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Nanomedicines and Nanocarriers

Introduction to Versatile Nanocarrier System; Exploring Their Morphology, Method of Preparation, Characterization Technique & Application in Different Field

Ms. Pooja S Murkute[*1], Dr. Mohammed Ismail Mouzam[2], Dr. Abubakar Salam Bawazir[3], Mr. Nakul P Kathar[4] and Mr. Krishna K Deore[5]

[*1,3]Y. B. Chavan College of Pharmacy, Dept. of Pharmacognosy, Dr. Rafiq Zakaria Campus, Dr Rafiq Zakaria Marg, Rauza Baug, N 2, Cidco, Maharashtra 431003.

[2,4,5]Y. B. Chavan College of Pharmacy, Dept. of Pharmaceutics, Dr. Rafiq Zakaria Campus, Dr Rafiq Zakaria Marg, Rauza Baug, N 2, Cidco, Maharashtra 431003.

Abstract: Nanomedicine is an emerging tool in biological science with a more prior application against no different disease conditions. The prefix 'nano' is a Greek prefix meaning something very small and near to around one thousand millionth of a meter (10^{-9} m). The American physicist and Nobel Prize laureate Richard Feynman introduced the concept of nanotechnology in 1959. During the annual meeting of the American Physical Society, Feynman presented a lecture entitled "There's Plenty of Room at the Bottom" at the California Institute of Technology (Caltech). This topic mainly emphasizes various Nano size ranges of medicine, especially Nanocarriers as Rigid & Non-rigid systems. Non-rigid nanocarrier systems are primarily of relatively soft structures that an external force can easily disrupt. Rigid nanoparticles are understood to retain the same form. Nanomedicines are employed in all different areas across the world in the field of Agriculture, Medicines & Cosmetics; Nanomedicines are best employed or designed for critical disease conditions such as Cancer, Diseases associated with the Brain, etc. Nanomedicine plays an active role in their therapeutic & diagnostic application. The selection of matrix materials depends on many factors such as Biocompatibility and toxicity, Degree of biodegradability, surface characteristics (charge and permeability), Antigenicity of the final product, Inherent properties of the drug (aqueous solubility and stability). The current topic particularly emphasizes different methods of preparation available in the market for Nanomedicine, Various methods of its characterization, such as Microscopy-Based Nanoparticle Characterization & Spectroscopy-Based Characterization Techniques. At the same time, High-resolution transmission electron microscopy imaging is an excellent methodology for differencing between micro or nano-crystalline diphasic and rigid polycrystalline and single crystalline phases. This methodology has been employed specifically for the surface study of nanostructure using the different chemical compositions of atoms and molecules in Nanoparticles to image the surface/body at the microscopic level.

Keywords: Liposomes, Polymeric Nanoparticles, Solvent Diffusion method, High-resolution Transmission electron microscope, X-ray Photoelectron Spectroscopy, Dendrimers.

***Corresponding Author**

Ms. Pooja S Murkute , Y. B. Chavan College of Pharmacy, Dept. of Pharmacognosy, Dr. Rafiq Zakaria Campus, Dr Rafiq Zakaria Marg, Rauza Baug, N 2, Cidco, Maharashtra 431003.

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1. INTRODUCTION

The term Nanoscience and Nanotechnology varies considerably. Nanoscience broadly can be defined as studying structures and molecules on a specific nanometer-scale ranging between 1 to 100 nm. Nanotechnologyis the same molecular study by utilizing it in practical applications such as various devices, healthcare applications, etc. It is called nanotechnology1. The origin of this nanoscience can be found back to the moment of the Greeks and Democritus in the 5th century B.C. Only. When there is a big question of whether the matter is continuous or divisible into smaller pieces or consists of small, indivisible, and indestructible particles in a scientist's mind, which scientists now call atoms. The bottom-up approach gives references specifically to the figure-up of nanostructures from the lowermost atom- by atom or molecule- by- molecule by physical and chemical methodologies, which are in a nanoscale range 1 nm to 100 nm) employing constrained manipulation of character-gathering of atoms and molecules. Self-gathering is a bottom-up passage in which molecules or atoms are arranged together and arranged in nanostructures by chemical-physical relations between them[1]. Nanotechnology gives drugs in minute nanometer size ranges, increasing the medicinal activity in various dosage forms. A nanoparticle formulation's size, shape, surface charge, and concentration profoundly affect particle uptake, bio-distribution, or payload-carrying efficiency[2]. Various advantages of the nanocarrier system are mentioned as follow[2].

- Decreased fasted variability
- Decreased patient-to-patient variability
- Enhanced solubility
- Increased oral bioavailability
- Increased rate of dissolution
- Increased surface area
- Less amount of dose required
- More rapid onset of therapeutic action

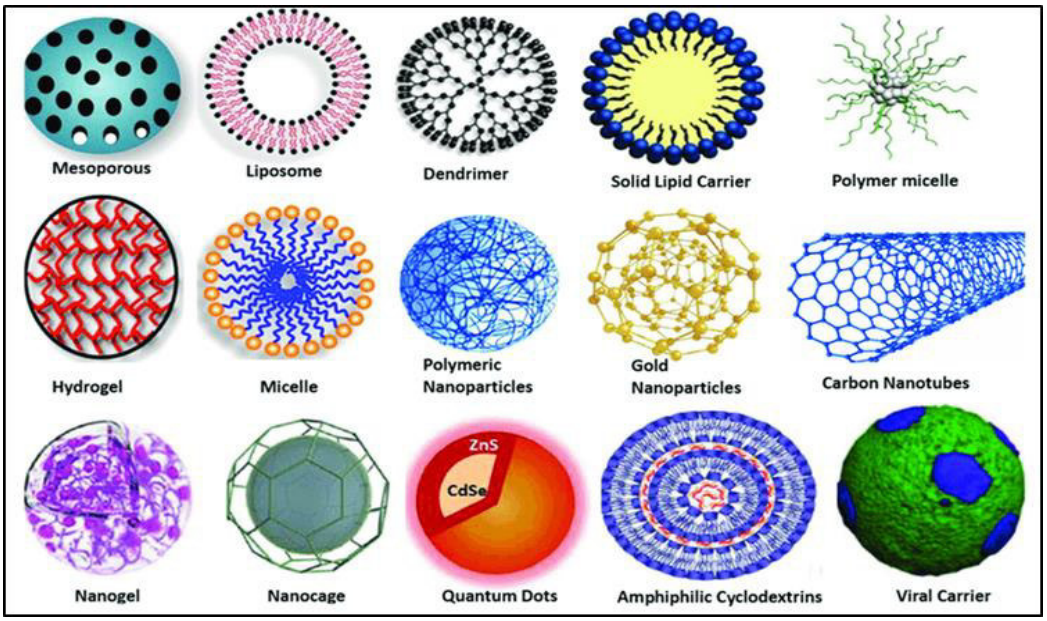

Fig. 1: Various nanocarrier system classification[3].

1.1 Nanoparticle

Nanotechnology is the science that deals with matter at the scale of 1 billionth of a meter (i.e., 10^{-9}m = 1 nm) and the study of manipulating matter at the very basic molecular scale. A nanoparticle is the major fragment in the nanostructure fabrication and is far smaller than the world of everyday objects described by Newton's laws of motion. The National Nanotechnology Initiative (NNI) & United States instituted the back in 2000, which was soon followed (2001) by a plethora of projects in nanotechnology in nearly all of the U.S. Departments and Agencies. About 20 Research Centres were subsequently funded by the Nationa1 Science Foundation (NSF), an agency responsible solely to the President of the United States and whose mandate is to fund the best fundamental science and technology projects. NSF was the lead U.S. agency to carry forward the NNI. The word "nanotechnology" soon caught the attention of various media (TV networks, the internet, etc.) and the imagination and fascination of the community at large[4]. Nanoparticles, microscopic samples with at least one dimension less than 100 nm, have attracted considerable scientific attention. Distinctive size-dependent properties of nanoparticles often exist, which are mainly due to their relatively large surface area[5]. The nanoparticles are the framework for adjuncts of chemical moieties that perform a specific medical function (e.g., hydrophilic coatings that improve solubility targeting ligands, drugs, imaging agents, etc.). Maintaining such a complex entity's safety and efficacy is difficult. Eventually, the achievement of the use of these multicomponent nanoparticles in clinical trials is largely suspended on rigid preclinical characterization[6]. Nanoparticles show different mechanical properties related to micro particles and bulk materials, providing more effective options for the surface modification of many devices in the mechanical strength or improving the quality of Nano manufacturing/nanofabrication, etc. To be more specific, on the other hand, the mechanical effects of nanoparticles can affect the tribological properties of lubricants with nanoparticles[6]. The small Nano size range is very effective in many characteristic advantages; hence, slight changes in these features can lead to significant variation in retention times, bio distribution, uptake, and cellular toxicity[7].

2. TYPES OF NANOPARTICLES

Nanoparticles are broadly classified into the 3 following mentioned ways.

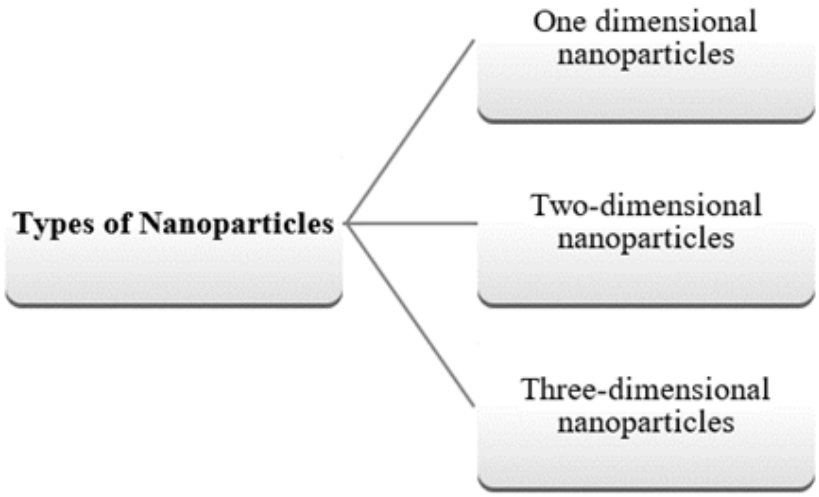

Fig. 2: Diagrammatic Presentation of Types of Nanoparticles.

