SCHEMATIC DIAGRAMMATIC PREPARATION METHODS OF POLYMERIC NANOPARTICLES FOR BIOMEDICAL APPLICATIONS IN RECENT AND FUTURE PROSPECTS

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ABSTRACT:

With an increased population, the globe is undergoing radical changes, resulting in shorter life cycles as living forms improve. Along with it comes the curse of mental life, as the curse of germ growth is gradually being replaced by the curse of death. The discovery of nanotechnology by world scientists is very significant in this context. Aside from everyday materials, the discovery of nanotechnology, in particular, plays a significant role in disease diagnosis, treatment, and prevention. The usage of nanosystems in medical care may aid in the treatment of cancer. Nanoparticles are appropriate for various biological objectives and have relatively high intracellular absorption compared to small particles; nonetheless, their widespread usage is still in the future. The following review discusses various methods of preparing nanoparticles, such as cross-linking, emulsion polymerization, polymerization dispersion, interfacial polymerization, solvent evaporation, double emulsion, emulsion diffusion, and salting out methods. A pictorial overview and classification, utility, and activity are provided. Specifically, drug delivery, drug dosage forms, and methods are described, as well as the appropriate polymer and its specifications. According to the initial review, further nanotechnology discoveries are essential for the survival of human life and the survival and development of organisms. In such a situation, multidisciplinary University collaboration, proper research, and proper research funding by the government and NGOs is the gap in nanotechnology, which we hope will be filled soon.

Keywords: Nanotechnology, nanopartcles, emulsion polymerization, double emulsion, emulsion diffusion.

INTRODUCTION:

Since the turn of the century, researchers have been studying nanotechnology; Nobel laureate Richard P. Feynman first discussed it in his speech "There's Plenty of Room at the Bottom: An Invitation to Enter a New Field of Physics". Following it, a variety of advancements in nanotechnology have been made[1]. The advancement of nanotechnology is crucial for illness detection, treatment, and prevention. The Greek word nanus, which meaning dwarf or exceedingly little, is where the name nanoparticle originates. Nanoparticles (NPs) are cutting-edge scientific discoveries in which pharmaceuticals are dispersed, entrapped, adsorbed, adhered,

and/or encased in or on a nanoparticulate matrix while being surrounded by a polymeric membrane[2]. Drug delivery systems typically have a minimum size of 100 nm and include a variety of biodegradable elements like lipids, metals, or polymers, whether they are manufactured or natural[3]. It has three layers, (a) A surface layer that can be changed with various small molecules, metal ions, surfactants, and polymers. (b) the centre, which makes up the majority of NPs; (c) the shell layer, which is chemically entirely distinct from the core in all respects[4]. Nanoparticles are made from a variety of polymers. Nanodelivery systems can easily and effectively deliver macromolecules such as peptides and proteins. Nanoparticles deliver drugs to the site of action at a consistent and controlled rate[5]. Owing to its special properties, including its surface-to-mass ratio and ability to adsorb and transport materials including drugs, probes, and proteins. Nanoparticles are an intriguing method for delivering anti-cancer medications to tumours; it has been used successfully to target medications for the brain[6]. The first nanoparticle drug to be delivered to the brain was the hexapeptide Dalargin (Tyr-D-Ala-Gly-Phe-Leu-Arg). Loperamide, phytotoxins, and antibiotics have also been successfully delivered to the brain[7]. This review focuses on the most promising applications of nanoparticulate polymeric formulations as nanocarriers, mainly those used to treat diseases with major morbidity, a significant reduction in patient quality of life, or even significant mortality.

Types of Nanoparticles:

Nanoparticles are classified according to their structure, size, and physical and chemical properties; these are polymeric nanoparticles, Carbon-based nanoparticles, ceramic nanoparticles,metal nanopartcles, semiconductor nanopartcles and lipid-based nanoparticles[1].

Polymer Used in Nanoparticle Preparation:

Polymer-based nanomaterials can either be adsorbed on their surface or entrapped inside to allow for controlled drug release. Biocompatible and biodegradable polymers should be used to create nanoparticles. It can be either natural or synthetic[8].

The natural polymers are chitosan, gelatin, alginate and the synthetic polymers includes poly acrylate, poly mathacrylate, poly lactide (PLA), polycaprolactones, and poly lactide-co-glycolide (PLGA)[9].

