mediated efflux of BBR is one strategy to address the low gastrointestinal absorption caused by the broad intestine first-pass effect, which results in low plasma levels of BBR [38]. Traditional Chinese and herbal remedies have made extensive use of berberine as a possible therapeutic agent to treat a variety of biological problems, including cancer. According to the biopharmaceutical classification system (BCS), Berberine is categorized as a class III medication in modern medicine because of its low membrane permeability. Nanotechnology has thus created a new path for the innovative creation of medication delivery systems to enhance the treatment of cancer. Anti-cancer drug nanodelivery techniques have, in fact, been viewed as an iron gate for cancer treatment. A variety of nanoencapsulation techniques, such as magnetic nanoparticles, semi-crystalline nanoparticles, phosphor-lipid drug carriers, silver nanoparticles, mitochondrial-targeted nanocarriers, alkylated berberine, berberine-loaded liposomes, pH-sensitive lipid-based nanocarriers, electrochemical DNA biosensors, chitosan nanoparticles, niosomes, and lipo-niosomes, have been developed by modern biotechnology to maximize the benefits of this promising biological compound [39].

Nanotechnology Approaches to Enhance the Oral Bioavailability of Colchicine

Because of its limited therapeutic index and off-target cytotoxicity, COL's clinical value is still restricted, requiring creative delivery methods to improve safety and efficacy. As seen in the figure, a viable strategy is to include COL into sophisticated delivery platforms, including lipid- and polymer-based nanoparticles, hybrid systems, polymeric matrices, microneedles, and molecular conjugates. These delivery systems based on nanotechnology have several benefits [40]. In vivo, it was also shown how eugenol affected the intestinal absorption of colchicine in an oral administration nanoemulsion formulation. Eugenol was employed as an oil phase in the formulation of the colchicine nanoemulsion, which had an average particle size of 41.2 ± 7.2 nm. The nanoemulsion was made with isopropyl myristate, eugenol, Tween 80, ethanol, and water. Colchicine's penetration through the intestinal barrier in the nanoemulsion differed markedly from that of the control group (0.2 mM colchicine) [41].

Nanotechnology Approaches to Enhance the Bioavailability of Artemisinin

Despite the development of numerous therapeutic strategies, the mortality rates for leishmaniasis, cancer, and malaria are still high worldwide. An aberrant, unchecked proliferation of any kind of human body cell is indicative of cancer, a persistent illness. The two categories of causes of cancer are internal (hormones, immunological disorders, genetic abnormalities, etc.) and external (pollution, smoking, radiation, infectious pathogens, etc.). The three most prevalent cancer kinds among the others are

colorectal, lung, and breast cancer [42]. The liver's quick metabolism and short half-life (about 2.5 hours) are the causes of this poor bioavailability following oral consumption. Therefore, developing new ART formulations is essential to improving its bioavailability and selectivity [43].

Nanotechnology Approaches to Enhance Bioavailability of Genistein

Preparing stable and biocompatible drug delivery systems has been a top priority in recent decades, primarily to increase medication bioavailability. Targeting ligands, such as transferrin (Tf), folic acid, antibodies, or biotin, can be attached to medication particles to increase the effectiveness of medicinal medicines. This method reduces side effects by precisely guiding the medication to its target with less dispersion to healthy tissues [44].

Nanotechnology Approaches to Enhance the Bioavailability of Resveratrol

When opposed to oral administration, several recent studies that have concentrated on employing nanotechnology to increase resveratrol's absorption have usually shown better stability and bioavailability with fewer adverse effects. Resveratrol's effects within cells can be amplified by using nanoformulations to increase its solubility and transport across the plasma membrane. In animal studies, there is growing evidence that resveratrol nanoformulations can enhance tissue absorption by shielding the compound from metabolism during the digestive process. When compared to free resveratrol, resveratrol placed onto lipid-core nanocapsules increased tissue levels in the liver, kidney, and brain of healthy rats [45].

NANOPARTICLE SYNTHESIS

Polymer Nanoparticles

There are two categories for these polymers: Polystyrene, poly(lactic acid) (PLA), poly(lactide-co-glycolide) (PLGA), and poly(ϵ -caprolactone) (PCL) are pre-polymerized.