2.1 *One dimensional nanoparticles*

Chemical and biological sensors, information storage systems, magneto-optic and optical devices, and fiber-optic systems.

2.2 *Two dimensional*

Carbon nanotubes etc.

2.3 *Three dimensional*

Quantum Dots, Dendrimers, Fullerenes, etc.

3. THREE DIMENSIONS OF NANOPARTICLE

Nanoparticle systems are classified into two broad categories such as 1) Non-rigid Nanocarrier system, which encompasses liposomes and solid lipid nanoparticles, and 2) RigidNanocarrier system, which encompasses polymeric and inorganic nanoparticles. The most common 3D nanostructures incorporate different nanoscale characteristics into a single construction. These nanomaterials are frequently believed to be more efficient in bio-sensing, signal amplification, and focusing on particular analytes of interest because they have a larger electroactive surface area. Nanocomposites and intricate hierarchical structures are among the principal categories of 3D materials. Inverse opals (IOs) and photonic crystals (PCs) with ordered 3D nanostructures are good candidates for detecting biomarkers and developing innovative biosensors, claims a study[8].

3.1 *Fullerenes (Carbon 60)*

Carbon 60 Comprised of 28 to 100 carbon atoms, fullerenes are spherical cages. A part of fullerenes is C60. This is a hollow, football-like object formed of intertwined pentagons and hexagons of carbon[9]. One of the strategies employed by Kroto and colleagues to produce fullerene derivatives, such as fullerenes C60 and C70, is the laser evaporation of graphite. They were discovered to be Cn clusters (n 20), the most prevalent of which was C60. Then, other useful fullerenes, like C76, C80, C240, etc., were produced using many carbon atoms. Numerous research has examined fullerene nano heterostructures almost three decades after their discovery[10].

3.2 *Dendrimers*

Dendrimers are a novel family of controlled-structure polymers with nanometric dimensions. Dendrimers are the best drug delivery vehicles since they typically range in size from 10 to 100 nm and have many functional groups on their surface[9]. With increasing dendrimer production, dendritic macromolecules often acquire a more globular form and linearly expand in diameter. To study the effects of polymer size, charge, and composition on biologically relevant properties like lipid bilayer interactions, cytotoxicity, internalization, blood plasma retention time, biodistribution, and filtration, dendrimers emerged as an ideal delivery vehicle candidate[11].

3.3 *Quantum Dots (QDs)*

Quantum dots are small, dense particles that contain a tiny droplet of free electrons. The diameter of QDs, colloidal semiconductor nanocrystals, ranges from 2 to 10 nm. From several types of semiconductor materials, QDs can be produced by electrochemistry and colloidal synthesis[9]. Quantum dots (QDs) are semiconductor nanometer-scale crystals constructed of elements from groups II-VI or III-V. QDs are particles with physical dimensions smaller than the exciton Bohr radius. When a photon of visible light impacts such a semiconductor, some electrons are encouraged into higher energy states; when they return to their ground state, they emit a photon at a frequency particular to that substance[12].

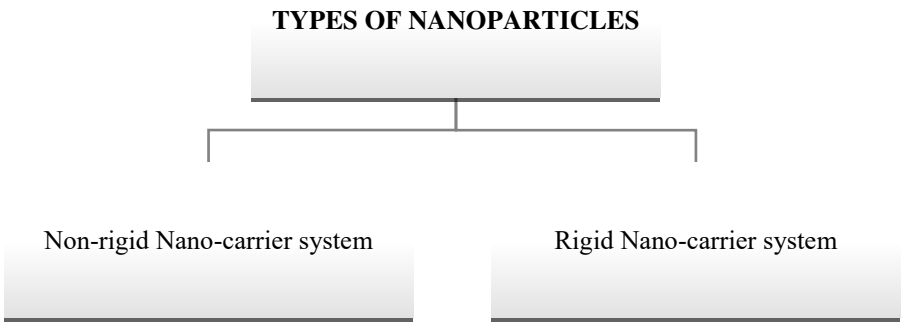

Fig. 3: Types of nanoparticles in drug delivery based on the integrity of the particles

4. MORPHOLOGY OF SOME NANO-CARRIER SYSTEM

4.1. Fullerenes

Fullerenes have a spherical, icosahedral shape and comprise 12 regular pentagons and 20 regular hexagons and sp2-hybridized conjugated bonds, contributing to their special physical and chemical characteristics. Due to the high degree of symmetry, C60 single crystals are frequently packed most tightly in face-centered cubic, which can improve the interaction between layers and increase the stability of the structure[13]. Fullerene C60 has great antioxidant capability and stability[14] and is soluble in common solvents at room temperature.

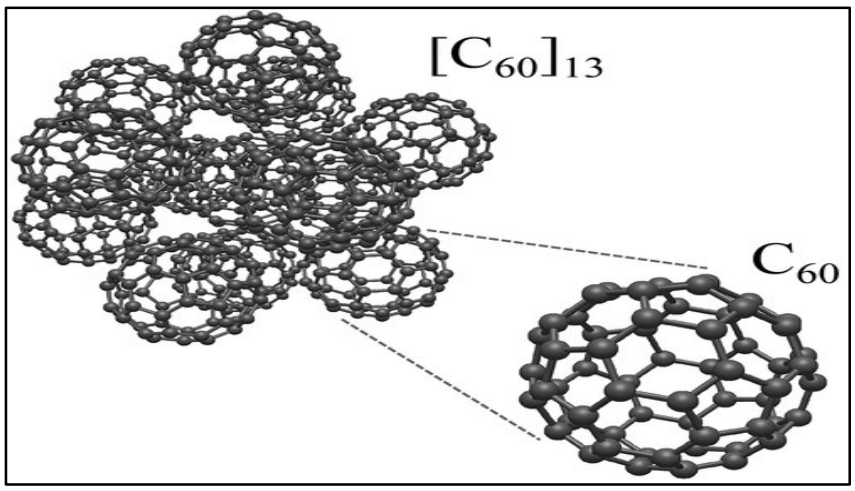

Fig.4: Morphology of Fullerenes[15]

4.2. Dendrimers

Dendrimers are three-dimensional macromolecules that are highly branched, perfectly monodisperse, and have well-regulated chemical structures. Dendrimers' internal structure, in which all bonds emanate radially from a central core with repeat units contributing a branching point that enables the potential to attach at least two monomers, gives them their globular shape[16].

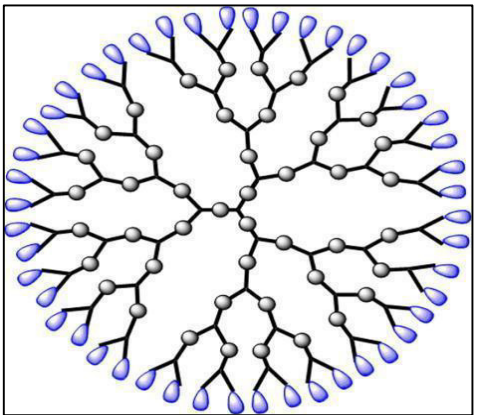

Fig.5: Morphology of Dendrimers [17]

4.3. Quantum dots

We observe that for the two most popular deposition processes, self-assembly and contact printing, the QDs are significantly depressed into the organic layer for the typical organic films used in QD-LEDs. To spin-cast the QDs and organic material into a suspension for self-assembly, a common solvent is needed[18].

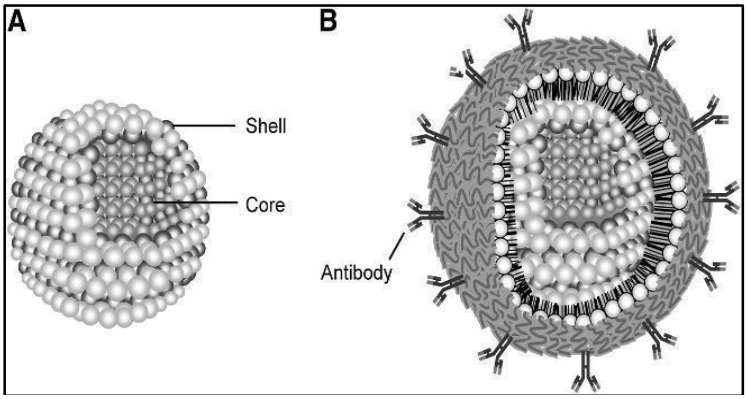

Fig.6: Morphology of Quantum dots[19]

4.4. Carbon nanotubes

Each carbon atom in CNTs is bonded with an sp^2 hybridization, stronger than the sp^3 bonds in diamond, and gives these compounds exceptional mechanical, electrical, optical, and thermal properties. Carbon nanotubes have been tested as drug transporters because of their ability to cross the cell membrane. Their large surface area, needle-like shape, and residual metal impurities are distinguishing characteristics. The carbon nanotube (CNT), a particular form of carbon, has a micrometer length and a nanometer diameter (where the length-to-diameter ratio is more than 1000). The atoms are arranged in hexagons, similar to the structure of graphite. The seamless cylinder of CNT's cylindrical graphitesheet, also known as graphene, with a diameter of the order of a nanometer, is formed by rolling up the material. It is well known that the substance that falls between fullerenes and graphite is CNT, a relatively new member of the family of carbon allotropes[25].

