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NANOFORMULATION OF HERBALS: A QUANTUM LEAP IN MEDICINAL PLANT APPLICATIONS

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ABSTRACT: Herbal medicines, with their rich history of use, often face challenges in achieving optimal effectiveness due to low absorption rates and limited bioavailability of their phytoconstituents. While these constituents are typically water-soluble, their inability to penetrate lipid membranes compromises their efficacy. To overcome these limitations, integrating herbal drugs with nanotechnology has emerged as a promising approach. Nanoparticles offer a potential solution by enhancing the absorption, permeability, and retention of herbal extracts within the body. This augmentation can lead to improved potency while minimizing the required dosage and reducing side effects. Importantly, the utilization of nanotechnology does not disrupt normal physiological processes. The primary objective of this study is to systematically explore the application of nanotechnology in crafting herbal nano formulations aimed at various pharmacological activities. Through this investigation, we aim to elucidate how nanoparticles can synergize with herbal extracts to unlock their full therapeutic potential, paving the way for enhanced herbal medicine utilization in modern healthcare practices.

INTRODUCTION: The word "nanotechnology" is derived from the Greek words "nanos," which means "dwarf," and "technology," which means "scientific knowledge." As a result of the merging of nanotechnology with medicine, new nanoparticle based drug delivery systems have been developed [1]. Since, ancient times, herbal remedies have been used extensively throughout the world to treat a wide range of illnesses and disorders. The active chemical ingredient in these remedies has successfully treated and cured a wide range of illnesses, but the potency of herbal remedies was generally lower than that of allopathic remedies, and some of their toxic side effects had also been observed [1].

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Therefore, novel drug delivery systems, many of which utilized nanotechnology, had to be developed in order to make them therapeutically more effective and much less harmful. The active chemical ingredient in the nanotechnology system of medicine is made up of very small particles that range in size from 1 to 100 nm (1 nm = 10^{-9} m). These particles are typically formed by cleaving the drug's macromolecule using a variety of techniques, which increases the drug's surface area and improves the drug's absorption, permeability, and retention time in the body. As a result, the therapeutic effect of herbal drugs is increased and the desired therapeutic effect can be achieved at lower drug dose can be achieved.

Background of Nanoparticles: According to R.D. Booker, it is difficult to sum up the history of nanotechnology for two main reasons: the word "nanotechnology" is ambiguous, and the time range relating to the early phases of nanotechnology development is unknown.

The absence of a widely acknowledged, formally established definition of nanotechnology is explained by the broad range of technologies that nanotechnology encompasses, which are based on numerous types of physical, chemical, and biological processes realized at the nanoscale. Furthermore, nanotechnologies are continually being updated and improved at this level of development, which explains why numerous ideas regarding the principles of their application are not totally obvious.

The first mention of consciously created and applied technological processes and means, which later came to be called nanotechnology, is usually associated with Mr. R. Feynman's well-known lecture delivered in 1959 at the session of the American Physical Society. For the first time, the potential of creating nanosized items using atoms as building particles was discussed in this lecture titled "There is a lot of space down there." This talk is now regarded as the birth of the nanotechnological paradigm [3].

Western European countries do nanotechnology research as part of governmental programs. Nanotechnology research in Germany is primarily financed by the Ministry of Education, Science, Research, and Technology. Nanotechnology development in England is overseen by the Council of Physics and Technology Research and the National Physical Laboratory. The National Centre for Scientific Research defines France's nanotechnology development plan. Nanotechnology development is receiving increasing attention in China, South Korea, and other growing countries. Nanotechnology research has just begun in the CIS nations, often within the context of official scientific programs [3].

Thus, the nanotechnology paradigm emerged at the turn of the 1960s, while the 1980s and 1990s marked the beginning of nanotechnology development in its own right. As a result, the entire time up to the 1950s may be regarded the pre-history of nanotechnology. The conclusion of this time saw the emergence of circumstances for regulated nanotechnology development, which was aided by the scientific and technological revolution that defined the second part of the nineteenth and the beginning of the twentieth centuries [3].

History of Nanoparticles: Lycurgus Cup, the most stunning specimen of a nanoparticle, was used to demonstrate the development of nanotechnology in the Roman Empire itself in the fourth century AD. But Paul Ehrlich's discovery of "Zauberkugel" a medication with extremely high target specificity that has no negative effects on the host cell led to the emergence of nanotechnology in medicine, ushering in the era of nanomedicine around the turn of the 20th century.

Unbeknownst to them, colloidal solutions of iron carbohydrate nanoparticles had been utilized in clinical settings for 10 years prior to Feynman's call to arms and for a full 25 years before Norio Tanaguchi first introduced the word "nanotechnology" in 1974.

The first nanomedicine, iron sucrase, was approved as an intravenous formulation in Switzerland in 1949. Asparginase, in its PEGylated version, or Pegaspargase, was the first FDA-approved medication in 1994 and was used to treat lymphoblastic leukemia.

The US National Science and Technology Council (NSTC) launched an initiative for nanotechnology in 2000 that facilitated nanoscale-related research and gave rise to nanomedicine as a new scientific principle because it appeared to be beneficial in the treatment and diagnosis of disease by understanding its biological interaction.

Yashuhiro Matsumura and Hiroshi Maeda first detailed the effects of "enhanced permeation and retention" in 1986. They found that doxorubicin nanoparticles penetrated malignant tissue more deeply than healthy tissue, which revolutionized the treatment of cancer.

Because of this, more than 15 original concepts have been proposed for use in treating cancer. More than 600 applications for the approval of novel drugs were registered in the US, but only 14% of them successfully completed phase 3 after completing phase I trials with ease (94%) [4].

Nanotechnology: It is derived from Greek word “Nano” In Greek word “Nanos” means (dwarfs), “Tech” in Greek “Techne” means (Manmade) and “Logy” in Greek “Logos” means (To Read). So Nanotechnology exactly means doctorate of the

artificial mastery of tiny things. They are as small as quark roughly the same proportion of tennis ball is to the earth. It is based on the scale of nanometer i.e. $1nm=10^{-9}m$ [5].

Since, advances in nanotechnology offer benefits like modified release systems and the potential to create new formulations that weren't previously possible (due to a number of factors related to the active constituents), the pharmaceutical industry has grown increasingly interested in them.

Although the contributions of nanotechnology are helpful in a number of medical fields, it is important to draw attention to specific drawbacks. The simple incapability of nanoparticles, which can result in hazardous lung diseases and frequently lead to other diseases that might lead to changes in homeostasis, or even mortality, have been cited by clinical researchers as negative reasons. Other negative factors mentioned include high cost, difficulties scaling up procedures, and high cost.[6]

Pharmaceutical industries have become increasingly interested in nanotechnological advances because these developments provide advantages, such as modified release systems and the potential to develop new formulations that were previously not possible (due to several aspects related to the active constituents [6].