Carbon-based Nanoparticles:

Carbon is present in these nanoparticles. It is made up of two main parts: carbon nanotubes (CNTs) and fullerenes. CNTs are graphene sheets that have been rolled into a tube. These materials are mostly utilised for structural reinforcement because they are 100 times stronger than steel. Carbon nanotubes are divided into two types: multi-walled carbon nanotubes (MWCNTs) and single-walled carbon nanotubes (SWCNTs) (SWCNTs). CNTs are unique in that they are thermally conductive along their length but non-conductive at the top[10].

Fullerenes are carbon allotropes. Figure 1 depicts their structure, which resembles a hollow cage. There are at least sixty carbon atoms below. C-60 is structurally similar to a hollow football and is known as Buckminsterfullerene. The carbon units in these structures are arranged in pentagonal and hexagonal patterns[11].

Ceramic Nanoparticles:

Ceramic nanoparticles are inorganic solids composed of oxides, carbides, carbonates, and phosphates. These nanoparticles have a strong heat resistance and are chemically inert. They can be used to deliver drugs for a variety of diseases such as glaucoma, bacterial infections, and cancer[12].

Metal Nanoparticles:

These nanoparticles can be produced using electrochemical, chemical, or photochemical methods. Metal nanoparticles can be created chemically by decreasing metal-ion precursors in liquid with chemical reducing agents. They have a high surface energy and can adsorb small molecules. They are commonly used in Environmental and bioanalytical applications, as well as biomolecule research, detection and imaging[13].

Semiconductor Nanoparticles:

They have properties with both metals and nonmetals. They are classified as periodic table groups II-VI, III-V, or IV-VI. Some examples include InAs, InP, GaN, GaP, Silicon, and Germanium. They can be used in electronics, photonics, photocatalysis, and water splitting, among other things[14].

Lipid-Based Nanoparticles:

They are typically spherical in shape and range in diameter from 10 to 100nm. It is made up of a strong lipid core and a network of soluble lipophilic particles. Surfactants and emulsifiers stabilise the outer layer of these nanoparticles. These nanoparticles have biomedical applications as drug carriers and delivery, as well as RNA release in cancer therapy[15].

The Dimensional Classification of Nanoparticles:

Nanoparticles are classified as 0D, 1D, 2D, or 3D nanoparticles based on their crystalline form and chemical composition. This division is based on how electrons move within NPs along different dimensions. In 0D NPs, electrons are imprisoned in a dimensionless region; in 1D NPs, electrons can only move down the x-axis, which is no wider than 100 nm; in 2D and 3D NPs, electrons can move along the x-y axis and the x, y, and z axes, respectively[16].

Mechanisms of Drug Release:

The drug is delivered to the tissue site via one of three general physicochemical the following mechanisms are described: The polymer nanoparticles inflate when they are hydrated, and then they disperse. The drug is released from the entrapped inner core drug de-adsorption by an enzymatic reaction that causes the polymer to rupture, degrade, or cleave at the site of delivery[17].

METHODS OF PREPARATIONS OF NANOPARTICLES:

1. Cross-Linking Techniques:

These nanoparticles are composed of proteins, amphiphilic macromolecules, and polysaccharides with aqueous and lipid solvent affinity. Their method of preparation entails amphiphile aggregation followed by further stabilisation via thermal denaturation or chemical cross-linking. The emulsification of bovine serum albumin, human serum albumin, or protein aqueous solution in oil is accomplished by high-pressure homogenization or high-frequency sonication. Pouring them into preheated oil (heat cross-linking) produces w/o emulsions. The preheated oil suspension is stirred at temperatures above 100 degrees Celsius to protein aggregation and denaturation components and evaporate the water. The formed particles are washed with natural solvents to remove any traces of oil before being collected by centrifugation. Chemical cross-linking is used to strengthen heat[18].