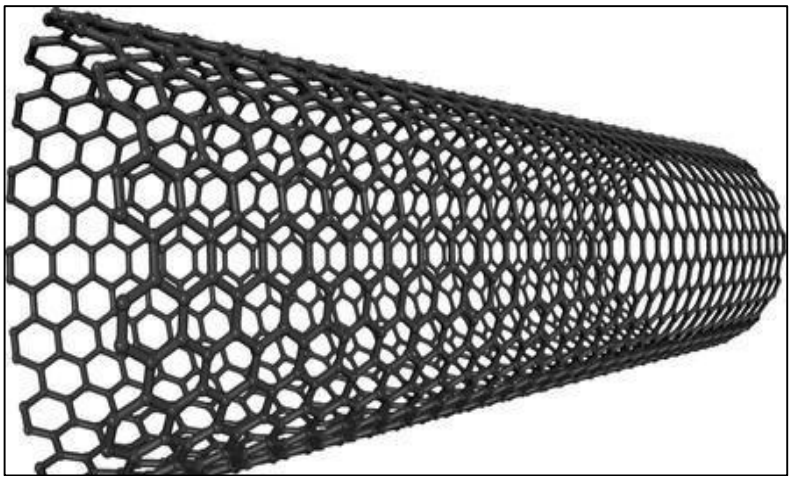

Fig.7: Morphology of carbon nanotubes[20]

4.5. Solid lipid nanoparticle

The normal shape of SLNs is spherical, and their diameter ranges from 50 to 1000 nm. The primary elements of SLN formulations are lipids, solids at room temperature, emulsifiers, and occasionally a combination of both, as well as active pharmaceutical ingredients (APIs) and a suitable solvent system[21].

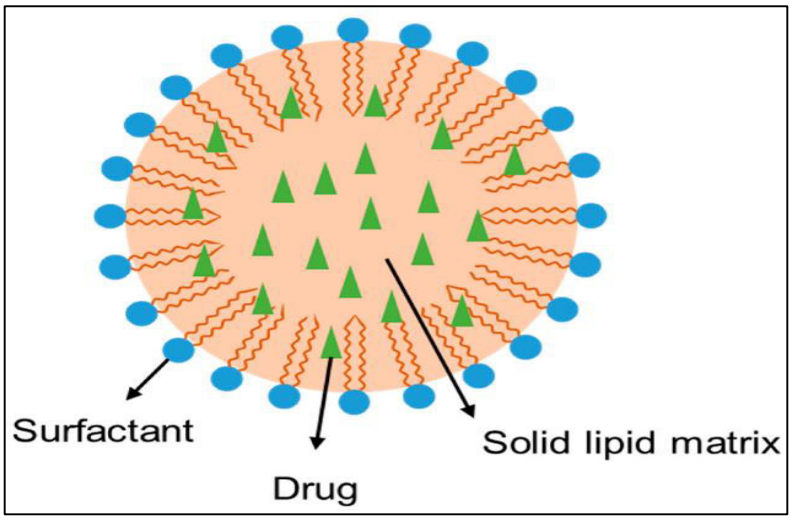

Fig.8: Morphology of Solid lipid nanoparticle[22]

4.6. Liposomes

Liposomes are made up of lipids and phospholipids. Diacyl-chain phospholipids (lipid bilayer) self-assemble in aqueous solutions to form multilayered, spherical, or spherical vesicles called liposomes. For hydrophilic substances, the efficacy of liposome encapsulation only declines with the number of bilayers and increases with liposome size. The size of the cysts significantly influences the duration of liposomes' circulation. The amount of medication contained depends on the size and quantity of bilayers. The necessary vesicles for using liposomes for medication delivery are typically between 50 to 150 nm in size[23].

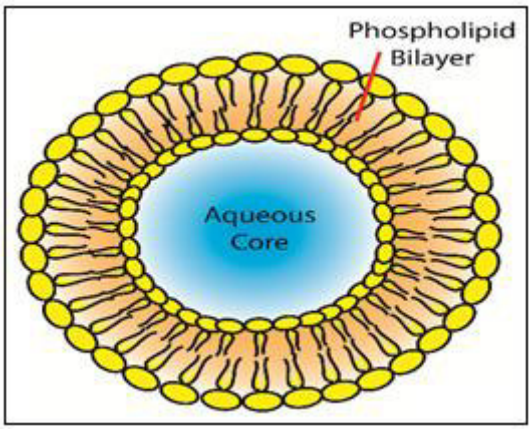

Fig.9: Morphology of Liposomes[24]

5. PREPARATION AND INTRODUCTION OF VARIOUS NANOCARRIER SYSTEM

The selection of the appropriate method is primarily based on the physicochemical character of the polymer and the drug to be loaded. Nanoparticles can be designed/formulated using various materials such as proteins, polysaccharides, and synthetic polymers[2]. The selection of matrix materials depends on many factors as mentioned below in the Tree diagram.

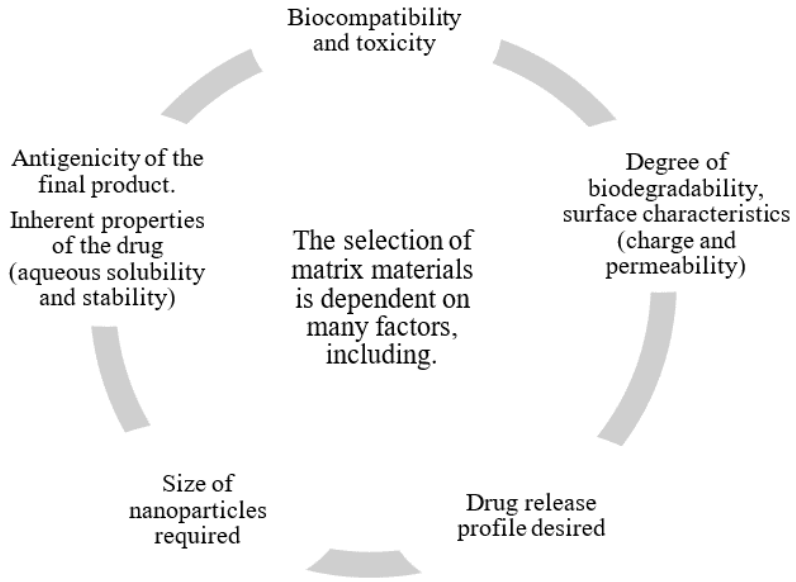

Fig. 10: Selection of matrix materials is dependent on factors including Nano-carrier system formulation

5.1. Non-rigid Nanoparticles

The Non-rigid nanoparticles primarily consist of relatively soft structures that an external force can easily disrupt. Lipids-based nanoparticles such as liposomes and solid-lipid nanoparticles are generally categorized as non-rigid.

5.1.1. Solid lipid nanoparticles

Solid lipid nanoparticles are the next generation of colloidal drug carrier systems containing solid surfactant-stabilized lipids at body and room temperatures. They give major advantages to liposomes, polymeric nanoparticles, and emulsions, minimizing disadvantages. This consists of a hydrophobic solid matrix core with a phospholipid coating. Core especially possesses a hydrophobic nature arrangement due to the presence of the hydrophobic tail regions of the phospholipid, which is deep inside the core matrix. Due to such an arrangement, solid lipid nanoparticles have a higher entrapment efficiency for hydrophobic drugs in the core. The parenteral route is one of the most commonly accepted routes of drug administration for lipid-based Nano systems, followed by the oral route. Both types of route administration are responsible for achieving systemic behaviour of the different encapsulated drugs. Still, the trend described is opposite to the present distribution of pharmaceutical products in the market, where the oral route of administration is the preferred and most widely used route for drug administration.[4]

Table - 1: Lipid & Surfactant use for most of the Nano-formulation system.

Category	Examples
Lipid	Triglycerides Tricaprin, behenicacidtrilaurin, trimyristin, tripalmitin, Glycerylmonostearate (Imwitor 900), glycerylbehenate (Compritol 888 ATO), W 35, cetylpalmitate, stearic acid, palmitic acid, decanoic acid, glycerylpalmitostearate (Precirol ATO 5)
Surfactant use	Egg lecithin (Lipoid E 80), phosphatidylcholine, poloxamer 188, 182, and 407, Tyloxapol, polysorbate 20, poloxamine 908, 60, and 80, sodium cholate, sodium glycocholate, taurocholic acid sodium salt, Soylecithin,taurodeoxycholic acid sodium salt, butanol, butyric acid, dioctyl sodium sulfosuccinate, monooctyl phosphoric acid sodium

6. METHODS TO PREPARE SOLID LIPID NANOPARTICLES

a. Hot Homogenization

This is the most common method for the preparation of solid lipid nanoparticles. The solid lipids are melted by heating to a temperature range of 5°C-10°C. Originally the active ingredient is dissolved, dispersed, & solubilized in the hot melted lipid, followed by dissipation of the medicine lipid melt into a polar surfactant solution (heated for specific) to produce an o/w pre-emulsion. A homogenizer properly homogenizes the pre-emulsion to obtain a nano-emulsion. Homogenizers Specifically in Lab scale batch, different homogenizer such as the Biozed Homogenizer 30000 psi, Avestin B3 homogenizer, Micron lab 40 homogenizer, M-110L, high-pressure pneumatic lab homogenizer is preferred for formulations of Nano-emulsion. For large-scale products, there are different homogenizers commercially accessible. Homogenization, similar to RETSCH Laboratory Homogenizers, M- 110EH or M- 700 series micro fluidizers. After completion, the consequent Nanoemulsion is chilled to room temperature to raise the recrystallization of the lipids to attain the SLN. The recrystallization procedure can be advanced by methods similar to lyophilisation; eventually, this methodology may not be capable of hydrophilic active ingredient as the active ingredient may partition between the polar phases and lipid. Pre-emulsion is formulated by adding the lipid melt-containing drug and aqueous emulsifier with the help of high mixing homogenizer at 500–1500 bar pressure, decreasing the emulsion globules' size. Minimum 5 cycles of homogenization are required to get the desired size of the globules. The colloidal hot oil in water emulsion is formed after homogenization, which upon cooling leads to the crystallization of the lipid in globules and solid lipid nanoparticles2,26. For the Nanoparticle preparation method,

continuous stirring was maintained for at least a 5-10 time limit with the rpm ranging from 2000 to 20,000. The increase in the rpm or stirring time may not directly affect the particle size, but it may cause minor variations in the poly-dispersibility index (PDI) [27].