Properties of Nanoparticles: The optimal nanoparticle drug delivery system should be capable of locating, identifying, binding to, and delivering its load to specific diseased tissues while minimizing or preventing drug-induced harm to healthy tissues. Thus, the most popular tactic is to encapsulate particular targeted ligand(s) on the surface of nanoparticles. Small compounds, peptides, antibodies, specially engineered proteins, and nucleic acid aptamers could all be used as these targeted ligands [7].

Mechanical: The mechanical characteristics of nanomaterials are primarily determined by the type of bonding that binds their component atoms and microstructures together throughout a wide range of length scales. Mechanical deformation can be reversible (elastic) or irreversible (plastic). Elastic nanomaterials respond to stress fields with strain fields, liquids with viscous strain rates, and complicated fluids with frequency-dependent viscoelastic responses. Many features of crystals, magnets, liquid crystals, superconductors, super fluids, and early universe field theories may be characterized by concentrating on large length scales and assuming that the materials are in close equilibrium. Plastic materials, on the other hand, can be described as irreversible deformation, for which many processes may be responsible: Amorphous material dislocation motion, vacancy motion, twinning, phase change, or viscous flow. The Hall-Petch relationship, which states that the yield stress and hardness are inversely proportional to the square root of the grain size, is well known for polycrystalline materials. The accumulation of dislocations at grain borders is responsible for the strengthening at smaller grain sizes. However, in the Nanocrystalline regime, the traditional Frank-Read dislocation sources fail to manage the deformation caused by stress to bend out a dislocation when it approaches the predicted shear strength. The mathematical relationship between yield stress and grain size is stated by Hall Petch relationship [8].

Thermal: Heat transport in NPs is largely determined by energy conduction caused by electrons and photons (lattice vibration), as well as the scattering effects caused by both. Thermal conductivity, thermoelectric power, heat capacity, and thermal stability are the primary components of a material thermal capacities & thermal characteristics. The electrical and thermal conductivity of NPs is directly affected by NP size. As the NP size drops, the particle surface area to volume ratio grows hyperbolically. Because electron conduction is one of the two major ways heat is carried, the larger surface-to-volume ratio in NPs gives a greater number of electrons for heat transmission compared to bulk materials via micro convection, which is caused by NPs Brownian motion.

Furthermore, micro convection, which comes from NP Brownian motion, promotes heat conductivity in NPs. However, this effect occurs only when solid NPs are disseminated in a liquid (creating a Nanofluid). When compared to equivalent bulk materials, NPs typically have a significantly lower melting temperature. The primary cause of this phenomena is because the average liquid/vapor interface energy is lower than the average

solid/vapor interface energy. When particle size reduces, the surface-to-volume ratio rises, and the melting temperature falls due to increased free energy at the particle surface [9].

Magnetic: Magnetic nanoparticles & chemical characteristics physical and chemical characteristics are mostly determined by their chemical structure and technique of manufacture. These nanocomposite magnets can provide high energy products and reasonably high coercivities. These magnets have a high remanence value and are inexpensive. Magnetic research in nanostructured materials have concentrated on the interaction of electron charges and magnetic spins, leading to the discovery of novel and unique phenomena that are neither visible in standard bulk materials nor explainable by classical theories [10].

Optical: Nanomaterial optical characteristics such as absorption, transmission, reflection, and light emission are dynamic and may differ dramatically from bulk material properties. By simply altering its form, size, and surface functioning, a wide range of optical effects may be achieved for a number of purposes. Depending on the composition, size, and orientation, this manipulation can be accomplished in a variety of ways. The optical quality of nanomaterials is critical in a number of ways. They are capable of restricting their electrical characteristics to generate quantum effects, with variations in form, size, or type influencing the color they produce. The optical characteristics of nanomaterials are known to be dependent on their internal electronic structure, which allows for a thorough knowledge of their structure. The color visible in nanomaterial is caused by the surface plasmon resonance phenomenon, which happens when the outer electron band of nanomaterial resonates with light wavelengths. The mathematical link between particle size and color can be stated. Various spectroscopic methods can be used to determine optical characteristics. The energy of the highest occupied molecular orbital and the lowest empty molecular orbital is affected by the reduction in the dimensionality of its electronic structure [11].

Electrical: Materials are frequently classed based on their capacity to conduct current. Conductivity is characterized in terms of electron characteristics in solids. The inverse of conductivity is resistivity. Metals have extremely low resistance (10-6 ohms.cm). Semiconductors have low resistance (a few ohms cm), whereas insulators have high resistivity. In theory, solid resistivity (or conductivity) may be measured by attaching electrically conducting wires to a solid material of known shape, applying a voltage differential across it, and measuring the current flowing through it. Ohm law governs the passage of current through it. Current voltage is a linear graph for a metal. In general, nanoparticles have higher resistivity than polycrystalline materials. Electrons are dispersed at grain boundaries, causing resistance to rise. As a result, polycrystalline materials have higher electrical resistance than matching single crystal materials. There are more boundaries in materials with nanocrystalline grains than in polycrystalline materials with micrometer-sized grains. As a result, the resistivity of materials with nano-sized grains is often fairly high [12].

Catalytic: Surface atoms are stated to be in a condition of physical instability and are chemically active and are prone to performing various chemical reactions. The primary and decisive factor for the appearance of catalytic capabilities in nanomaterials is their extremely high surface-to-volume ratio. The greater this ratio, the greater the catalytic capabilities of nanomaterials due to an increase in surface energy. In theory, these changes are caused by changes in the electronic structure of materials, which may be explained by quantum mechanics. When the particle size is too tiny, the density of the capacitance band states varies, resulting in a collection of distinct levels. As the particles decrease, they eventually get so large that the surface of the particles is separated by an order of magnitude electron wavelength. The quantum mechanical behavior of a particle in a box may be used to simulate energy levels in this circumstance. This is known as the quantum size effect. The creation of novel electron characteristics may be explained using Heisenberg's uncertainty principle, which asserts that the more sparsely an electron is confined, the greater its range of motion [13].

Particle size and Surface area Characterization: To estimate the size of the NPs, many methodologies may be utilized. SEM, TEM, XRD, AFM, and dynamic light scattering (DLS) are a few examples. Although SEM, TEM, XRD, and AFM

can provide a better understanding of particle size, the zeta potential size analyzer/DLS can be utilized to determine NPs size at an incredibly low level. In addition to DSC, nanoparticle tracking analysis (NTA) is a relatively modern and unique technology that can be useful in the case of biological systems such as proteins and DNA. We can see and analyze NPs in liquid medium using the NTA approach, which connects the Brownian motion rate to particle size. This approach allows us to determine the size distribution profile of NPs in a liquid media with diameters ranging from 10 to 1000 nm. When compared to DLS, this approach gave some good findings and was shown to be quite exact for sizing monodisperse as well as polydisperse samples, with significantly greater peak resolution [14].