Polymerized in process: copolymer of aminoalkylmethacrylate methyl methacrylate, poly (isobutylcyanoacrylates) (PICA), poly (butylcyanoacrylates) (PBCA), polymethyl (methacrylates) (PMMA), and polyhexylcyanoacrylate (PHCA) [46]. Technologies or systems that release medications at preset and/or adjustable rates, or in reaction to certain external stimuli and triggers, are often referred to as controlled release systems. Because polymers have special physicochemical, synthetic, biocompatible, and degrading features, they can be employed as a controlled release method. Furthermore, polymeric nanoparticles are superior to lipidic carriers like liposomes [47].

Metabolic Nanoparticles

Approximately 20–30% of people worldwide suffer from metabolic problems. Insulin resistance, obesity, dyslipidemia, and cardiovascular disease are a few factors that can lead to metabolic disorders. To address these conditions, medications are used to measure blood pressure, hypoglycemia, and other markers like neutral fat. One drawback of these treatments is that some side effects make patients bloated and make it harder for them to accept medications. Because nanotechnology has superior biological distribution, stability, and the capacity to make natural substances more soluble, it is a potential technique [48].

A thorough discussion of the applications of metallic nanoparticles (NPs) in a variety of industries, including medicine, wastewater treatment, agriculture, etc., is provided in this article along with a critical overview of the synthesis of NPs using biological methods and several factors affecting the preparation process. Current issues highlighting the toxic effects of NPs and future perspectives in each section give us a comprehensive roadmap for the near future [49].

Magnetic Nanoparticles

MNPs, or magnetic nanoparticles, have been the focus within the last ten years. Developing several methods that can produce MNPs with specific characteristics, like size, shape, magnetic properties, and stability, have been the focus. Being compatible with living things is a critical concern that must be addressed, particularly when using them in biological applications. With time, a variety of synthesis techniques were created. Physical, chemical, and biological processes are the categories into which

these synthesis techniques fall. The techniques used in this study include thermal breakdown, coprecipitation, laser ablation, ball milling, and other physical procedures (Figure 7) [50]. Magnetic nanoparticles (MNPs) emerge as potential solutions to the aforementioned problems. Regarding the area of molecular diagnosis, they are presented as promising tools that can be utilized to develop faster, simpler, and cheaper diagnostic tests through the application of magnetic separation processes. MNPs can also be used to improve the sensitivity and specificity of MRI [51].