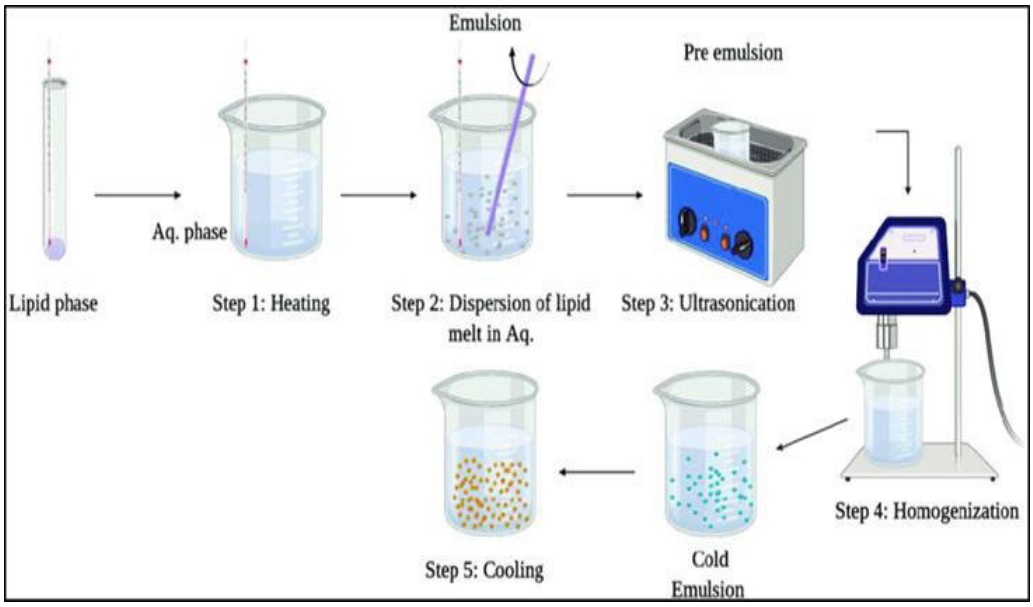

Fig.12: Hot Homogenization Method of Preparation[28]

b. Cold Homogenization

The solid lipids are melted by heating to a specific temp 5˚C – 10 ˚C. The active pharmaceutical ingredient is dissolved, dispersed, or solubilized in the hot melted lipid succeeded by chilling to RT. The substance is then ground to gain lipid micro-particles. The lipid micro-particles are also suspended in a cool aqueous surfactant solution to gain a. pre-suspension. Finally, the lipid micro-particle suspense is homogenized below room temperature to gain the SLN to minimize the loss of hydrophilic drugs; the aqueous phase can be replaced with liquids in which the dispersed drugs have low solubility, similar to choice oils or PEG 600[2, 26].

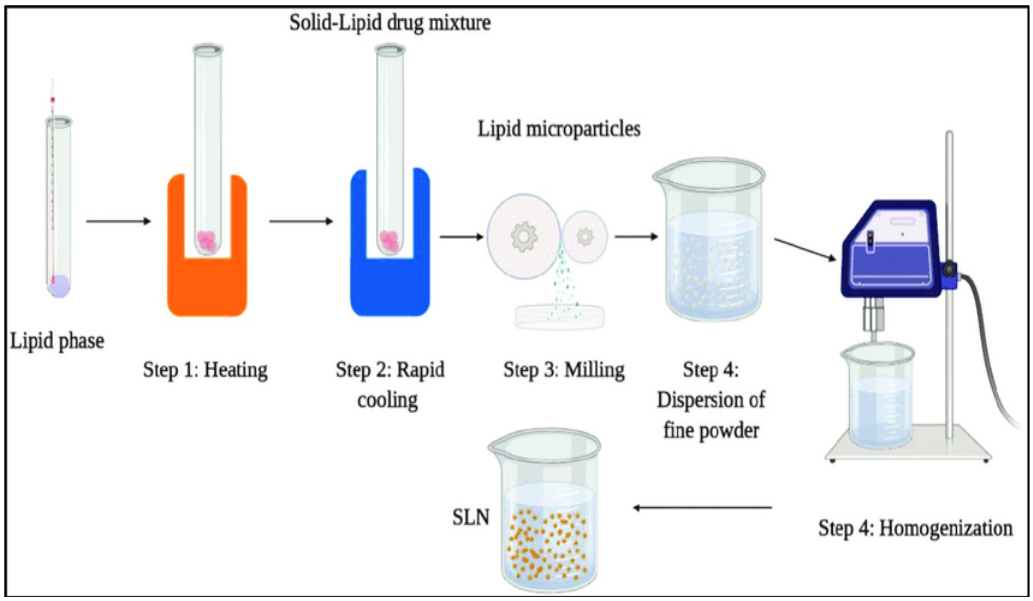

Fig.13: Cold Homogenization Method of Preparation[29]

c. Micro-emulsification

The surfactants / co-surfactants, such as bile salts, lecithin & butanol, are mixed in water to form an aqueous phase. This aqueous phase is heated to the same stable temperature as molten lipids, which is adjoined to the different molten lipids under stirring to gain a thermodynamically stable micro emulsion. This admixture is transferred to a cold aqueous medium (2 ˚C- 3 ˚C) under mild stirring to gain the solid lipid nanoparticles by precipitation [2]. One of the ways to tackle this major problem is to use a mixture of ionic and non-ionic surfactants, as ionic surfactants are effective with a broad area of temperature, whereas non-ionic surfactants exhibit high solubilizing power. A proper admixture of ionic and non-ionic surfactants could

accelerate the temperature range for delivering O/ W microemulsion[2, 30].

d. Solvent Emulsification Evaporation Method

This method is mainly applicable to heat-sensitive compounds. The lipids are mixed in an organic solvent that is immiscible in water, such as toluene or chloroform. Also, the lipid result is made over to a polar phase to form the direct emulsion succeeded by the evaporation of organic detergent under degraded pressure or vacuum. After finishing off the evaporation, the lipids precipitate to form solid lipid nanoparticles [2].

e. Solvent Emulsification Diffusion

Organic solvents are usually partially miscible with water. First, the organic solvent, such as ethyl formate or benzyl alcohol, allows for saturation with water, and then the lipids are mixed in it. This surfactant solution is added to a lipid solution in an organic solvent at elevated temperatures. Ultimately, adding extra water leads to the diffusion of the organic phase from the emulsion globules to the continuous phase and precipitation of the solid lipid nanoparticles[2].

f. Drug Incorporation

In this type, the active drug may be incorporated into the solid lipid nanoparticles in three major pathways grounded on the properties of the active drug and excipients and their relation(s). The three models are the homogenous matrix model, the Drug enriched shell model, and the Drug-enriched core model. Homogenous matrix entrapment results when employing cold homogenization or hot homogenization with highly. Emerging Nanotechnologies for Diagnostics, Drug Delivery, and Medical Devices lipophilic drugs. Drug release by this model is very fast & is desirable when the formulation is intended for external application.

6.1. Liposomes

a. Lipid Film Hydration Method for Preparation of Liposomes

Liposome preparation involves four basic steps. First, the lipids (either natural or synthetic) are dissolved in suitable organic solvents. Types of liposomes depend upon the size and number of layers. Nano particulate Systems for Therapeutic and Diagnostic Applications solution is placed against an appropriate surface with agitation/rotation, and the organic solvent from the lipid solution is evaporated to generate a thin layer of spread-out lipids. The evaporation of the organic solvent is promoted either by increased temperature or by vacuum. Later, the dried thin lipid layer is hydrated with an aqueous phase (usually at or slightly above the transition temperature for the lipids), typically accompanied by agitation. Due to the hydrophobic nature of the tail zones of phospholipids, the liposomes are formed by the proceeding of self-assembly as small portions of the lipids come waterlogged in contact with the aqueous medium. Eventually, the liposomes are cleansed using styles similar to ultracentrifugation, gel saturation chromatography, cross-flow microfiltration, liposome extruder purification, etc. Liposome drug loading can be done by either passive or active loading methods[2,31].

b. Drug Loading Liposomes by the Passive Loading Method

The hydrophobic or hydrophilic drugs are directly added to the thin film of lipids during the formation of cysts. 100% trapping efficiency is achievable for hydrophobic drugs. At the same time, trapping the effectiveness of hydrophilic drugs. Due to the small volume of the enclosed water component in the liposome core, the physical and chemical nature is relatively low (30%). The passive encapsulation method adds a drug candidate to the dried lipid film before hydration. Based on the physical and chemical nature of the drug, it can either be incorporated into the lipid bilayer or trapped in the central aqueous core or aqueous spacing between the bilayer. Highly water-soluble drugs show lesser encapsulation efficiency than poorly water-soluble (lipophilic) drugs in passive loading techniques[2,32]. Several passive loading ways for liposome preparation involve mechanical dispersion, solvent dispersion, and detergent disposal manners.

Mechanical Dispersion Sonication Method

- Dispersion Extrusion Method
- Dispersion Freeze-Thaw Technique
- Solvent Dispersion Ether Injection Method
- Solvent Dispersion Ethanol Injection Method
- Solvent Dispersion Reverse Phase Evaporation Method

6.2. Rigid Nanoparticles

Rigid nanoparticles are known to have more mechanical strength compared with lipid-based non-rigid nanoparticles. Rigid nanoparticles are divided into three major subcategories: biodegradable polymeric nanoparticles, carbon nanotubes, and iron nanoparticles.

6.2.1. Biodegradable polymeric nanoparticles

Biodegradable polymer nanoparticles can be formulated into various formulations, such as core-shell structures, solid nanoparticles, polymeric micelles, and polyplexes. The nanoparticle formulation and synthesis method depends upon the different properties of the selected polymer, but either self-assembly or emulsion generally forms polymeric nanoparticles. Self-assembly methods include intermolecular and intramolecular interactions between the polymer itself, such as complexation of cationic polymers with anionic nucleic acids to form poly-plexes, as well as spontaneous micelle assembly, when amphiphilic block co-polymers reach a critical micelle concentration (CMC) and form particles due to hydrophobic interactions. Nanoparticles can also be formed by methods such as emulsification, where nanoparticles are formed as droplets of one phase dispersed in a second phase. Typically, the polymer is mixed in an organic phase that is then mixed with a surfactant and sonicated in an aqueous phase with high intensity to form a nano-droplet. The emulsion is stirred until the solvent evaporates, leaving behind hardened polymer nanoparticles. These hard nanoparticles can also be coated with another material to form core-shell nanoparticles with favourable surface properties. Preparation method[33].

a. Solvent Evaporation Method

In this system, the preformed polymers similar to polylactic acid or poly (D, L- lacticco-glycolic acid) are dissolved in an organic solvent such as chloroform, acetone, or ethyl

acetate. The drug is generally dissolved in the polymer solution, which is transferred to a polar phase that contains a surfactant similar to polyvinyl alcohol to form an oil-in-water emulsion. The evaporation of the organic solvent can be supported by continuing the homogenization procedure for a sufficient period. At the end of the homogenization period, the nanoparticles are re-collected by ultracentrifugation. A schematic of this system is mounted. Procedure variables similar to polymer-to-organic solvent rate, organic solvent class, homogenization speed, and time duration can be qualified to attain the particle size and distinctive properties[33].