Classification of Nanoparticles:

Classification Based on Dimensions [15]:

Class
One dimension nanoparticle: nanorods, nanotubes, nanobelts, nanoribbons
Two dimension nanoparticle: carbon nanotubes, nanofilms, nanolayers
Three dimension nanoparticle: fullerenes, dendrimers, quantum dots

Classification Based on Carbon [16]:

Class
Fullerene
Carbon nanotubes
Graphene
Carbon nanofiber
Carbon black

Classification Based on Metal Oxides [17]:

Class
Aluminium oxide
Cerium oxide
Iron oxide
Magnetite
Silicon dioxide
Titanium dioxide
Zinc oxide

Classification Based on Metals [18]:

Class
Aluminium nanoparticles
Gold nanoparticles
Silver nanoparticles
Cadmium nanoparticles
Cobalt nanoparticles
Copper nanoparticles
Iron nanoparticles
Lead nanoparticles
Zinc nanoparticles

Classification Based on Lipids [19]:

Class
Liposomes
Solid lipid nanoparticles
Nanostructured lipid carriers
Nano emulsions

Need of Nanoparticles: Hydrophobic and hydrophilic medications can be distributed throughout the body thanks to the employment of several types of nanomaterial in nanoparticles. As the human body is mainly made of water, one of the main therapeutic advantages of nanocarriers is their capacity to transport hydrophobic medications to patients in an efficient manner [20].

Drug delivery uses nanoparticles, particularly in chemotherapy. Nanocarriers have the ability to reduce the toxicity of many chemotherapeutic medications because they can be employed to selectively target the small pores, lower pH, and higher temperatures of malignancies. Additionally, because nearly 75% of anticancer medications are hydrophobic and consequently have trouble entering human cells, using micelles to maintain and successfully hide the hydrophobic properties of hydrophobic medications opens up new options for hydrophobic anticancer medications [21].

As a result of the greater active surface energy, there is a increasing in the bioavailability and binding receptor selectivity of herbal medicine when it is administered in nanoparticle form, which would increase the potency and safety of the active ingredient. Formulations containing nanoparticle herbal active components have become known as nano-phytomedicines in recent decades due to their unique nature, broad appeal, and efficacy. The potential for herbal drugs with nanoparticle drug delivery structures to improve processes and address issues with plant-based medicine is growing [22].

Targeted Drug Delivery: Because of the broader epithelial associations, nanoparticles are capable of travelling through inflamed or injured tissue. This penetration can take place either passively or actively. The drug carrier system is linked to a tissue or cell-specific ligand for active targeting, whilst the nanoparticle enters the target organ through leaky junctions for passive targeting.

Liposomes are another valuable finding that can help with medication distribution. Because they imitate the cell membrane, individual lipid monomers may be designed to control physicochemical features like as size and charge, as well as integrate surface targeting ligands as previously stated. Because the liposomal composition is comparable to that of the targeted cell membrane, an increased [23].

Increased Absorption & Bioavailability: Drug nanoparticles have increased solubility and hence better bioavailability due to their tiny size and wide surface area, as well as the capacity to penetrate the blood brain barrier (BBB), enter the pulmonary system, and be absorbed through the tight connections of skin endothelial cells. Nanoparticles made from natural and synthetic polymers (biodegradable and non-biodegradable) have received the most attention because they can be tailored for targeted drug delivery, improved bioavailability, and controlled release of medication from a single dose; through adaptation, the system can prevent endogenous enzymes from degrading the drug [24].

Increased Duration & Plasma Half-life of Drug: Endocytotic mechanisms such as caveolar- and clathrin-mediated endocytosis, potocytosis, pinocytosis, and patocytosis can allow nanoparticles to enter cells. Larger particles, on the other hand, can be swiftly opsonized and eliminated from the circulation by reticuloendothelial system (RES) macrophages. It is vital to minimize opsonization and extend the circulation of nanoparticles in therapeutic application while designing nanoparticle formulations. Surface coating of nanoparticles with hydrophilic polymers/surfactants and/or formulation of nanoparticles with biodegradable copolymers with hydrophilic segments, such as polyethylene glycol (PEG), polyethylene oxide, poloxamer, poloxamine, and polysorbate 80 (Tween 80), can achieve this. Because of their rich sulphate sialic acid and sugar moieties, nanodrugs with a positive surface charge can interact with the negative charges of mucin, resulting in accelerated transportation across mucus and higher internalization by epithelial cells. Strategic functionalization with membrane permeability enhancers or ligands for cellular membrane receptors may potentially boost transcellular transport of entrapped medicines. In addition to transcellular transport, nanodrugs containing bio adhesive polymers or chelators may improve entrapped drug paracellular trafficking via tight junction modulation [25].

Reduction in Drug Dosages and Dosing Regimen: Because particle size is reduced in nanoparticulate formulation, the surface area of the particle increases, resulting in increased drug solubility and availability, and thus plasma concentration required to achieve therapeutic effect is achieved in low doses and dose concentration, and thus use of nanoparticle formulation reduces drug dosing and dosing regimen [26].

Nanoparticulate Herbal Drug Delivery System: Currently developing, herbal nanotechnology offers a wide range of views in the medical field. Due to their greater therapeutic activity and minimal side effects, herbal medications are becoming more and more popular these days. However, due to their dosage, palatability, and administration method, these medications are not preferred by patients. To get around this, it needs to be modified to make it widely accepted.

There are various issues with the stability and bioavailability of herbal preparations. Therefore, it should be enhanced to address any such shortcomings. Because nanocarriers may permeate plasma membranes and deliver medications in the desired concentration at a specific site of action, the delivery of these drugs can be improved. They also increase the bioavailability of herbal medicines.

Combining nanotechnology with herbal medicines may result in the best medications to treat a variety of disease conditions [27]. Biologically active components such flavonoids, volatile chemicals, polyphenols, tannins, terpenoids, resins, and others are present in the majority of herbal plants which are responsible for giving biological effects. However, due to their high molecular size and poor capacity to permeate lipid membranes, these elements exhibit poor absorption, which further contributes to their reduced bioavailability and effectiveness. Lipid crystal systems, solid lipid nanoparticles, liposomes, and polymeric nanoparticles are a few of the emerging

nanotechnologies. These methods improve the drug's solubility, bioavailability, stability, and other qualities [28]. The highly acidic pH of the stomach will cause many of the active components of herbal medications to break down, and some of these components will be metabolized in the liver, preventing the bloodstream from receiving the full therapeutic dose. There will be less of a therapeutic effect from the drug if it does not enter the bloodstream. The particle size of the herbal drug is decreased by the use of nanotechnology, allowing it to get over obstacles including an acidic pH, liver metabolism, and it enhances the circulation of drug into the blood. Therefore, decreasing particle size will increase surface area, which will further increase absorption [29].

Nanotechnology used for Herbal Medicines:

Method for Emulsion Inversion Point: The EIP is a low energy approach that is based on catastrophic phase transition. When water (aqueous medium) is titrated with a mixture of oil and hydrophilic surfactant, the catastrophic phase develops due to the significant oil phase: water phase ratio at the beginning of the titration, an unstable without emulsion was created. The addition of water causes a number of changes in the oil and hydrophilic surfactant mixture that result in catastrophic phase inversion (CPI). Important parameters for the EIP process include the flow rate of the aqueous phase over the oil phase, the concentration, the kind of stirring, and the type of surfactant utilized [30].