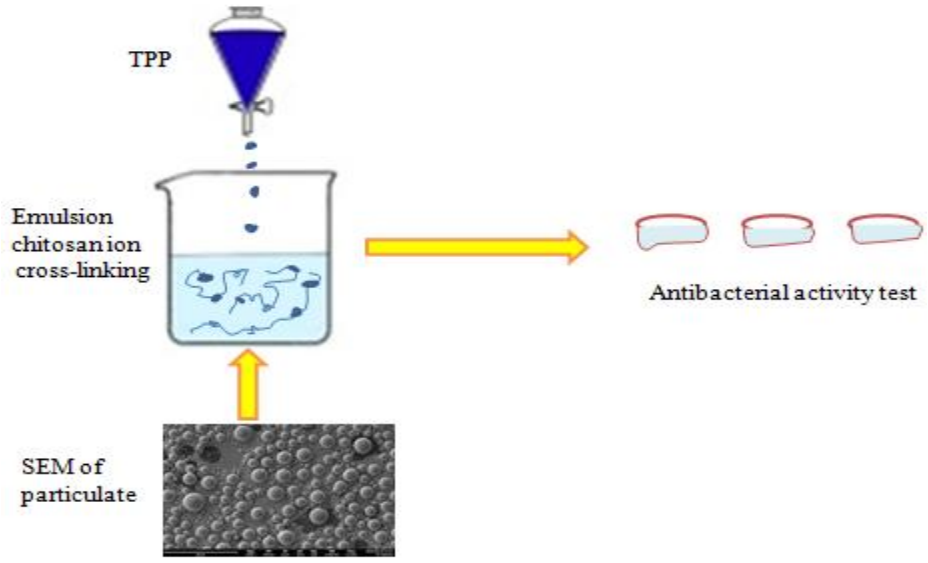

Figure 1: Nanoparticles Preparation by Cross Linking Techniques

2. Methods based on polymerization:

A) Emulsion polymerization:

Emulsion polymerization (EP) is the process of polymerizing emulsions containing water, monomers, and surfactants. Oil-in-water emulsions are the most prevalent type of emulsion polymerization, in which droplets of monomer are emulsified in a continuous phase of water. One of the most effective processes for creating nanoparticles is EP. Monomers must be dispersed in a solvent that doesn't dissolve the monomer (non-solvent). Surfactants or protective soluble polymers are employed to stop aggregation during the initial phases of polymerization. The polymerization process can then be started by employing a variety of techniques, such as applying high energy radiation like UV or visible light, turning the monomers into initiator radicals. Initiation takes place when one of these radicals encounters a monomer. Before or after the polymerization reaction is finished, phase separation and the creation of solid particles can take place[19].

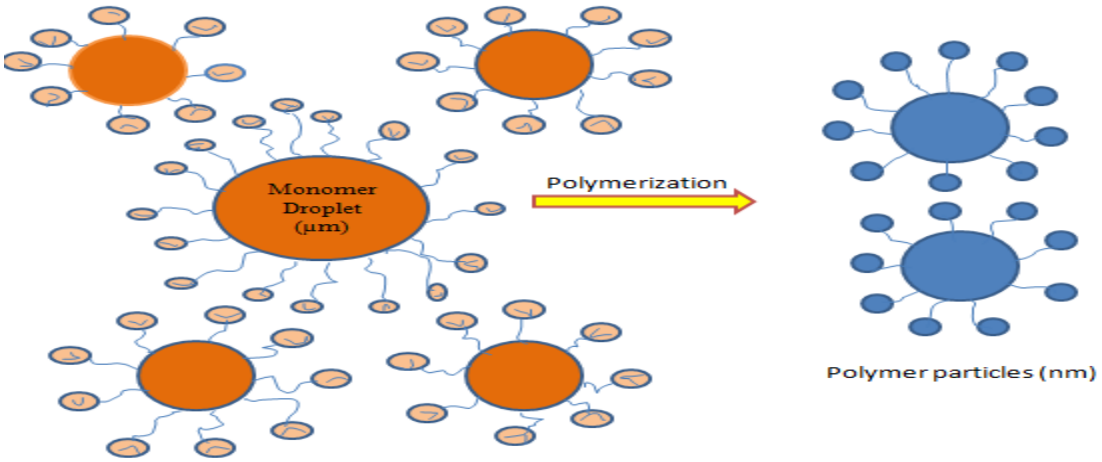

Figure 2: Nanoparticles prepared by emulsion polymerization method

B) Dispersion polymerization:

It is a homogeneous system in which monomers, initiators, and a stabiliser are dissolved in a solvent to form polymer particles. The monomers and initiators are easily dissolved in the solvent used for the reaction medium, which is a non-solvent in this method. Stabilizers/surfactants are not needed because nucleation is directly triggered in aqueous monomer solutions. The starting process is identical to that of emulsion polymerization by high energy irradiation. Polymerization begins with the addition of a catalyst and proceeds through the nucleation stage, which is followed by the development stage[20].