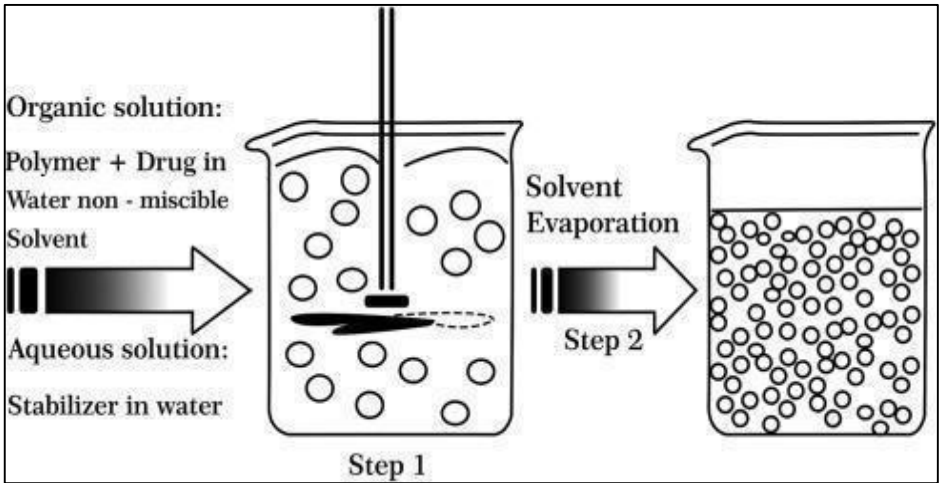

Fig.14: Solvent Evaporation Method Methods of Preparation[34]

b. Spontaneous Emulsification/Solvent Diffusion Method

This is a modification of the solvent evaporation technique. In this system, water-miscible solvents like Methanol and acetone are employed in the Organic phase, and water-immiscible solvents like dichloromethane or chloroform are used in the organic phase II. The interfacial turbulence created when these two phases are crossed leads to the conformation of nanoparticles. Indeed, though this system produces significantly lower-sized patches, some in commodities are similar to the sight of residual organic solvent [33].

c. Salting Out/Emulsion Diffusion Method

Mechanical mixing is being carried out to form an oil-in-water emulsion of two phases. The oil phase is a solution of a water-insoluble polymer and an active admixture in a water-soluble solvent. In contrast, the aqueous phase is a solution or gel containing a colloidal stabilizer and a high concentration of salting-out the agent. The solvent diffusion is hindered by the presence of the salting-out agent in the aqueous phase. The resulting oil-in-water (o/w) emulsion is then diluted with a sufficient amount of pure water to lower the concentration of the salting-out agent below a threshold, enabling the organic solvent to diffuse further into the aqueous phase rapidly and leading to interfacial turbulences and the formation of Polymeric Nanoparticles(PNP) in next step, the solvent is being removed from the Polymeric Nanoparticles (PNP) suspension through distillation at reduced pressure. The subsequent ultracentrifugation and repeated washing steps remove the salting-out agent and the remaining stabilizer; alternatively, the solvent and the salting-out agent can be eliminated by cross-flow filtration[35].

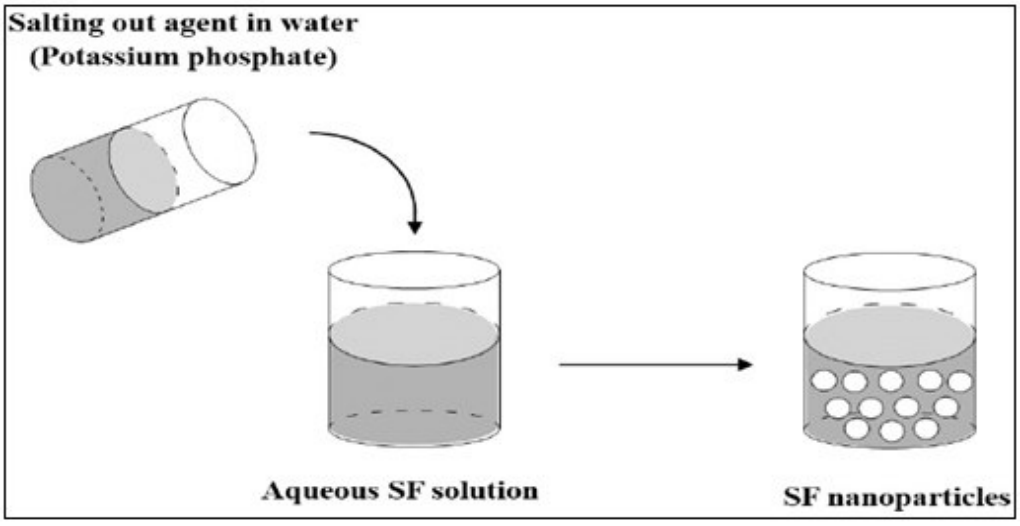

Fig.15: Salting Out/Emulsion Diffusion Method of Preparation[36]

d. Non-aqueous Phase Separation Method

This system is capable of both hydrophilic and lipophilic active ingredients. Commonly, the hydrophilic active ingredient is mixed in water and also adjoined to the organic phase. On a different aspect, the lipophilic active ingredient is mixed in a polymer solution. Once the aqueous and organic phases are mixed to form an emulsion, a second organic non-solvent, such as silicone oil (miscible with the first organic phase but doesn't dissolve the drug), is adjoined under dynamic motion. This results in the extraction of the foremost organic solvent, which causes a decrease in the solubility of the polymer, succeeded by phase separation of a polymer coacervate. This polymer coacervate adsorbs onto the drug granules to form drug-loaded nanoparticles[33].

e. Nanoparticle Preparation by the Emulsion Polymerization Method

In this system, monomers similar to poly alkyl cyanoacrylates are mechanically polymerized in the sight of active ingredients to gain active ingredient-loaded nanoparticles. The monomers are primarily spread in an aqueous acidic medium in the sight of a surfactant and improving agent similar to polysorbate- 20. The active ingredient can be adjoined to the surfactant solution before or after the polymerization procedure. The mechanism of polymerization has been explained schematically [33].

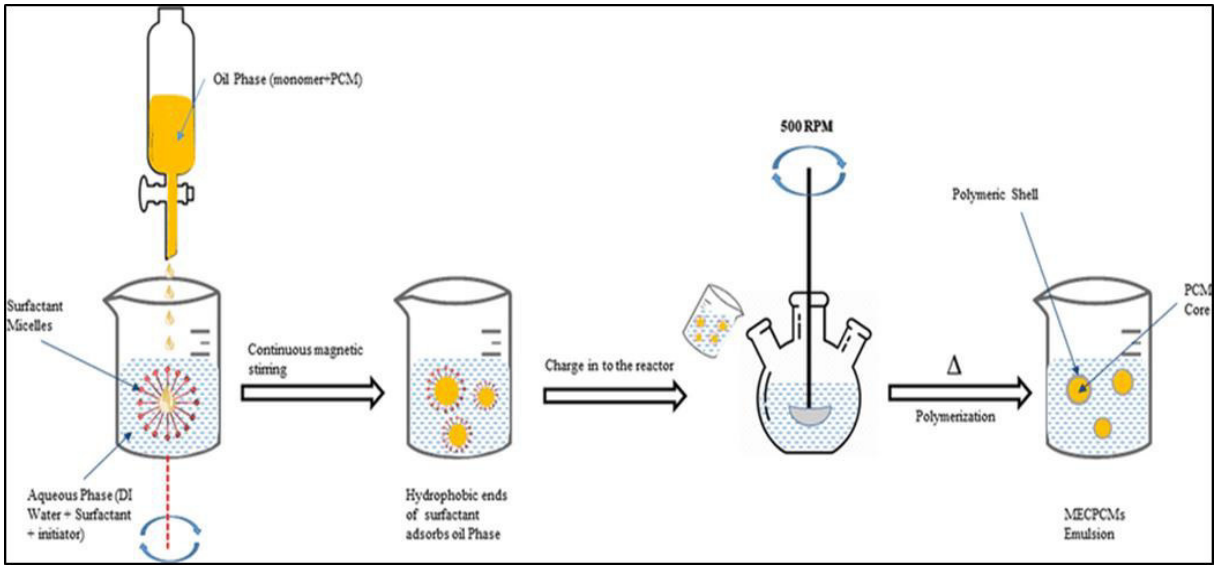

Fig.16: Nanoparticle Preparation by the Emulsion Polymerization Method[37]

f. Large-Scale Production of Nanoparticles

Supercritical fluid technology is commonly used to formulate nanoparticles from drug solutions. No different styles can be used for the supercritical solution procedure, the supercritical anti-solvent procedure, and precipitation with the condensed anti-solvent procedure (PCA). In the system, the drug solution is expanded in supercritical fluid with a nozzle, which causes the loss of solvent authority of the supercritical fluid and precipitates the drug as powdery particles. In the PCA system, the drug solution is powdered into a closet with compressed CO2 powdery chargers precipitate out, with the solution getting supersaturated after the solvent is removed. In the supercritical anti-solvent procedure, a supercritical fluid in which a drug is inadequately soluble is employed. The drug is then dissolved into a miscible solvent with the supercritical fluid. After injecting the drug solution into the supercritical fluid, the supercritical fluid extracts all the solvent, and the drug solution turns supersaturated. Also, the drug will precipitate as fine chargers. Compared with different methods, the considerable disadvantage of the discussed methods is that most solvents employed are dangerous. A large quantum of surfactants and stabilizers are employed during the preparation process[38].

g. Spray Drying technology[39]

Spray drying is a quicker and more economical, single-shift drying manner that can be allowed as a continued drying procedure. Spray drying is substantially suitable for heat-sensitive materials, despite the high temperatures of the drying gas, owing to the chilling effect of the evaporating solvent, which keeps the droplet temperature low enough. Besides this, another advantage of spray drying methodology is its capability to govern the particle size and the dried powder's morphology by differing the procedure parameters and formulation agents. This methodology is substantially similar to the route of administration via inhalation, so this methodology is of high significance for the pulmonary discharge of protein pharmaceuticals. However, low powder yield is quite the major problem with the growth of spray-dried pharmaceuticals because of the small quantities of expensive active ingredients accessible after the early stages of progress. Recent progresses achieved in the different regions of particle engineering, like spray drying in the last two decades, were attending with the elaboration of dissimilar pulmonary rectifiers apportioned traditionally by injection.