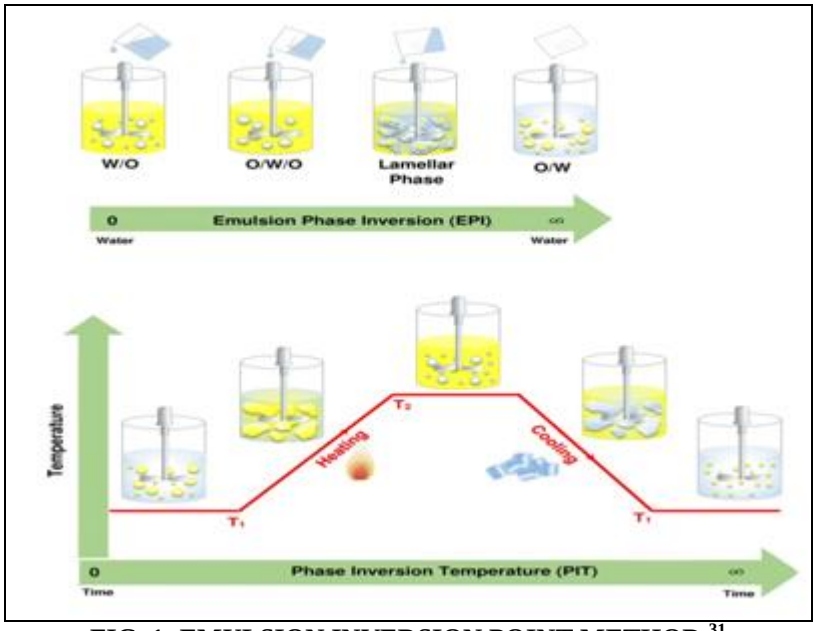

FIG. 1: EMULSION INVERSION POINT METHOD [31]

Fessi Method: The Fessi method was employed to create curcumin nanoparticles after the turmeric was dissolved in an appropriate solvent and sonicated. With vigorous agitation, the resulting solution was added to clean water and a suitable surfactant [32].

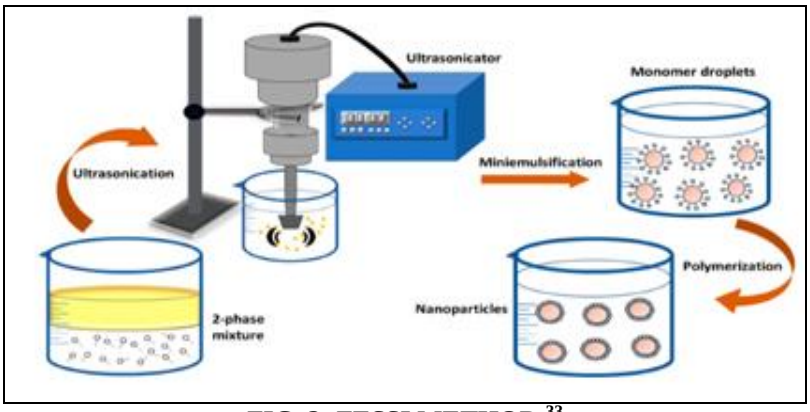

FIG. 2: FESSI METHOD [33]

Thus, using this technique, curcumin nanoparticles were produced spontaneously. Curcumin is dissolved in a suitable solvent under sonication conditions in this technique of production. With steady stirring, the resulting solution is added to clean water along with a surfactant. Curcumin nanoparticles may be synthesized spontaneously using this approach. Curcumin nanoparticles were created using this technology. This is a straightforward way for producing nanoparticles [33].

Ionic Gelation Method: In this method, hydrophobic drugs were completely dissolved in a suitable solvent before being combined with polymeric solutions while being constantly stirred. This technique is dependent on the drug's polymer and polymer's ability to crosslink. Curcumin, a hydrophobic medication, is dissolved in a suitable solvent that demonstrates 100% solubility of curcumin in it, and this solvent is then added to a polymeric solution under continual stirring conditions. This approach is based on the cross-linking of polymers with drugs such as curcumin. Chitosan was employed as a polymer in the manufacture of curcumin nanoparticles. This polymer increased the solubility and stability of curcumin nanoparticles.

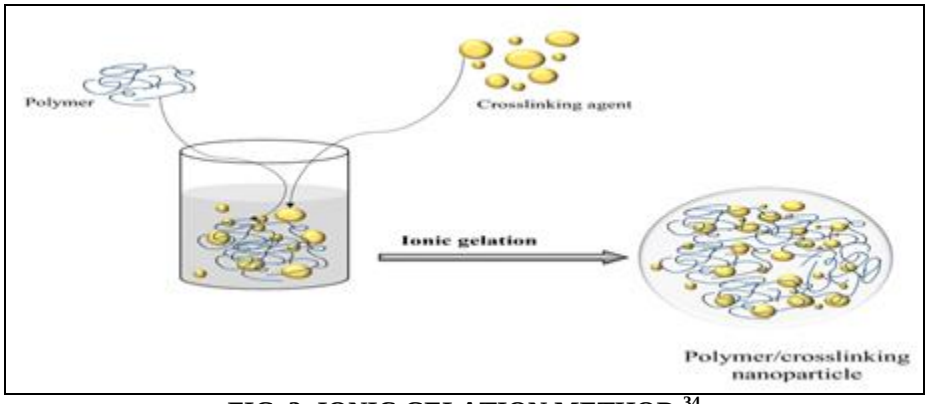

FIG. 3: IONIC GELATION METHOD [34]

Antisolvent Precipitation Method: In the antisolvent approach, which is used to create hydrophobic pharmaceuticals, the drug is first dissolved in an organic solvent before being introduced to deionized water while being constantly stirred. The technique of synthesis of the weakly water-soluble medication is antisolvent precipitation. Curcumin is dissolved in an organic solvent before being added to deionized water with steady stirring in this technique of production. As a result, curcumin nanoparticles may be synthesized using this technology. This approach was used to create curcumin nanoparticles. This method of synthesis has the advantage of being suited for the production of poorly soluble curcumin nanoparticles [35].

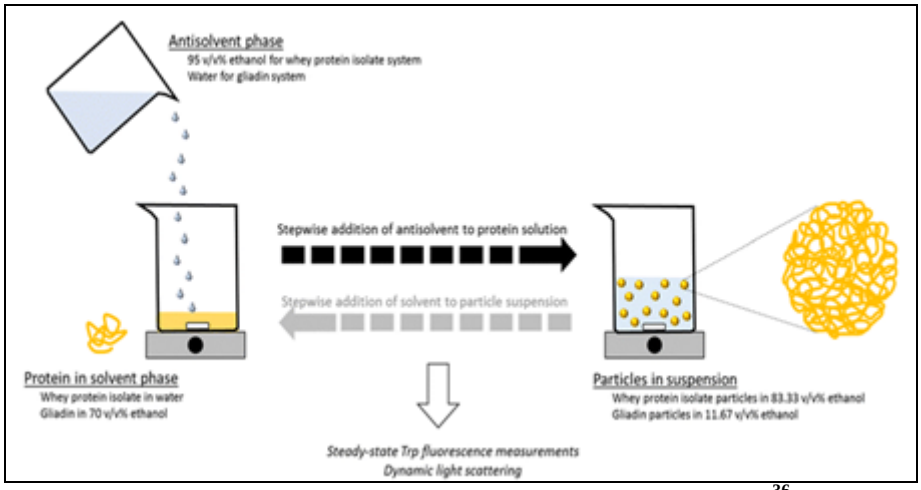

FIG. 4: ANTISOLVENT PRECIPITATION METHOD [36]

Supercritical Fluid Method: This approach is useful for manufacturing nano-sized formulations. A supercritical fluid (SCFs) is liquid or gas that is utilized above its thermodynamic critical temperature and pressure. Carbon dioxide and water are most often utilized SCFs.