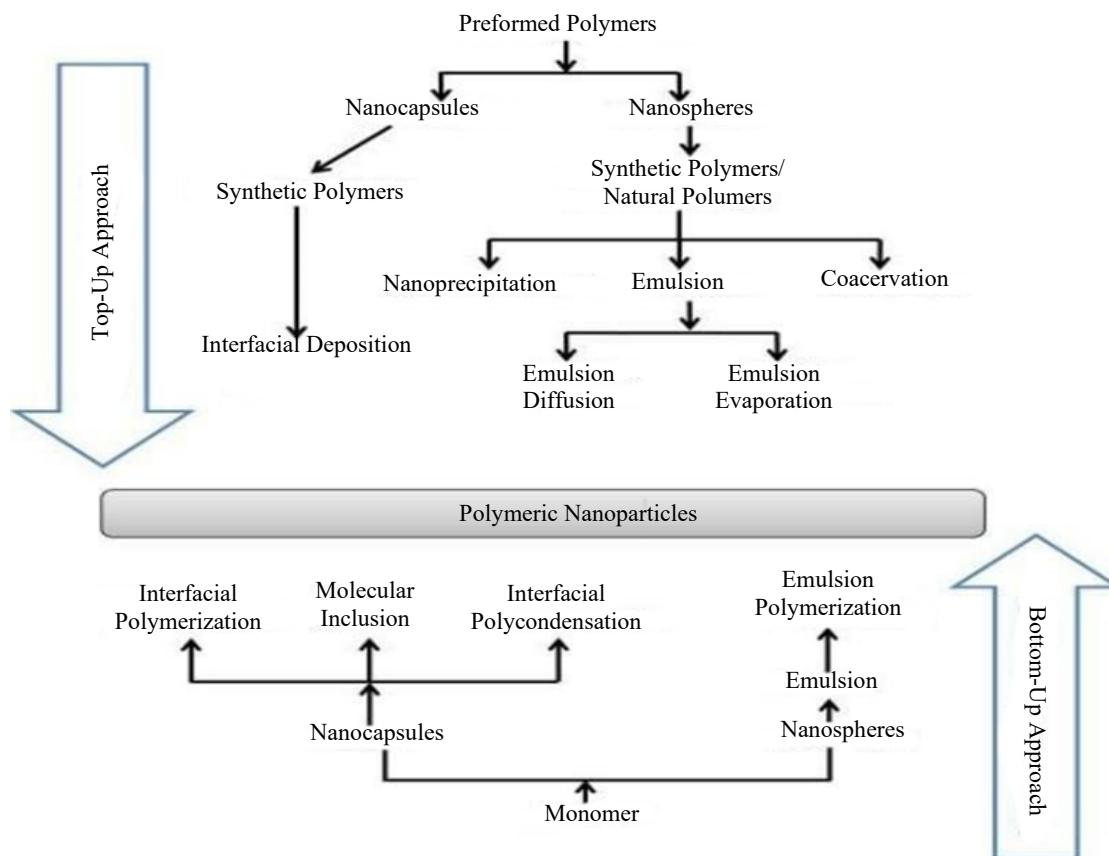


Figure 7. Top-down approach and bottom-up approach.

CHARACTERIZATION OF SYNTHESIZED NANOPARTICLES

Scanning Electron Microscope

The electron fascicle's scanning of the specimen's surface and the examination of the signal – which consists of electromagnetic waves and particles – that results from the primary fascicle's interaction with the specimen. The depth of information obtained about the material varies from 5 μm (characteristic X radiation) to 1 nm (Auger electrons). Different sorts of contrast can be seen with SEM such as magnetic contrast, atomic number contrast, and topography contrast [52]. SEM and EDX are used to assess the surface morphology and elemental makeup of nanoparticles, respectively. Both the EDX and the SEM are attached procedures. According to Hodoroaba et al. (2014), it includes an optional electron detector that provides information on the size, shape, and dispersed and agglomerated nanoparticles. Using energy-dispersive X-ray spectroscopy (EDX), elemental analysis of nanoparticles is performed and can reveal whether elements are present in the particles [53].

Transmission Electron Microscope

TEM is a type of microscopy in which an electron beam is passed through a very thin object and interacts with it as it moves through it. Electrons are observed in a spiral trajectory when the electron beam is focused on strong magnetic fields. The electrons that pass through the specimen are magnified and focused on an objective lens to create a picture that is displayed on an imaging screen [54].

Materials' interior composition can be ascertained using a high-resolution electron microscope, or TEM. It can provide information on a variety of material properties, including shape, tension, crystallization, and magnetic properties. It could take high-resolution, high-magnification pictures [55].

An EM208S (PHILIPS) transmission electron microscope running at an accelerating voltage of 100 kV and a digital camera are used in this study to examine samples of materials such as nanoparticles, nanotubes, bulk metals, graphene, graphene oxide, and polymer nanocomposites. Additionally, several materials' electron diffraction patterns are explained, and the results of these patterns are used to anticipate the structure of the materials (Figure 8). The in-situ phase characterization, microstructural observation, dislocation pile-up, and chemical composition of the in-situ nanocomposite made by planetary ball milling of Al/BN composite powders and hot extrusion, on the other hand, are assessed using TEM/STEM (STEM, JEOL JEM-2100F) equipped with an energy-dispersive X-ray spectrometry (EDS) and an operating voltage of 200 kV [56].