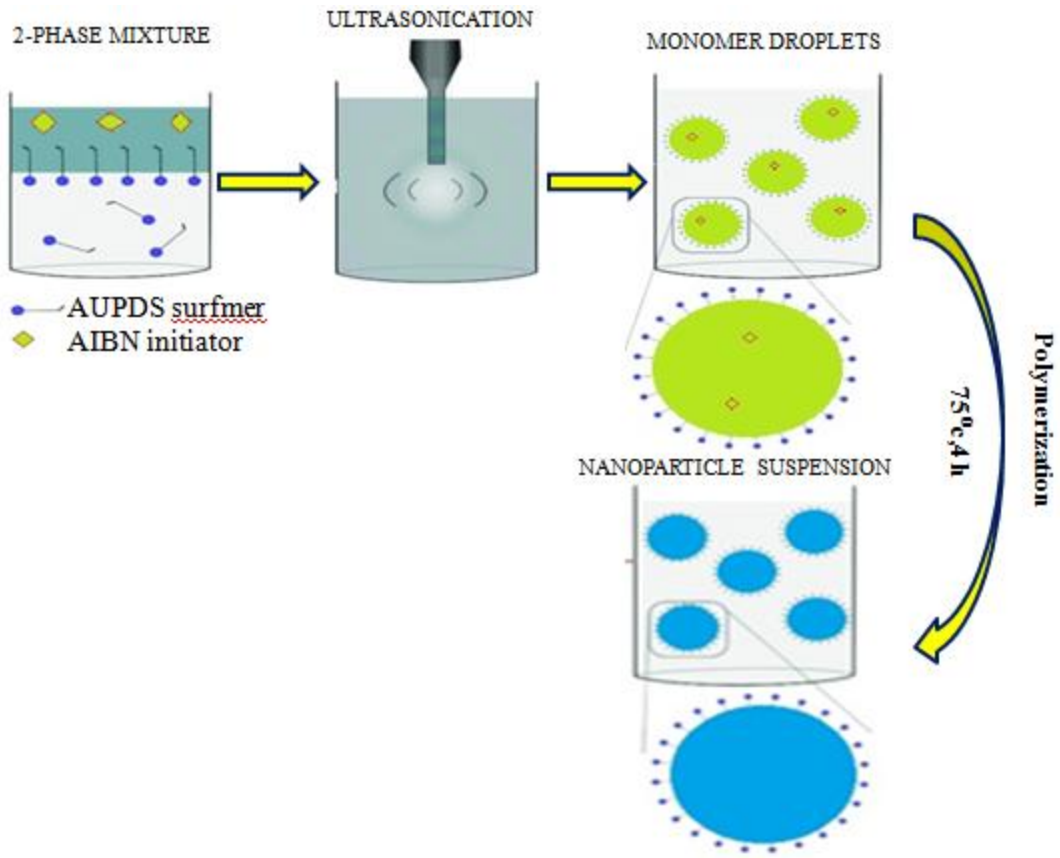

Figure 3: Nanoparticles prepared by polymerization dispersion method

C) Interfacial polymerization:

This is a step-growth polymerization that happens at the interface of two immiscible phases (often two liquids). This is a well-known method for creating nanoparticles. The polymerization of two reactive agents or monomers that dissolve in two phases (ie, continuous- and dispersed-phase) happened at the interface of two liquids. Monomer polymerization at the oil/water interface of very fine oil-in-water microemulsions produced oil-encapsulating nanocapsules[21].