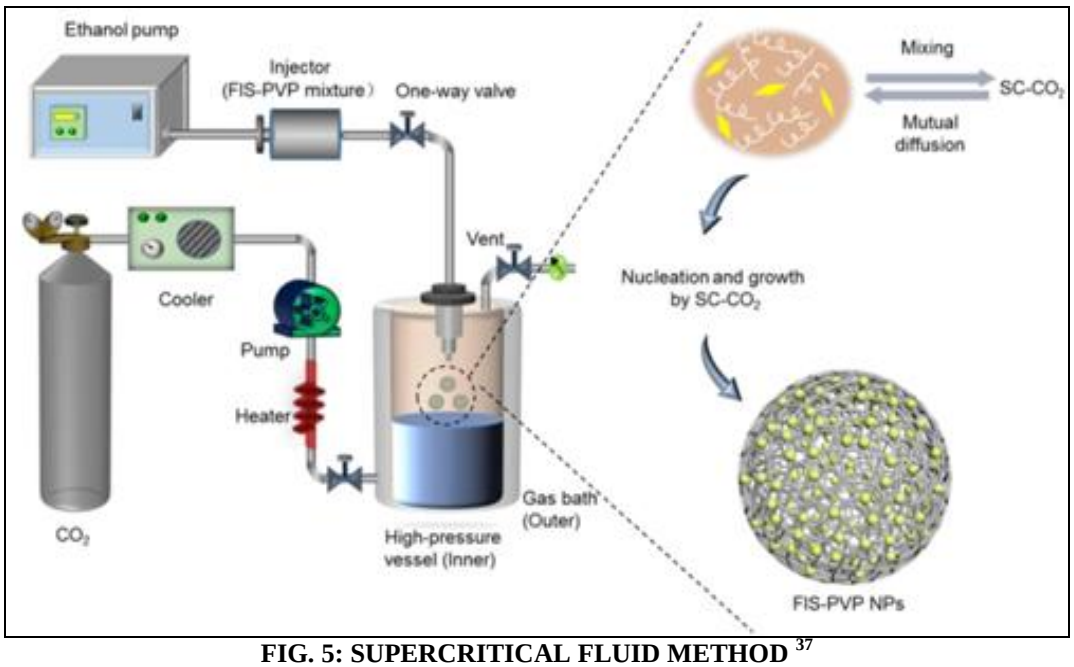

FIG. 5: SUPERCRITICAL FLUID METHOD [37]

Self-assembly Method: It is the physical process in which pre-existing disordered components organize themselves into nanoscale structures by physical or chemical reactions without any external source. This spontaneous assembly of nanoparticles is the result of particle interactions aimed at establishing thermodynamic equilibrium and lowering the system's free energy. Nicholas A. Kotov proposed the thermodynamic concept of self-assembly. He defines self-assembly as a process in which system components acquire non-random spatial distributions with regard to each other and the system's boundaries. This formulation accounts for mass and energy fluxes that occur during self-assembly processes.

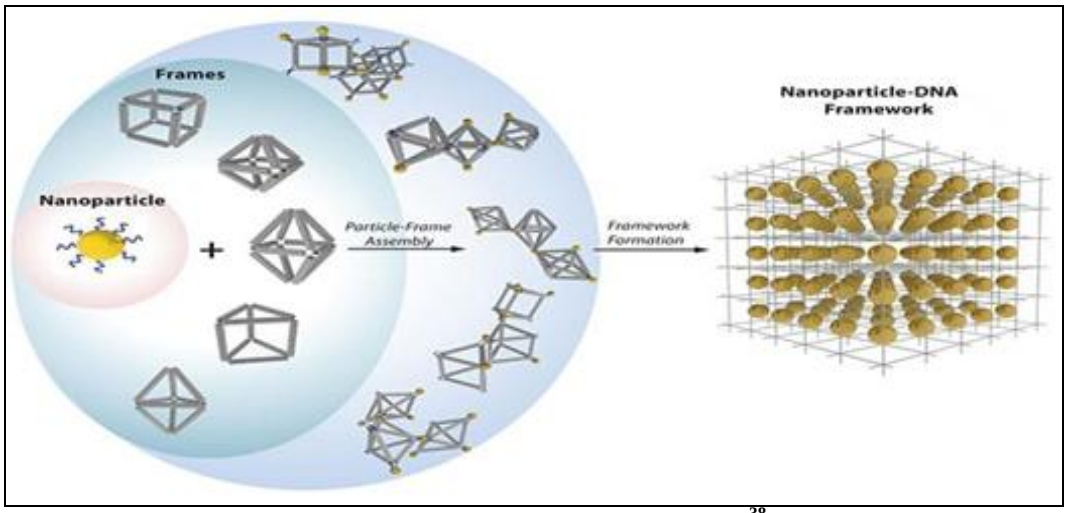

FIG. 6: SELF-ASSEMBLY METHOD [38]

High-pressure Homogenization Method: In this approach the lipid is driven with high pressure (100 to 2000 bar) via a very high shear stress, resulting in breakdown of particles to the sub micrometer or nanometer range. High-pressure homogenization method is a very useful technique for manufacturing of nanostructured formulations.