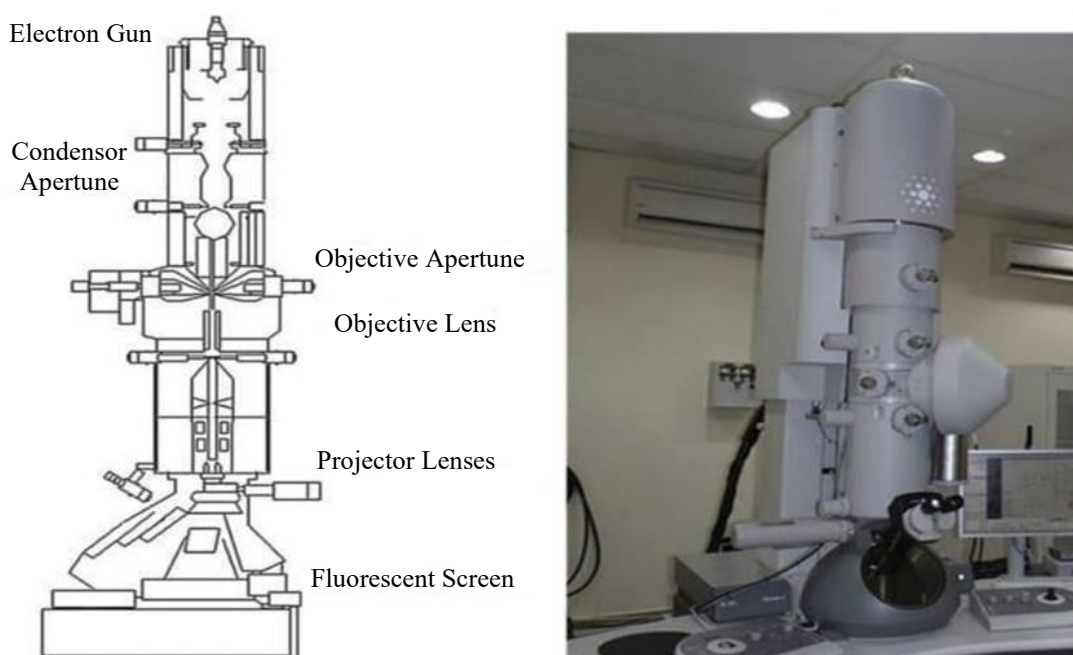


Figure 8. The transmission electron microscope (TEM) is shown along with its parts; on the other hand, the physical image of TEM has been shown. the image has been taken from (Tang and Yang, 2017), and permission has been taken to use this image by the Rights link.

Particle Size Analyzer

Size reduction efficiently increases the surface area of pharmaceuticals, which helps to speed up the development of solutions in chemical substances. Because of the larger surface area, solvents can more easily penetrate the tissues and facilitate quick extraction of active components from animal glands (such as the liver and pancreas) and crude vegetable medicines [57]. The optimal particle size to enter the lower airway and alveoli is between 1 and 5 microns. Smaller particles target regions where biofilm-forming pathogens are present, where antibiotics must pass through the mucus layer and biofilm to reach bacterial colonies, while larger particles are typically retained in the upper airway. Measurements of size fractions smaller than 10 μm in aerodynamic diameter are also crucial in these circumstances. This is due to the possibility that these particles could enter the nasal cavity and travel through the ducts that go to the lower respiratory tract or oropharynx (Mitchell & Nagel, 2004) [58].

Dynamic Light Scattering

The physical characteristics of the sample can be inferred from the scattered light of suspended particles in a colloidal suspension (Figure 3). Brownian motion causes these suspended particles in the

solution to move continuously; when an electrical potential is added, the particles reach a certain velocity. During World War II, radio frequency was developed for use in radio detection and ranging (RADAR) systems [10]. The Doppler effect was used to determine the position and velocity of particles in DLS, which was developed using the same approach. DLS measures a particle's velocity using laser Doppler velocimetry (LDV) light [59].

It is the quickest way to figure out the particle size. It is utilized frequently to determine the size of colloidal particles in the nano and submicron range. The particle size distribution can also be determined via dynamic light scattering [60].

Atomic Force Microscopy

It is desirable to have several methods for diagnosing and confirming a cancer. Multiple diagnostic techniques are required because the great biochemical diversity of diseased cells and the morphological variance within normal, dysplastic, and malignant cells undermine the traditional diagnostic procedures of cytology and immunohistochemistry [61].