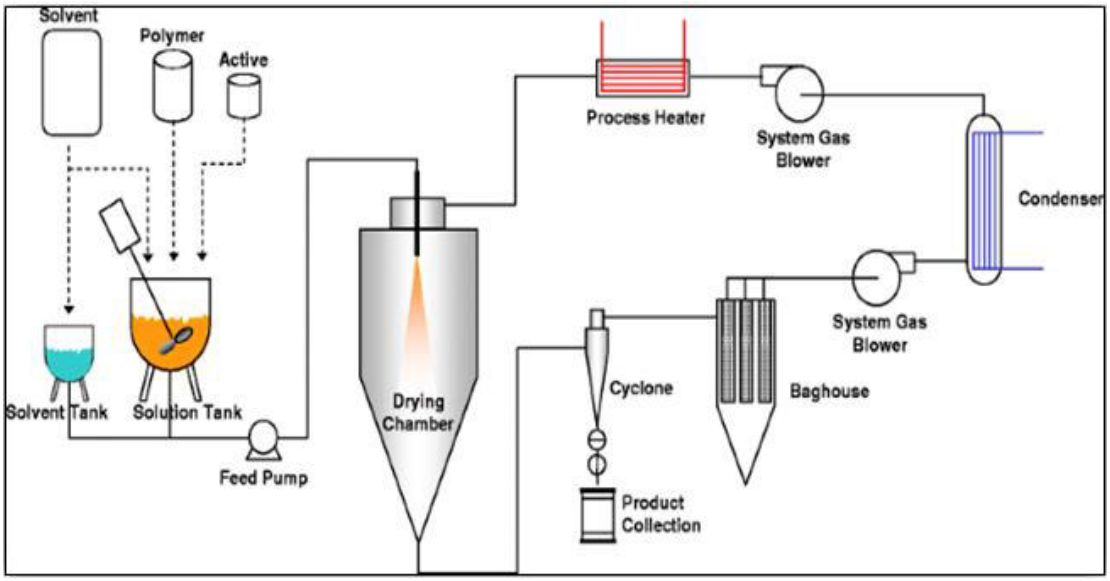

Fig.17: Spray drying technology Method of Preparation[40]

h. Carbon nanotubes

Carbon nanotubes (CNTs) were first observed by Iijima in 1991 and are characterized by their Nano-sized hollow tube-shaped structures. Based on the composition of layers, CNTs can be categorized as either single-walled carbon nanotubes or multi-walled carbon nanotubes. Both types are more popular nanomaterials for commercial applications and are widely used in fuel cell designs, photovoltaic, and biomedicine. The distinct properties of nanomaterials have been considerably studied in various actions, and for example, the objectification of nanotechnology is anticipated to contribute to defensible energy. Nanotechnology-predicated consumer products have been commercially accessible to appointment. Market Research Report data shows 20,000 tons of CNTs will be produced by 2022. There are at least 38 marketable products containing CNTs on the market[41].

i. Iron nanoparticles

Iron oxide nanoparticles can substantially donate to current imaging, identifying, and therapeutic applications. Magnetic nanoparticles comprise a magnetic core (iron oxide or magnetite) and a biocompatible polymeric shell (dextran or starch). These nanoparticles command superior targeting capacities compared with dissimilar nanoparticle networks due to their responsive properties to magnetic waves. Magnetic nanoparticles are undertaken to retain advantages beyond the improved permeability and retention effect, a common yielding targeting methodology for tumor-targeted nanoparticles. The iron oxide core in the magnetic nanoparticle contains magnetite or magnetite or a nonstoichiometric composition of both. Magnetic nanoparticles are produced using traditional solution-grounded wet chemistry, laser pyrolysis, aqueous co-precipitation, and high-temperature decomposition of organometallic precursors[42].

6.3. Methods of Preparation[42]

i. Co-precipitation
ii. Thermal decomposition
iii. Micro emulsion
iv. Hydrothermal synthesis
v. Sono-chemical synthesis

6.4. Co-precipitation

This method, Fe3O4 or Fe2O3 is synthesized by mixing ferrous and ferric ions (usually in a 2:1 molar ratio) in basic solutions at a basic RT or elevated temperatures. The size and shape of the nanoparticles produced by this system depend on the ferrous or ferric salt used, the ferrous/ ferric ions rate, temperature, etc. This method produces nanoparticles with a wide size distribution. As the process requires high-pH solutions, the by-products of this process require further purification.

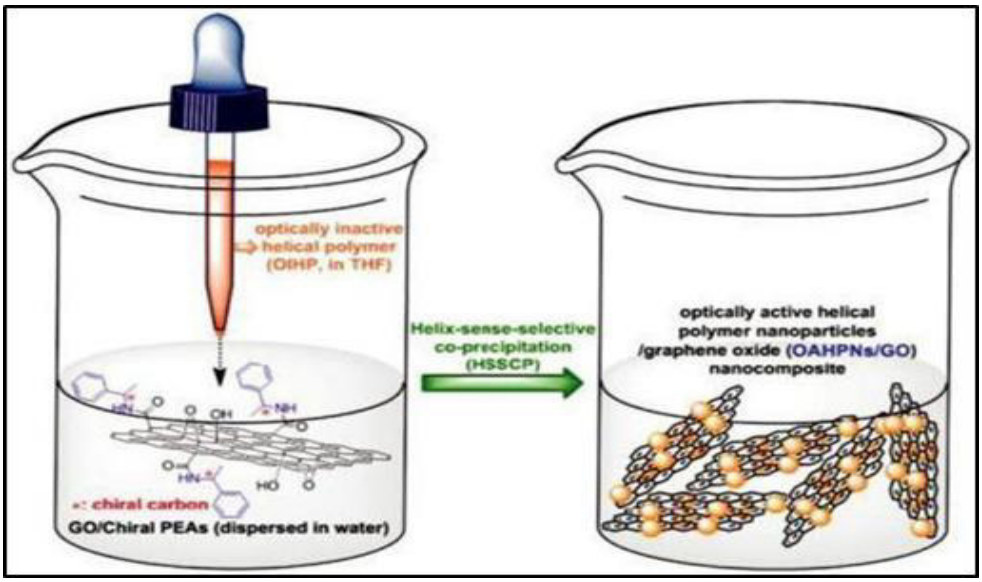

Fig.18: Co-precipitation Method of Preparation Co-precipitation[43]

6.5. Thermal Decomposition

This process involves the thermal decomposition of organic composites similar to Fe (CO) 5, Fe (N-nitrosophenylhydroxylamine) 3, or Fe (acetylacetonate) 3. The corruption is followed by oxidation, which produces high-quality monodispersed iron oxide nanoparticles. The drawbacks of this system include high-temperature conditions and the production of nanoparticles that disperse and disappear only in nonpolar solvents.

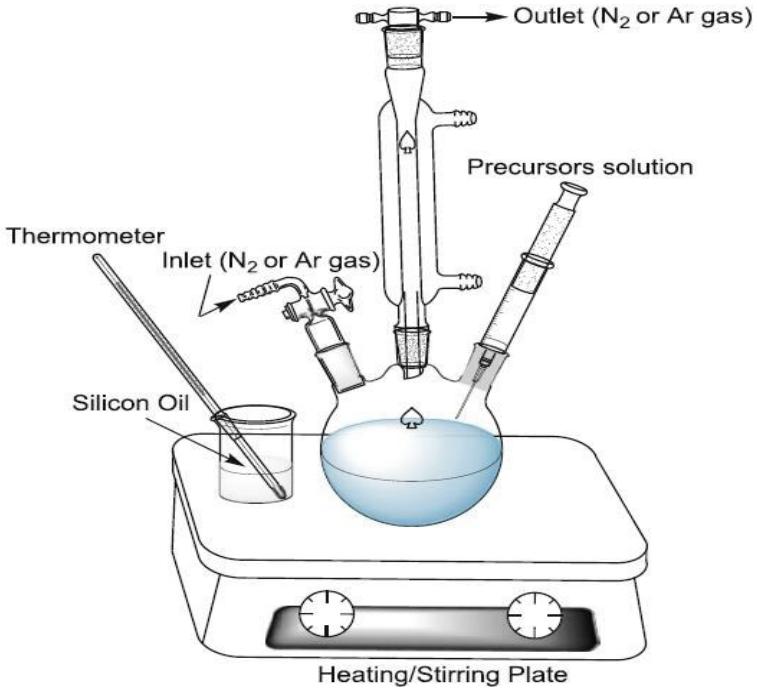

Fig.19: Thermal Decomposition Method of Preparation[44]

6.6. Microemulsion

In this system, first, the microemulsion in the aqueous phase is prepared with ferric and/ or ferrous ions in the presence of 0.1 M HCl to avoid oxidation of the ions. The microemulsion is additionally precipitated by injecting organic precipitating agents such as cyclohexylamine or oleylamine. The disadvantages of this method include aggregation and stability issues with the nanoparticle's Hydrothermal Synthesis. This system involves the production of nanoparticles by crystallization from an aqueous solution of ions at a high temperature under high vapor pressure. The crystallization can be facilitated using various wet chemical technologies, producing nanoparticles with good monodispersity.

6.7. Sonochemical Synthesis

This system involves the operation of sonochemical ways similar to the sonication of an aqueous solution of ions to developed nanoparticles. For example, magnetite nanoparticles can proceed by sonicating an iron (II) acetate aqueous solution. Other iron oxide nanoparticle preparation

methods include electrochemical synthesis, laser pyrolysis technique, and microorganism or bacterial synthesis[42].