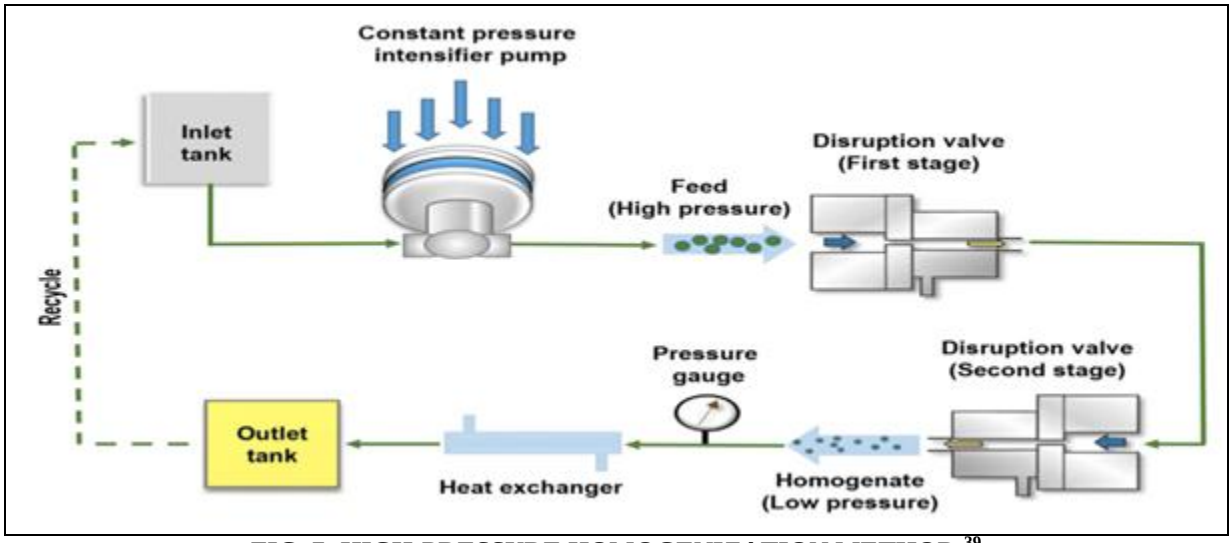

FIG. 7: HIGH-PRESSURE HOMOGENIZATION METHOD [39]

Nano Formulation:

Nano Emulsion: Nano emulsion is additionally known as micro emulsion, which is a fine oil/water or water/oil dispersion stabilized by an interfacial coating of surfactant and molecule with particle sizes ranging from 22 to 600 nm. They are open and honest. The emulsifying agent, aqueous phase, and oil are the primary components of nano emulsion. Emulsifying agents, often known as interfaces, are in charge of stabilization. Oil in water nano emulsion, water in oil nano emulsion, and bi-continuous nano emulsion are a variety of nano emulsion. A colloidal dispersion type known as nano emulsion has the potential to increase the bioavailability of many active drugs. Nano emulsions have good stability, quick digestion, degradation resistance, controlled release, and a great capacity for increasing medication bioavailability. Furthermore, nano emulsions may be manufactured with significant flexibility to deliver several drug moieties with varying properties. To create nano emulsions with variable physicochemical and biological features, the oily phase can be created with various lipids and oils such as triglycerides and essential oils. The aqueous fraction might be controlled further by adding other water-soluble components. The nanoscale size of the emulsion is responsible for the increased bioavailability of several medicines [40].

Nanoparticles: Nanoparticles are also referred to as 'zero-dimensional' nanomaterials. (Ahmad *et al*, 2017) Nanoparticles with sizes ranging from 1 to 100 nm. At present, varied metallic nanoparticles are made utilizing copper, zinc, titanium, magnesium, gold, and silver, (Saharkhiz *et al*, 2015) and they can be synthesized using a variety of methods including chemical, physical, microbiological, and green synthesis. Nanoparticles are divided into several categories based on their size, shape, and material qualities. Some classifications divide nanoparticles into organic and inorganic categories; the former includes dendrimers, liposomes and polymeric nanoparticles, while the latter includes fullerenes, quantum dots, and gold nanoparticles. Other classifications split nanoparticles into carbon-based, ceramic, semiconducting, and polymeric nanoparticles. Because NPs are not simple molecules, they have three layers. The surface layer, which may be functionalized with a range of small molecules, metal ions, surfactants, and polymers. The shell layer, which is chemically distinct from the core in every way, and the core, which is essentially the centre section of the NP and typically referred to the NP itself [41].

Nanosphere: They are colloidal Nano formulations made from hot oil in water microemulsions that have the advantage of being constructed with biocompatible lipids. They can also avoid precipitation of the main product (drug). They have been determined as artificial lipoprotein-like particles with sizes ranging from 25 to 50nm. The medicine is dissolved, entrapped, encapsulated, or bonded to a polymer matrix. Nanospheres can be amorphous or crystalline in form, and they help to protect the medicine against chemical and enzymatic breakdown.

A medication will be equally distributed as well as physically and uniformly dispersed in the matrix of this polymer. Biodegradable nanospheres and nonbiodegradable nanospheres are the two types of nanospheres. Albumin nanospheres, polypropylene dextran nanospheres, gelatine nanospheres, and modified starch nanospheres are examples of biodegradable nanospheres [42].

Nano Capsule: Nano capsules comprise of a solid/liquid core which holds the medicine and is surrounded by a distinctive polymer membrane made from synthetic or natural polymers. Because of the protective coating, they are more stable and do not oxidize readily. The size of nano capsules ranges from 10 nm to 1000 nm. The nano capsules are nanovesicles because they are made up of a polymeric matrix that forms the shell and an oily core that is associated with surfactants that can be hydrophilic or lipophilic. The active compounds used in this system might be solid or liquid. Furthermore, if the active ingredient is lipophilic, it may be solubilized in the core or adsorbed on the polymeric matrix, depending on its solubility. Liposoluble compounds dissolve readily in the core, but amphiphilic chemicals have a higher affinity for the polymeric matrix. Because of these qualities, this system may be classified as a reservoir-type system, and the active substance's release is determined by the affinity between it and the system components. The particle size of nano capsules differs from that of microcapsules. The nano capsules have a diameter less than 1 m, with optimal sizes ranging from 100 to 500 nm [43].

Nanogel: Nanogels are ionic or non-ionic nanoparticles that are made up of physically or chemically cross-linked polymers that can be hydrophilic, hydrophobic, or amphiphilic. These are designed to be extremely successful in increasing the drug payload at the target site while also controlling the leaking propensity of other nanocarriers. Nanogels, which have diameters ranging from 1 nm to 1000 nm, have properties of both hydrogels and nanomaterials. Nanogels are most commonly utilized in nanomedicine as innovative drug carriers for response-based treatment. A new drug carrier should have two primary characteristics: it should carry the medication at the desired rate and it should deliver the drug to the site of action effectively. As a result, nanogels have numerous sophisticated qualities to meet the demand for modern medications. Nanogel is defined by the US Pharmacopoeia as "a semisolid system consisting of a dispersion of either small inorganic particles or large organic particles enclosed and interpenetrated by liquid." Nanogels have crucial properties such as improved medication absorption across the physiological barrier and prolonged drug release. Nanogels outperform conventional transdermal delivery methods in terms of drug release kinetics stability and control. Nanogels are employed for both local and systemic drug action due to their intrinsic swelling feature caused by chemical modification, which aids in drug release in the required dose form. Because they are constructed of hydrophobic polymer chains, they absorb a lot of water [44].

Nano Sponge: Nano sponges are drug carriers that are nanosized and have a three-dimensional structure generated by crosslinking polymers. They have the benefit of being able to contain a variety of medications of varying sizes. Nano sponges are available in a range of forms and sizes. They are distinguished by the research technique employed, the kind of polymer employed, and the type of medication that may be present. Nano sponges outperform other delivery methods due to their ability to provide a regulated medication release pattern with targeted drug delivery. The duration of effect as well as the duration of the drug's residence time can be controlled. It has a minimal toxicity and is safe to use because it is constructed of biodegradable components.