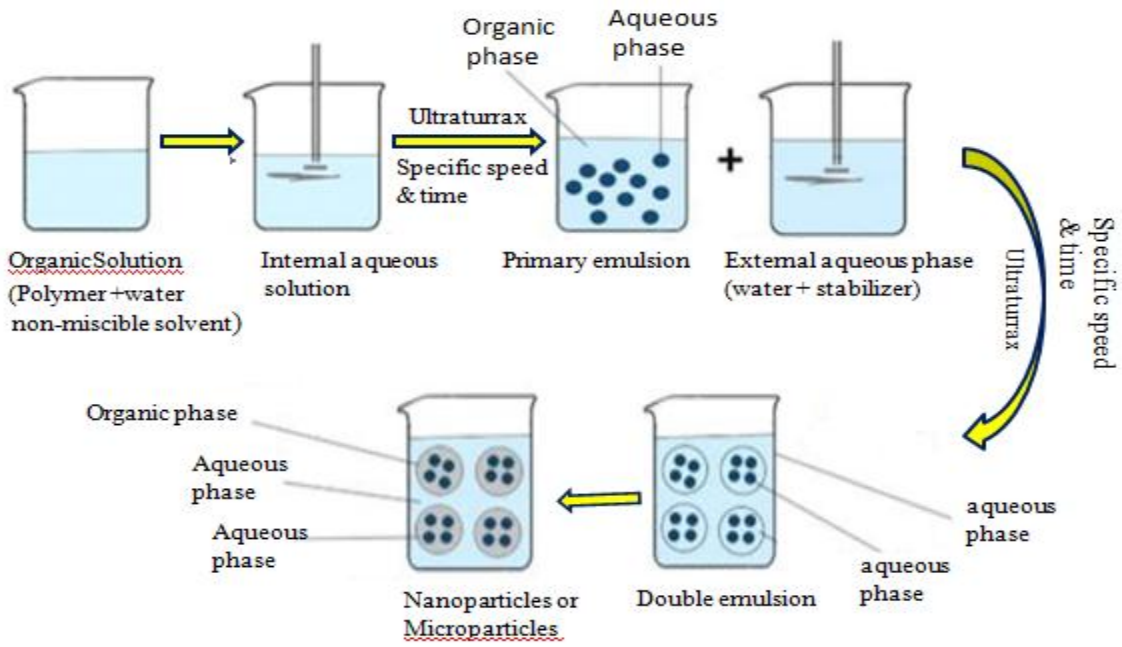

Figure 4: Nanoparticles prepared by iterfacial polymerization method

3. POLYMER PRECIPITATION METHODS:

a) Solvent evaporation:

The drugs and polymers are dissolved in an organic solvent such as chloroform or dichloromethane, and the combination is then emulsified into an aqueous phase with surfactants such as sodium dodecyl sulphates. Make oil-in-water emulsions (high-pressure homogenization) by mechanical stirring, sonication, or microfluidization. The organic solvent is then evaporated by gradually increasing the temperature and decreasing the pressure while stirring constantly. Controlling the size of the nanoparticle can be accomplished by adjusting the stirring rate, the kind and amount of dispersing agent, the viscosity of the organic and aqueous phases, and the temperature. Cellulose acetate phthalate, PLA, Poly-hydroxybutyrate and PLGA, are the polymers used in this method (PHB)[22].

b) Double emulsion method:

In this method of preparation technique the double emulsification approach is employed because emulsification and evaporation procedures do not effectively capture hydrophilic medicines. Aqueous drug solution and organic polymer solution are constantly stirred to create the w/o emulsion. The w/o/w emulsion is then created by aggressively stirring this manufactured emulsion into the aqueous phase. The organic solvent is then removed by high centrifugation[23].