After being attached to a flexible cantilever, the probe is carefully moved across the sample surface under controlled conditions, encountering a variety of forces, including Van der Waals, contact, electric, magnetic, and electrostatic forces. A laser beam is used to measure the cantilever's deflection. It is reflected off the cantilever's back and then directed onto a position-sensitive detector. The forces acting between the probe and the sample surface are then calculated using this deflection data. Contact mode, tapping mode, and non-contact mode are among the various modes of operation for AFM. When in contact mode, the tip stays in constant touch with the sample surface, and a topographic image of the surface is produced by the deflection data collected. In the tapping mode, the tip keeps in continuous contact with the sample surface, and the deflection data gathered creates a topographic representation of the surface while tapping [62].

Surface Area Analysis

At the nanoscale, surface area becomes a crucial component. Thus, the measurement of surface area is a crucial quantity when considering phenomena at the nanoscale. The surface area of the material increases at the nanoscale. At the nanoscale, the material gains unusual properties due to its increased surface area. Why, therefore, should surface area be measured? There is a direct correlation between surface area and the following factors [63].

Particle Size

When describing produced nanoparticles, the two most crucial criteria are their shape and particle size distribution. The primary uses of nanoparticles are in drug targeting and release. Most of the medications loaded onto smaller particles will be exposed to the particle surface, resulting in faster drug release. This is because smaller particles have a larger surface area. Conversely, medications gradually permeate bigger particles. One disadvantage of nanoparticle dispersion is that smaller particles have a propensity to agglomerate when being stored and transported [64].

Morphology

The cellular absorption and internalization of nanocarriers are influenced by a variety of significant criteria, including size, shape, surface charge, surface functionalization, and the interactions among these elements. The significance of managing the size and form of nanocarriers is emphasized in this section [65].

HEALTH IMPLICATIONS OF NANOPARTICLES

As we move down from the macroscopic size to the micrometer and then to the nanoscale, the characteristics and behavior of matter usually undergo significant changes. Because of these changes in characteristics, nanoparticles (NPs) and nanotechnology are very significant for a variety of applications and have a significant impact on health. For example, NPs can be used to remove pollutants from soil

and water in environmental remediation; they can be added to food and beverages to improve flavor, texture, and stability; and they can be used to deliver chemotherapy drugs directly to cancer cells, increasing drug efficacy and lowering side effects [66].

Most of the research included in this review was on evaluating the properties of nanoparticles and their effects on human health in particular. The use of nanoparticles in human health, particularly in the treatment of cancer, has shown encouraging outcomes in recent years. This is because nanoparticles have the potential to offer creative ways to overcome the drawbacks of conventional treatment modalities like chemotherapy and radiation. In contrast to traditional cancer treatment techniques, medication delivery systems based on nanoparticles [67]. Concerns regarding NPs' possible health hazards have grown as a result of their extensive use in the industries of food, electronics, medicine, and cosmetics. NPs can interact with biological systems in complicated ways, often resulting in unanticipated harmful effects, because of their small size and strong reactivity. Because airborne nanoparticles (NPs) can enter the lungs deeply and reach the alveolar region, inhaling them poses a serious risk to respiratory health. Once deposited, they can cause oxidative stress, cellular damage, and inflammatory reactions, which can result in chronic respiratory problems or worsen pre-existing lung ailments. An elevated risk of respiratory conditions, like asthma and chronic obstructive pulmonary disease, has been linked to long-term inhalation of airborne nanoparticles (NPs). Chronic inhalation of airborne nanoparticles (NPs) has been associated with illness [68].

SOLID LIPID NANOPARTICLES AND NANOSTRUCTURED LIPID CARRIERS

Nanoscale lipid particles have distinct mechanical, chemical, biological, and physical characteristics that can be very different from those of their main constituents in SLNs and NLCs (Figure 9). Therapeutic chemicals can be delivered to target tissues by encapsulation, incorporation, or surface attachment using these nanostructures, which are mostly made of lipids and surfactants [69].