It is a form of encapsulating nanoparticle that can keep the medication molecule in its core. The functional groups present in the crosslinker and their concentration impact the porosity of the NSs and provide adjustable polarity. The crosslinker aids in the creation of cavities in the framework, allowing for drug release pattern modification. NSs are nonlethal and stable up to temperatures of around 300 °C. The NSs have an adherent characteristic, which allows them to cling to the surface and so aid in regulated and predictable drug release. The drug release pattern is for 12 hours, which allows for the integration of immiscible liquid, which aids in material processing and can subsequently be turned into powder. They have strong aqueous solubility, which allows them to be

used to give medications that are insoluble in water. They can transport both oil-loving and water-loving medicines. They have fewer adverse effects, are more stable, and are more aesthetic. They have more formulation flexibility [45].

TABLE 1: HERBAL NANO FORMULATION

Name of Herbal Nano formulation	Active Constituent	Pharmacological Activity	Method of preparations	Ref.
Curcumin loaded nano-emulsion	Curcumin	Anti-inflammatory	Emulsion inversion point method	46
Insulin nanoparticles using Chitosan and Arabic gum	Insulin	Anti-diabetic	Ionic Gelation Method	47
Quercetin nanoparticles	Quercetin	Anti tumor	Anti solvent precipitation method	48
Curcumin-Piperine Nanoparticles	Curcumin	Anti-cancer and enhance potency	Fessi method	49
Poly(lactide-co-glycoside) encapsulated extract of Phytolacca Decandra	Spinasterol	Chemo preventive action against lung cancer and on A549	Polymeric nano particles PLGA en-capsulation	50
Ocimum Sanctum leaf extract treated iron oxide nanoparticle	Essential oils, camphor, eugenol	Antibacterial	Co-precipitation method	51
Ocimum Sanctum sodium alginate chitosan nanoparticle	Methanolic extract	antimicrobial	Cation induced control gelatin method	52
Curcumin loaded PLGA nanospheres	Curcumin	Anticancer (prostate cancer)	Solid/oil/water emulsion solvent evaporation method	53
Cuscuta Chininsis nanoparticles	Flavonoids and lignans	Anti oxidant	Nanosuspension method	54
Curcumin loaded polymeric nanoparticles	Curcumin	Antimicrobial activity	Wet Milling method	55
Honokiol loaded	Honokiol	Anti cancer activity	Solvent extraction method	56
Harungana Madagascariensis PLG-NPs	Flavonoids and terpenoids	Antibacterial activity	Interfacial polymer deposition solvent diffusion method	57
Triptolatic poly (DL-lactic acid) nanoparticles	Triptolite	Antirheumatic	Modified spontaneous emulsification solvent diffusion method	58
Glycyrrhizic acid loaded nanoparticles	Glycyrrhizic acid	Anti hypertensive	Rotary evaporated ultra sonication method	59
Radix Salvia miltiorrhiza nanocapsule	R.Salvia Miltirrhiza	CAD,Angina pectoris	Spray drying technique	60
Witepsol SLNPs	Thujone,Pinene	Antioxidant activity	Hot melt ultrasonication	61
Gold conjugated green tea nanoparticles	Catechin	Anti cancer activity	Green nanotechnology	62
Phytofabricated selenium nanoparticles from fruit extract of Emblica officainalis	Gallic acid	Antioxidant activity	Simple reduction method	63
Mentha Piperita nanogel	Essential oil	Analgesic effect	Modified emulsification diffusion method	64
Nanosponge loaded herbal gel of Wrightia Tinctoriaa	Hydro alcoholic extract	To treat psoriasis	Melting method	65
Ni/Nio nanoparticles using Gymnema Sylvestre	Gymnemic acid	Antifungal activity	Green synthesis	66
Eugenol nanoemulsion	Eugenol	Antibacterial activity	High speed shearing technique	67
Genistein loaded biodegradable TPGS-b-PCL nanoparticles	Genistein	Antitumor activity	Modified nanoprecipitation method	68
Poly-E-caprolactone (PCL)nanoparticle of *Sambucus nigra* L	Rutin, naringenin	Anti inflammatory action	Solvent displacement method	69
Liposome encapsulated magnolol	Magnolol	Inhibit vascular smooth muscle	microencapsulation method	70

		inhibition		
Nanocapsulated Curcumin	Curcumin	Antitumor activity	Emulsion diffusion evaporation method	71
Nanolipid parentral	Silybin	Anti hepatotoxic activity	Solvent evaporation method	72
Ginseng capped gold nanoparticles	ginseng	Antioxidant activity	Solvent evaporation method	73
Microencapsulation of Radix Salvia Miltiorrhiza nanoparticles	Radix Salvia Miltiorrhiza	Anti angina activity	Spray drying method	74
PLGA nanoparticle	Paclitaxel	Antitumor activity	Semi reduction coprecipitation method	75
Microemulsion of Neem oil	Azardicta Indica	Antifungal, Antibacterial activity	Emulsification method	76
Microemulsion	Matrine	Antibacterial, Ant inflammatory activity	Micro emulsification method	77
W/O emulsion	Rhubarb	Cathartic, laxative activity	Emulsification method	78
Microemulsion	Docetaxel	Anticancer	Emulsification method	79
Microsphere	Ginsenoside	Anticancer activity	Solvent evaporation method	80
Sustained release microsphere	Zedoary oil	Hepatoprotective activity	Emulsion solvent diffusion method	81
Ethosome	Sophora	Anti endotoxic	Injection sonication method	82

Evaluation Parameters for Nanoparticles:

Direct Counting Methods:

A Particle size Analysis:

Transmission Electron Microscopy (TEM): Electron microscopy (EM) techniques such as SEM and TEM have lately been utilized to characterize particle sizes. It is crucial to visualize the particle's form. In the realm of nanomedicine, TEM has been used to image liposomes, polymeric micelles, nano emulsions, lipidic nanoparticles, and nano vesicles. Prior to imaging in the presence of artefacts, an accurate approach for sample preparation should be used. The final image shows a drastically altered structure that may not be indicative of the NEP sample. Drying, negative staining, freeze fracture, and cryo TEM are common sample preparation processes [83].

Indirect Counting Methods:

Particle size Tracking: Particle tracking analysis (PTA) is a single particle size measurement that, unlike batch mode DLS, does not overstate bigger aggregates or larger particles, allowing the PSD of extremely complex samples to be measured. The equipment captures the Brownian motion of each individual particle (diffusion) and converts it into a single particle diffusion coefficient. Finally, the hydrodynamic diameter is determined using the Stokes-Einstein equation, yielding a high-resolution number-based PSD. The program analyses a sequence of recorded films lasting around 30-60 seconds, tracking the centre of each particle frame by frame [84].

Tunable Resistive Pulse Sensing: Tunable Resistive Pulse Sensing (TRPS) is an indirect counting approach based on the Coulter counter concept that uses resistive pulse sensing to determine particle size, charge, and concentration. The particles suspended in an electrolyte medium (e.g., PBS buffer) are forced through a conductive membrane (nanopore) that is subjected to an applied electrical potential, and thus to an ionic current, by combining specified pressure and voltage values. Each particle's passage generates a resistive pulse signal or "blockade" that is recognized and recorded by the instrument's software. Particle volume is estimated from the magnitude of the pore blockage and then translated into particle size, whereas surface charge and particle concentration are computed from the length and frequency of the blockade [84].