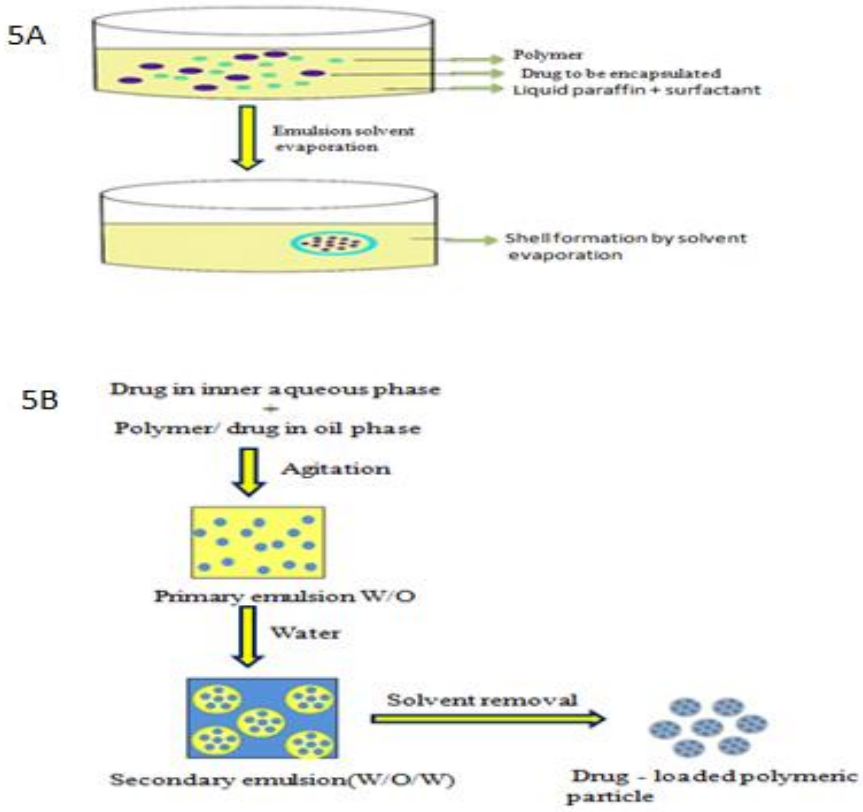

Figure 5: 5A Nanoparticles prepared by solvent evaporation method; **5BNanoparticles prepared by double emulsion method**

c) Emulsions- Diffusion Method:

This technique can be used instead of the emulsification-evaporation technique to get around toxic solvent problems. It is simple to implement and highly reproducible. The encapsulating polymer is partially dissolved in a water-soluble solvent, such as propylene carbonate, then saturated with water to achieve the initial thermodynamic equilibrium of two liquids. It is also used to encapsulate pharmaceuticals, such as peptides and proteins. The water-polymer saturated solvent phase containing a stabiliser is then emulsified in an aqueous solution, dispersing the solvent into the external phase according to the oil-to-polymer ratio and resulting in the formation of nanocapsules or nanospheres. Finally, the solvent is eliminated either through evaporation or filtering, depending on the solvent's boiling point[24].

d) Salting Out Method:

The salting out method is a variation on the emulsification/solvent diffusion approach in which the medication and polymer are dissolved in a solvent rather than a hazardous solvent. Acetone is frequently employed because it can be easily removed and is miscible with water. The resulting aqueous gel is composed of salting-out agents like magnesium chloride, electrolytes like calcium

chloride and magnesium acetate, or non-electrolytes such sucrose and polyvinyl hydroxylidone, a colloidal stabiliser. When water or other aqueous solutions are added to oil/water emulsions to enhance the dispersion of acetone in the aqueous phase, nanospheres are created[25].