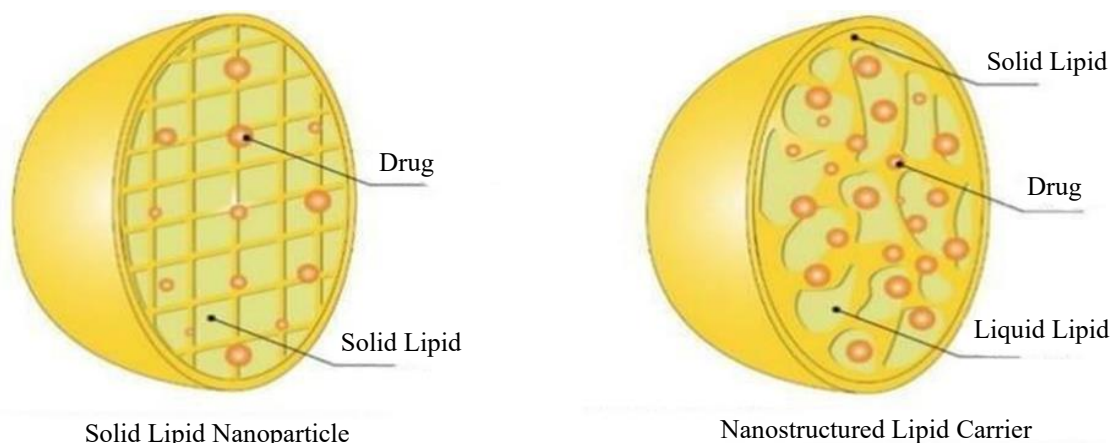


Figure 9. Structural matrix of SLN and NLC. adapted with permission from.

One crucial factor is the drug's mobility inside the colloidal nanocarriers; if it is high, leaks or releases of the medication could happen unexpectedly or in undesirable locations. This is the reason that SLNs provide a less mobile encapsulation option than lipid liquid formulations, which results in improved physicochemical stability [70].

Brain tumors are a deadly cancer due to several factors, including the complexity of the brain structure, a lack of reliable biomarkers to monitor whether a drug reaches its target location in the brain, ineffective technology, a lack of validated animal models for preclinical research, and an inadequate understanding of the pathophysiology of oncogenesis. Due to the limited drug penetration in the central nervous system and the impact of medications carried from the brain to the blood circulation, this is made even more difficult by the blood–cerebrospinal fluid barrier and the blood–brain barrier [71].

NLCs have also become more well-liked in the cosmetics sector because of their possible advantages, which include better targeting, occlusion, skin hydration, and bioavailability (Chauhan et al. 2020). Using nanostructured lipid carriers (NLCs) loaded with three active ingredients – azelaic acid (AZA), white willow bark extract (WBE), and panthenol – Arsenie et al. (2020) investigated cosmetic formulations. By mixing NLC-AZA-WBE-Ph into a Carbopol gel, a sophisticated cosmetic formulation was created that ensures a broad hydration effect [72].

Nanotized Herbal Medicines in Some Conditions/Diseases

Chronic diseases are those that have persisted for a year or more and either necessitate ongoing medical care or restrict daily activities. Cardiovascular illnesses (CVD), diabetes, hypertension, cancer, chronic respiratory conditions, and neurological problems are the main types of these diseases. Globally, chronic diseases are the leading cause of morbidity and mortality, and their incidence has increased dramatically as a result of environmental factors, aging populations, and changes in lifestyle. For example, the prevalence of NCDs including diabetes, hypertension, and CVD is rising in Bangladesh as a result of urbanization, changes in nutrition, and physical inactivity. The need for preventative measures, innovative treatments, and public health initiatives has increased due to the rise in chronic diseases worldwide [73].

Contaminated food, water, and surfaces, as well as contact with an infected person, can all spread the Giardia parasite. E. coli, Shigella, Vibrio cholera, Staph aureus, Giardia, Salmonella, protozoa, like Entamoeba histolytica, and viruses like rotavirus, are common causes of acute diarrhea. They often take less than three to four days to incubate. The primary causes of diarrhea are fever, vomiting, and abdominal pain. Significant issues result from electrolyte and fluid imbalance brought on by dehydration and fluid loss [74].