Scanning Electron Microscopy Studies: Scanning electron microscopy (SEM) is a valuable electron microscopy method that may provide a

comprehensive visual picture of a particle with excellent clarity and spatial resolution. In SEM, the sample is subjected to a high-energy electron beam, which provides information on a material's topography, morphology, composition, chemistry, grain orientation, crystallographic information, and so on. As a result, SEM is a helpful tool for material characterization. Morphology refers to an object's shape and size, whereas topography refers to its surface characteristics, or "how it looks," such as texture, smoothness, or roughness. Similarly, composition refers to the elements and compounds that make up the substance, whereas crystallography refers to the arrangement of atoms in the material [85].

Differential Scanning Calorimetry (DSC) Studies: DSC is a thermodynamic method used to directly analyze the heat energy intake that happens in a sample during a controlled temperature increase or reduction. Calorimetry is particularly useful for monitoring changes in phase transitions. DSC is frequently used to examine biological processes, which are defined as a single molecular change of a molecule from one conformation to another. Thermal transition temperatures (Tt; melting points) of materials in solution, solid, or mixed phases such as suspensions are also calculated. A simple DSC experiment involves simultaneously introducing energy into a sample cell (which contains a solution containing the chemical of interest) and a reference cell (which contains simply the solvent). Both cells' temperatures rise at the same rate over time. The amount of extra heat absorbed or released by the molecule in the sample (during an endothermic or exothermic reaction, respectively) would be the difference in the input energy necessary to match the temperature of the sample to that of the reference. Because the presence of the molecule of interest requires more energy to raise the sample to the same temperature as the reference, the idea of heat excess enters the picture [86].

Atomic Force Microscopy (AFM) Studies: Atomic force microscopy (AFM)-based technologies have evolved into a potent nanoscopic platform for characterizing a diverse variety of biological and synthetic bio interfaces, including tissues, cells, membranes, proteins, nucleic acids, and functional materials. Although AFM's remarkable signal-to-noise ratio allows for imaging of biological interfaces from the cellular to the molecular scale, AFM-based force spectroscopy allows for the investigation of their mechanical, chemical, conductive or electrostatic, and biological characteristics. The combination of AFM imaging and spectroscopy structurally maps these characteristics and enables for molecular precision 3D modification. Height may be measured with sub-nanometer precision and excellent resolution using AFM, although lateral resolution is influenced by the form of the AFM probe [87].

X-Ray Diffraction Studies: One of the most often used methods for characterizing NPs is X-ray diffraction (XRD). XRD typically offers information on the crystalline structure, phase nature, lattice parameters, and crystalline grain size. The latter parameter is calculated using the Scherrer equation and the widening of the most intense peak from an XRD measurement of a given sample. Extended X-ray absorption fine structure (EXAFS) and X-ray absorption near edge structure (XANES, also known as NEXAFS) are both types of X-ray absorption spectroscopy (XAS). The X-ray absorption coefficient of a material as a function of energy is measured by XAS. Each element has a unique set of absorption edges that correlate to the varied binding energies of its electrons, resulting in XAS element selectivity [88].

Determination of Zeta Potential: Unlike traditional light scattering techniques, nanoparticle tracking analysis (NTA) visualizes Brownian motion. NTA allows nanoparticles to be sized on a particle-by-particle basis, resulting in better resolution. A small (250ml) sample containing particles at concentrations ranging from 106 to 1010 particles/ml is introduced into the scattering cells, through which a finely focused laser beam of (approx. 40mW) is passed. Particles within the beam's path are observed using a microscope-based system (NanoSight NS500) equipped with a CCD camera. And the particles visible in the beam were individually studied by an analysis program [88].

***In-vitro* Release Study Using Franz Diffusion Cell:** To track drug release from nanoparticles, a Franz diffusion cell was employed. The receptor phase was thermostatically maintained at 37°C in phosphate buffered saline (PBS, pH 7.4), with each

release experiment performed in triplicate. To separate the receptor and donor phases, a dialysis membrane with a molecular weight cutoff of 12,000 to 14000 Daltons was utilised. The latter was a 2 ml suspension of nanoparticles carrying 10 mg of medication in a 1% w/v Tween 80 solution in PBS, stirred for 5 seconds to assist re-suspension. At periodic intervals, 1 ml samples of the receptor phase were obtained and an equivalent volume of PBS was reintroduced into the receiver compartment. The drug's diffusion into the receptor phase was measured spectrophotometrically [89].

***In-vitro* Release of Nanoparticles by Simple Diffusion:** The *in-vitro* release of nanoparticles was investigated using a basic diffusion cell setup with one end linked with a sigma dialysis membrane that serves as a donor compartment. Freshly produced phosphate buffer saline pH 7.4 was utilised as the dissolving media. The dissolving medium was steeped overnight in the Sigma membrane. The magnetic stirrer was used to agitate the medium, and the temperature was kept at 37^{o}C. A spectrophotometric analysis of 5 ml of material was performed on a regular basis [89].

***In-vitro* Drug Release Using Dialysis Tube:** Dialysis tubes with an artificial membrane were used for *in-vitro* release investigations. The produced nanoparticles and 10 ml of phosphate buffer pH 7.4 were introduced to the dialysis tube, which was then immersed in the receptor compartment containing 250 ml of phosphate buffer pH 6.8. The medium in the receptor was continually stirred with a magnetic stirrer while the temperature was maintained at 37 1°C. 5 ml of receptor compartment sample was obtained at various periods during a 24 hours period, and new buffer was replenished each time. Spectrometric analysis was used to quantify the quantity of medication emitted [89].

***In-vivo* Bio Distribution of Nanoparticles Containing Drug:** *In-vivo* bio distribution tests were conducted in Wistar rats weighing 100 to 150 gm and split into three groups of three animals each. The three groups were as follows: group 1 was given free drug, group 2 was given drug-loaded nanoparticles, and group 3 was given solvent control. Each group of mice received an IV injection of free drug and drug-loaded nanoparticles at a dosage of 3.6 mg per body weight, as well as a solvent control at pH 7.4. Animals were slaughtered 18 hours after drug injection, and blood and plasma were separated. Organs such as the liver, lungs, kidney, and spleen were removed and homogenised in phosphate buffer saline (pH 7.4) before centrifugation. HPLC was used to evaluate the supernatant of homogenised tissue to determine the bio distribution [89].

CONCLUSION: The application of nanotechnology-based delivery systems for herbal drugs plays an important role in public healthcare across the world. The use of herbal drugs is increasing day by day worldwide, Therefore, the development of herbal medicines with nanotechnology-based delivery systems might be an alternative strategy for increasing their pharmacological activity. However, the development of these nanotechnology-based delivery systems must be studied further, particularly in terms of safety and toxicity profiles, in order to assure their safety and efficacy for healing various types of diseases.

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