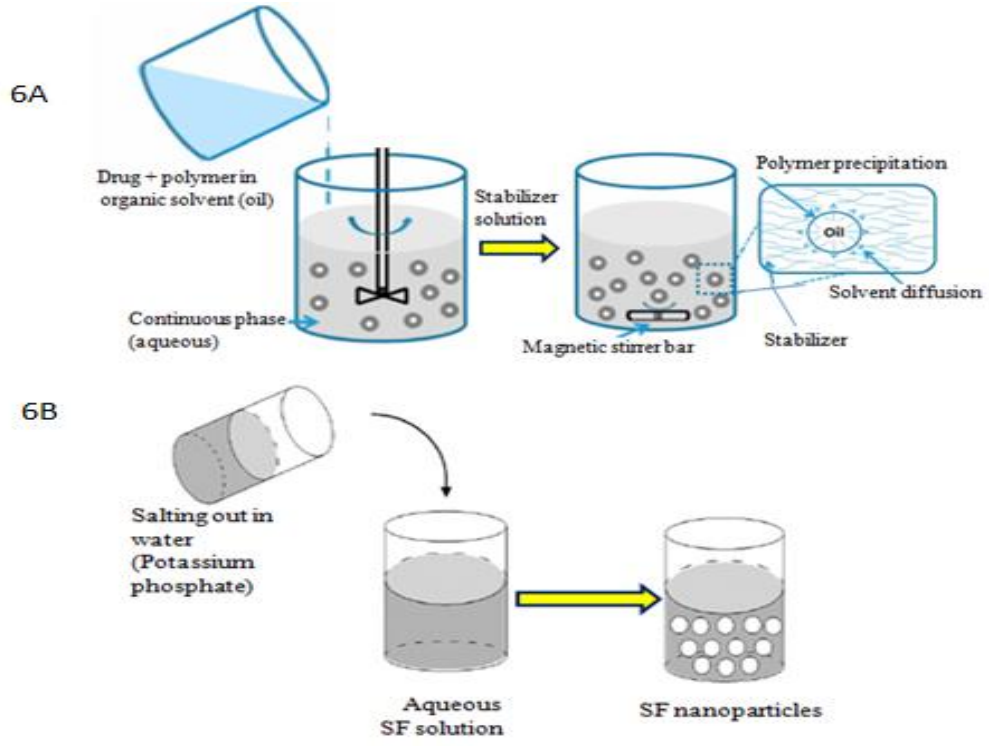

Figure 6: 6A Nanoparticles prepared by emulsion diffusion method and 6B Nanoparticles prepared by salting out method

BIOMEDICAL APPLICATION

Nanotechnology is being used in a wide range of applications around the world, including diagnostic and therapeutic uses. Biomedical experts are continually investigating ways to better the biomedical sectors of today and tomorrow. The following are some of the applications of nanoparticles that have been reported in various research publications[26]. The reducing toxicity and increasing the therapeutic activity, nanoparticles can effectively deliver in the field of chemotherapeutic drugs. Nanoparticles are effective at targeting drugs to specific areas with minimal side effects. By increasing retention time, nanoparticle systems can improve drug delivery to the eye. It can be used as a radionucleotide carrier for diagnostic purposes. This is extremely effective for increasing the bioavailability and solubility of poorly soluble drugs while also protecting the drug from gastrointestinal enzymes[27]. Solid nanoparticles can be used in hair and skin care treatments. Drugs can be delivered across the blood-brain barrier using nanoparticle drug delivery systems. Many macromolecules, such as proteins and peptides, can be delivered effectively using nanoformulations. It works well as a vaccine adjuvant, increasing

drug uptake and systemic circulation. Despite numerous preclinical studies, only a few of them have received marketing approval; some of them are discussed below: Because of their high capacity, nanoparticles are useful for tumour targeting; for example, doxorubicin nanospheres have higher concentrations in the liver, spleen, and lung than free doxorubicin[28].

In addition, gold nanoparticles (AU NPs) are now being used in medical imaging for early diagnosis or detection, as well as treatment of diseases such as tumour targeting. Gold nanoparticles are made up of gold atoms surrounded by negative reactive groups, allowing them to be easily biofunctionalized with a wide range of biomolecules. Surface plasmon resonance (SPR) bands on these nanoparticles transform light into heat, which is then dissipated to kill cancer cells[29].

Some polymers, such as degradable hydrophobic polymers like PLA and PLGA, are also suitable for the development of nanoformulations because they slowly decompose into their monomeric units over time. Leuprolide (a testosterone-blocking drug) combined with polylactide-co-glycolic acid (PLGA) nanoparticles, for example, has been shown to be extremely effective in the treatment of prostate cancer[30].

CONCLUSION

In today's rapidly expanding biomedical (drug delivery, drug discovery) and diagnostic disciplines, nanotechnology is a flexible component. However, finding the appropriate materials and processes to create nanomaterials is a challenge for scientists. Because biomedical materials are directly related to human life, choosing the appropriate material and method is of particular importance. The aforementioned discussion covered the use of several nanotechnology techniques, materials, and some of their applications. According to the preceding review, nanotechnology and its applications will play a unique role in the medical sector of human existence. Nanotechnology provides effective therapy, diagnostic, and treatment alternatives at a low cost and with few side effects. According to the above assessment, biological nanotechnology still needs to be fully revealed in many circumstances, which makes it a special attraction for nanotechnology researchers/scientists/students. There is a chasm between awareness, proper procedures, judgments, accountability, and government and non-government organizations.

ACKNOWLEDGEMENT

We would like to acknowledge, Bengal College of Pharmaceutical Sciences and Research, Durgapur, Maulana Abul Kalam Azad University of Technology, West Bengal, India for encouragement and support.

CONFLICT OF INTEREST: Nil

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