Phytochemicals are bioactive substances found in functional foods and herbal remedies that are used as medications, dietary supplements, and nutritional supplements. Additionally, these exhibit pharmacological characteristics such as immunomodulatory, antidiabetic, anti-inflammatory, antihypertensive, anticancer, antioxidant, antimicrobial, antiangiogenic, and modification of enzymatic activity. Table 2 lists phytochemicals such as terpenoids, alkaloids, glycosides, saponins, phytosterols, carotenoids, and organic acids. Functional foods include primary metabolites that contribute to their pharmacological effects, such as proteins, amino acids, carbohydrates, dietary fibers, and nucleic acids, in addition to phytochemical substances (secondary metabolites). Phytochemicals have been used to treat several illnesses, including cancer, kidney disease, diabetes, COVID-19, and Alzheimer's [75].

Challenges of Phytochemical Formulations via Nanotechnology

The main issue is that nanoparticles may be harmful. Numerous elements of nanoparticles, including proteins, peptides, antibody fragments, and nucleic acids, can act as antigens and promote immunotoxicity. Furthermore, humans would be ingesting or receiving significant quantities of nanocarriers containing surfactants, co-surfactants, or emulsifiers if the encapsulation efficacy and loading capacity of nanoparticles were poor. This could have negative consequences. The potential for long-term toxicity resulting from chronic exposure and accumulation must be carefully considered, even though clinical studies can be used to evaluate the short-term toxicity of nanoparticles [76].

To properly address the limitations of nanoparticle-based formulation processes and enhance existing approaches, formulations, and encapsulating systems, more research is required. The potential advantages of using nanoencapsulation for bioactive substances emphasize the necessity of international regulations to ensure their commercialization and safe use. The positive effects of nanostructured bioactive compounds have been demonstrated by several studies in the past, making this a promising field for additional research. Another interesting field is sustainable agriculture, where nanotechnology could maximize the delivery of plant-based chemicals for increased agricultural output while reducing environmental effects (Yadav et al., 2023). More emphasis is being paid to novel nanomaterials with enhanced biocompatibility and efficiency, which could lead to more efficient phytochemical delivery systems [77].

A scientific measure to assess the effectiveness and safety of herbal medicines is lacking. It is necessary to test the trial drug's quality for batch-to-batch matching of the active ingredients. Having active and control groups that share the same hue, aroma, and flavor of the herbal medication is quite challenging. By using the most modern clinical trial protocols and procedures, these difficulties might be lessened. More efforts should be made to integrate traditional medicine into national healthcare systems because the quality control of herbal medicines is complex and relevant, and appropriate requirements must be established for the assessment of safety and efficacy for various categorized herbal medicines To reduce cost and expenditure [78].

Specifically, combining nanotechnology with natural phytochemicals can improve tumor targeting and boost the effectiveness of anticancer drugs with improved absorption and solubility as well as fewer adverse effects. Additionally, medications, and various materials, such as DNA, RNA, fluorescent agents, and so forth, can be precisely and carefully transferred to tumor areas using nanomedicine. Better outcomes in the treatment of cancer patients may result from controlling the continuous production of anticancer medications utilizing NPs through controlled light intensity and preventing phagocytic clearance of NPs through surface changes. Furthermore, NPs provide imaging for therapeutic delivery as well as detection, diagnosis, and treatment outcome monitoring. Thus, to assess their safety, future clinical trials should assess the anticancer efficacy of different NPs [79].

Nanotechnology developments are tied to the future of modern technologies. The development of nanomaterial-based engineering techniques is making the goal of producing clean energy a reality. These materials have demonstrated great hydrogen storage capacity, functioned as effective catalysts for water splitting, and produced new generations of hydrogen fuel cells and solar cells. In the realm of nanomedicine, nanomaterials have a bright future. Therapeutic compounds can be delivered by nanocarriers [80].

CONCLUSION

Nanotechnology offers a transformative approach to enhancing the therapeutic potential of herbal medicines. By improving solubility, stability, bioavailability, and targeted delivery of plant-based compounds, nanoformulations help overcome many of the limitations traditionally associated with herbal treatments. Nanocarriers, such as liposomes, nanoparticles, and nanoemulsions enable controlled and sustained drug release, maximizing efficacy while minimizing side effects. As research continues to bridge the gap between traditional medicine and modern nanoscience, the integration of nanotechnology into herbal medicine holds great promise for the development of safer, more effective, and scientifically validated natural therapeutics. However, further studies on toxicity, standardization, and large-scale production are essential to ensure their safe and sustainable use in clinical practice.

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