7. NANOPARTICLE CHARACTERIZATION TECHNIQUE[45]

7.1 Microscopy-Based Nanoparticle Characterization

7.1.1 Scanning Electron Microscope Mechanism and Principles

In scanning electron microscopy, an electron beam is directed toward the specimen instead of a light beam, as in the case of an optical microscope. A largely concentrated electron ray is shot at the device's lid from an electron gun. The two main electron gun types are field emigration guns, which induce a strong electric field that rips electrons from the atom, and thermionic guns, in which the filament is heated until the electrons stream away. The SEM scans the initial surface of the sample with high-energy electron beams. Therefore, SEM makes some diversity from standard glow microscopes by using light swells to create a magnified image. In SEM, when the electron beam strikes the sample surface, it interacts with the surface. When the incident ray of electrons hits the sample, X-rays and three types of electrons are emitted backscattered (or immediate), derivative, and Auger electrons. SEM makes exercise of the primary, or backscattered, and the secondary electrons. High-resolution images are delivered by SEM discovering items of about 1 – 5nm employing the secondary electrons. For relating beginning pieces, distinct rays are utilized by a methodology understood as EDX. The backscattered electrons are likewise exercised to form the image in this methodology[45].

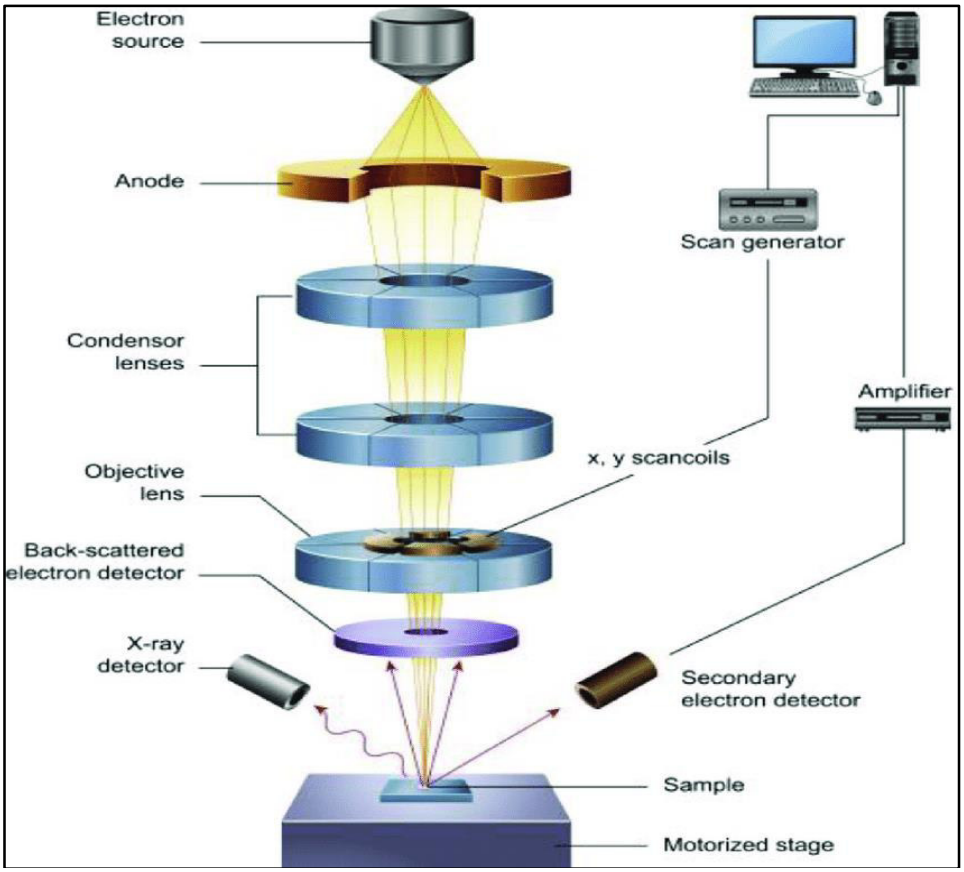

Fig. 20: Scanning Electron Microscope[46]

7.1.1 Energy Dispersive X-Ray Analysis

EDX is used in combination with SEM. An electron ray with an energy of 10 – 20 keV strikes the channeling sample's surface, causing X-rays to expel initially from the material & energy of emitted rays on the material under test. EDX doesn't suit under a methodology for surface wisdom, as the X-rays are generated in a region of about 2 micrometersin depth. Moving the electron ray across the material can give an image of each factor in the sample. It typically takes extended hours to develop the icons, as the emphasis of the X-ray is tropical. The number or quantity of nanoparticles near and at the prime surface can be evaluated employing the EDX, delivered if they hold some massive metal ions. For example, surface nanoparticles like silver, gold, and palladium can subsist fluently by exploiting EDX. Elements of low infinitesimal numbers are delicate to describeby EDX[45].

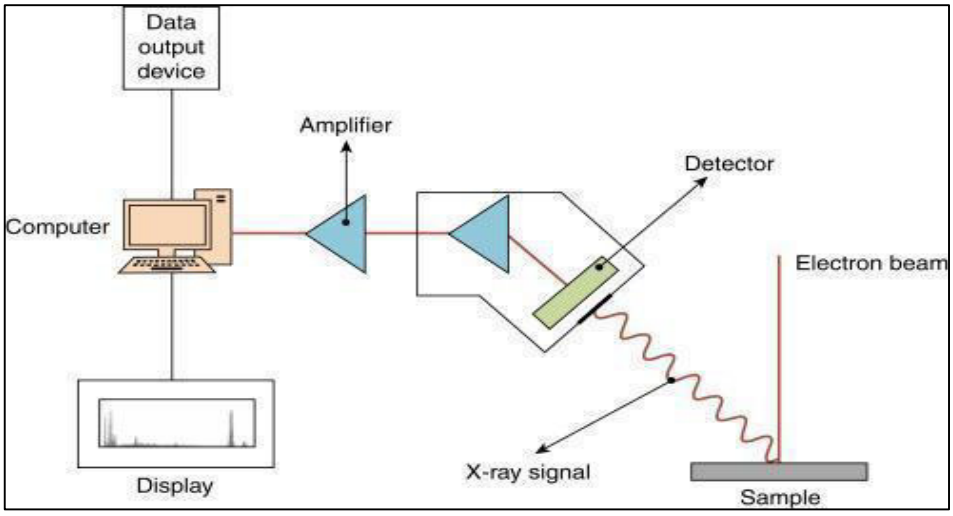

Fig. 21: Energy Dispersive X-Ray Analysis[47]

7.1.2 Atomic Force Microscopy

AFM is a scanning probe microscope employed to compute properties similar tocrest, magnetic force, surface eventuality, and conflict, and it also can measure intermolecular forces. AFM amplifies the images of specimens and uses a stake made from silicon or silicon nitride with a low spring constant to image the sample. AFM contains an optic head, a portable scanner, and a multimode base. The head contains the probe, laser, photodiode array, and adaptation cloudsemployed to align the network. The sampling is deposited on the scanner holding the piezo tube, which controls the shifting of the sampler. The base controls the raising and lowering of the probe. A laser ray is reflected from the cap of the stake continually, and the ray detects the bend in the stake and calculates the effective capacity of the stake. AFM records a three-dimensional image of the sample's surface topography under a steady applicable force, resulting in a full-resolution image [48].

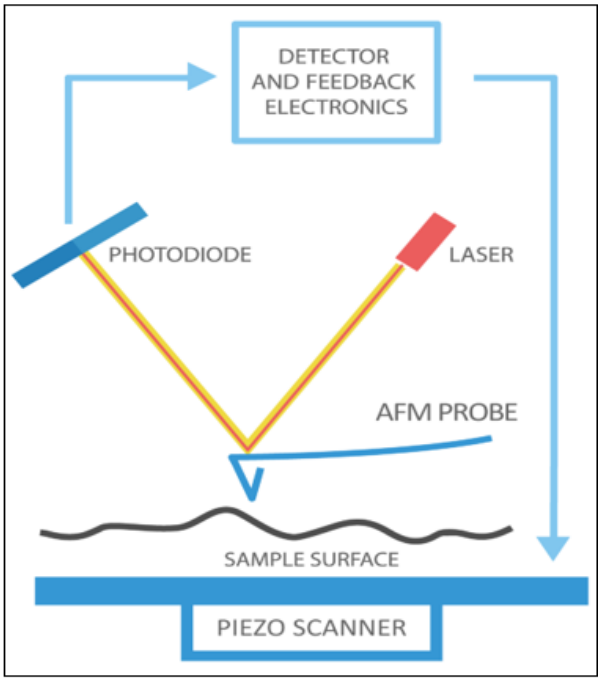

Fig. 22: Atomic Force Microscopy[49]

7.1.3 Transmission Electron Microscopy

This is another applied methodology for the characterization of Nanomaterials. It's a quantitative system to rule shape distribution (PDI) & size of particles. TEM is also an electronic spectroscopic imaging methodology with a higher resolution than SEM. The advantages of TEM over SEM are more spatial determination with the additional capability of logical dimensions. Many boundaries of this methodology are a demand for high vacuum, slim sampler district, and sample preparation is time-consuming. The sample preparation is extremely consequential for getting high-class images for sample information[50].

7.1.4 High-Resolution Transmission Electron Microscopy

HRTEM imaging is an excellent methodology for differencing between micro or nano-crystalline diphasic, rigid polycrystalline, and single crystalline phases. The composite

of radiant field black field imaging is specifically applicable in adjudicating crystallite size divisions. Two boundaries to this avenue are (i) the small quantity of a substance that can be imaged and (ii) the expenditure and complication of sampler preparation. There's also the potentiality of fluctuations in morphology during sample preparation or under electron ray imaging. In addition to furnishing immediate imaging, cross-sectional HRTEM likewise provides an accessible way for carrying diffraction data. The sign of the diffraction pattern discriminates between on-crystalline, micro- or nano-crystalline, polycrystalline, and single crystalline phases. Reflection high-energy electron diffraction (RHEED) provides another way of probing morphology, but because of the grazing prevalence employed, it's especially applicable for actual slim films[51].

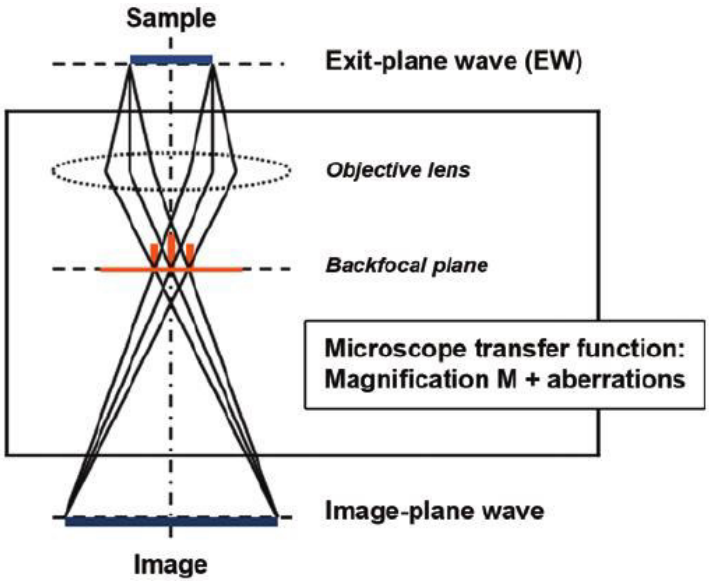

Fig. 23: High-Resolution Transmission Electron Microscopy[52]

7.1.5 Scanning Tunneling Microscopy

This methodology has been employed specifically for the surface study of nanostructure using different chemical compositions of atoms and molecules in Nanoparticles to image the surface/body at the microscopic level. STM was the first methodology exploited to study nanostructure morphology and size. STM cannot simply work at ultra-high vacuum provisions but likewise in air, liquids, and gases at a range of temperatures from near 0 K to over 1000 °C. The STM working principle is quantum tunneling, where a tip is moved across the surface area of a sample. An image is formed due to variation in tunnelling current as the tip moves across the surface. STM offers a good side resolution of 0.1 nm and a deepness resolution of 0.01 nm. At this resolution, respective atoms within materials are routinely pictured. STM can be an exacting technique, as it requires veritably clean, firm surfaces and sharpened channeling tips[53]

7.2 Spectroscopy-Based Characterization Techniques

Following mentioned are some Spectroscopy-Based Characterization Techniques.

- Ultraviolet-Visible Spectroscopy
- Raman Spectroscopy
- Fourier Transform Infrared Spectroscopy
- X-Ray-Related Characterization Techniques
- X-Ray Diffraction

7.2.1 X-ray diffraction

X-ray diffraction (XRD) is an extensively used methodology to impose the crystallinity and structure of solid samples. In summary, the crystal X-ray diffraction phenomenon results from a dispersing process in which X-rays are dispersed by the electrons of atoms present in the sample without modifying the wavelength. Since X-rays have wavelengths (between 0.2 and 10 nm) similar to the interatomic distance of a crystalline solid, the incident X-ray ray diffracts in special directions, called to Bragg's law. The functional diffraction design, given by the connections and emphasis of the diffraction holdings, is a beginning material property of the material, delivering not only the identification but also the comprehensive explanation of its building[54].

7.2.2 X-Ray Photoelectron Spectroscopy

This surface analysis methodology is extensively used to decide the essential composition and oxidation countries of essentials at the surface/Phase of MNPs by excitation of inner orbital and relating electrons by a focused-ray ray. The XPS spectrum is obtained by measuring electrons' kinetic energy and volume. Energy dispersive spectroscopy (EDS) is a surface microanalysis technology in which an electron ray irradiates nanoparticles to excite diagnostic X-rays. EDS provides data about the fundamental analysis, chemical composition, and forecast particle structure[55].

7.2.3 Dynamic Light Scattering

This provides a means of the size of the particles from the scattered light as a result. DLS can determine the alteration in the configuration of the DNA due to intercalation because of the difference in the size allocation caused by it. The DLS study on the intercalation of ethidium bromide to calf thymus DNA exemplified two binding modeswhere one is low, and the other one is stronger. The stronger binding mode was deemed intercalation, and the weaker was the outside-set stat[56].

7.2.4 Zeta Potential

The zeta potential (ζ [=] mV) of slurry particles is often used as a metric to gauge the particles' stability in the colloidal sense; it is the electric potential at the slipping plane relative to a point in the bulk medium and is not similar to the holding potential or the surface potential as those are detected at different locations on and about the particle. Ions within the Stern layer and slipping plane are generally conveyed with the particle in transport proceedings. Thus the zeta eventuality is frequently counted as the operative complaint on the particle. These two layers, with which the particle's surface possibly decays to path the eventuality of the body solution, are inclusively applied as the electric double-layer. Particles of like charge will have a lower propensity to agglomerate as their absolute zeta eventuality increases, and slurries with particle zeta capabilities ζ>|30| are counted as colloidal stable[57].

Table - 7. Principal techniques for evaluation of the physicochemical characterization of Nanocarrier system

Sr No	Technique	Characterization	References
1.	Differential scanning calorimetry (DSC)	Melting point confirmation	58
2.	Dynamic light scattering (DLS)	Hydrodynamic size distribution	59
3.	Fluorescence spectroscopy	Critical association concentration (CAC) determination	60
4.	High-performance liquid chromatography (HPLC)	Drug content, In-vitro drug release	61
5.	Infrared spectroscopy (IR)	Functional group detection	62
6.	Mass spectrometry (MS)	Molecular weight	63
7.	Near-field scanning optical microscopy (NSOM)	Shape, Size of nanomaterials	64
8.	Nuclear magnetic resonance (NMR)	Structure Composition	65
9.	Scanning electron microscopy (SEM)	Morphology of sample, Fracture analysis	66
10.	Scanning tunneling microscopy (STM)	Size and size distribution Shape Aggregation	67
11.	Transmission electron microscopy (TEM)	Particle Size & Size distribution	68
12.	Zeta potential	Particle size, Charge identification	69
13.	X-ray diffraction (XRD)	Nature of crystallinity	70

Table - 8. Application of nanotechnology in the different fields

Sr.no	Applied field	Application	References
1.	Healthcare sector	Ocular disease condition, Breast cancer in diagnostics, real-time in vivo bio-imaging	71
2.	Agriculture	Nanotechnology has the potential for precise delivery of agrochemicals for improving disease resistance, plant growth, and nutrient use	72
3.	Food Industry	Silver is mixed with polymers to preserve the quality of fresh food during extended storage.	73
4.	Cosmetic	Nanocrystals allow safe and effective passage through the skin	74
5.	Textile	Nano-Tex improves the water-repellent property of fabric by creating nano-whiskers, which are hydrocarbons and 1/1000 of the size of a typical cotton fibre,	75
6.	Chemical Industry	chemical sensor: a self-contained analytical device that may provide information about the precise chemical composition of its environment	76

8 HEALTH IMPLICATION OF NANOPARTICLES

8.1 Nano-carrier system in Skin disease

Controlled drug delivery, improved bio-distribution, effective targeted accumulation, and skin medication physicochemical stability[77]. The responsiveness of certain NPs allows for the regulated release of encapsulated cargos, reducing adverse effects and increasing the efficacy of the therapy[78].

8.2 Nano-carrier system in Brain

These nanoparticles help hydrophobic drugs better cross the BBB for the goal of brain-related therapy[79].

8.3 Nano-carrier System in Lungs

These nanoparticles have found extensive usage in cancer therapy due to their naturally small dimensions, which allow them to specifically collect in tumour cells as they permeate through the leaky vasculature in the area of the tumour cell mass (increased permeability and retention effect)[80].

8.4 Nano-carrier system in Heart

Fluorescent carbon nanoparticles (CNP) have drawn much interest because of their unique fluorescent properties and safety. In many studies, PEG-CNP and CNP's potential are invented for non-invasive cardiac imaging[81].

8.5 Nano-carrier system in Kidney

Nanobubbles (NBs) are ten times smaller than ordinary microbubbles (MBs), making them new-generation UCAs12,13. Numerous studies have demonstrated that NBs may achieve significant nonlinear contrast enhancement at the standard frequency used in clinical US14,15 despites being off-resonance. Furthermore, it has been shown that NBs can extravagate from the vasculature into the interstitial

space[82] throughout their protracted existence in blood circulation.

9 FUTURE OPPORTUNITIES AND CHALLENGES

Nanoparticles have been utilizedto deliver medications with great effectiveness in the past. Nanoparticles are one of the main tools in nanomedicine due to their potential for combining diagnostic and therapeutic, drug transport, and drug targeting. There are many technical difficulties with the following strategies: Viral-like intracellular systems; biomimetic polymer architecture; bioresponsive trigger systems; systems engaging with me-body smart delivery; management of sensitive medications; nanochips for nanoparticle release; carriers for enhanced polymers for therapeutic delivery of peptides and proteins; etc. Drug delivery systems were created to provide or control the dosage and rate. Most famous and ongoing internal drug delivery formulation and dispersion research efforts use nanoscale components. Nanomedicine offers greatpromise for developing novel therapies for diseases once considered difficult or incurable and for improving already available medications. Even though there has been extensive research on medical nanoparticles recently, and several nanomedicines are currently available, a product breakthrough has yet to occur.

10 CONCLUSION

Means of an informal survey on several nanocarrier systems conducted for effective & informative review. We conclude that nanocarriers are the most cutting-edge tool in medical, cosmetic, and other fields. The last section of this topic provides a thorough introduction and descriptive information about the Nanocarrier system, including its classification, introduction, morphology, three-dimensional arrangement, various preparation and characterization methods, Health Implications of Nanoparticles & Future opportunities, and challenges.

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12 AUTHORS CONTRIBUTION STATEMENT

All authors from this review article contributed together with Dr. Abubakar Salam Bawazir&Dr. Mohammed Ismail Mouzam guided about this entire topic & proper data input. Ms. Pooja S Murkute designed the entire review article. Mr. Nakul P Kathar& Mr. Krishna K Deore analysed these data, and necessary input wasgiven towards the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

13. CONFLICT OF INTEREST

Conflict of interest declared none.

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