



Nanotechnology - A Review article

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ABSTRACT

Nanotechnology is going to revolutionize the world. For pharmacists, the applications of nanotechnology mean drugs containing nano-sized active ingredients. These drug delivery systems allow deposition of medications in previously inaccessible areas of the body, improved diagnostic tests and medical devices and targeting the drug to the specific area of the body. Its embraces applications of nanoscience to pharmacy is nanomaterials and nanodevices Nanotechnology helps in improving the drug solubility and bioavailability by enhancing the drug release, the formulation quality, decreasing toxicity, and efficient targeted therapy. In the area of nanotherapy, employing nanosystems can be as, liposomes, miniemulsions, nanotubes, emulsions and quantum dots, etc. In our review, we will discuss the role of nanotechnology in the development and improvement of drug delivery techniques. We will deal with how the biological system affected by nanosystems. The different method of production also will be discussed taking in consideration properties of the polymer used and the drug. Evaluation of the nanoparticles gives full information on how the drug delivered. The present article mainly introduces about the nanotechnology, potential benefits, potential risks and key characteristics. Some current developments which are achieved with the aid of nanotechnology are also explained in this article

Keywords: Nanomaterial, Nanodevices, Nanoparticles, Nanotechnology.

INTRODUCTION

Nanotechnology is going to revolutionize the world. For pharmacists, the applications of nanotechnology mean drugs containing nano-sized active ingredients.¹ The smaller drug delivery systems allow deposition of medications in previous inaccessible areas of the body; it also has a great importance in the treatment and diagnosis of certain diseases as cancer. A recent discovery in the drug delivery form is target therapy and improving the diagnostic tests and medical devices.² But with the advances comes concern, the science behind nanotechnology is still in its' original state.

According to the National Nanotechnology Initiative (NNI), nanotechnology refers to the study of all particles have about 100 nanometers or less. A nanometer is one-billionth of a meter in size.³ One of the most important advantages of the smaller particle size is the ratio of surface atoms or molecules to the total number increases. That means they have large surface areas which lead to increase their surface activity and produce changes in their physical properties, and biological properties.

We can summarize the nanoparticles advantages as follows: (i) Improved bioavailability, (ii) Reduced toxicity, (iii) Sustained and controlled release, (iv) Ability to target, (v) Provide effective delivery to the brain and intracellular compartment, (vi) Improved the permeability (vii) Faster, safer and more accurate disease diagnosis, (viii) More accurate, less invasive surgery, (ix) Inexpensive, and (x) Large-scale production is feasible, (xi) Smaller dosage

form (i.e., Smaller tablet), (xii) Stable dosage forms, (xiii) Faster dissolution especially in an internal aqueous fluid. Faster dissolution generally equates with greater bioavailability, smaller drug doses, less toxicity. (xiv) Stability of drugs in biological fluids as it can prevent allergic reactions, pain at the injection site, and / or precipitation of the drug as a result of its' dilution in the blood.^{4,5}

Despite all that advantages, there were certain disadvantages in pharmaceutical applications of nanotechnology. Nanoparticles have a very large surface area compared to their volume, so they are active to react quickly, e.g. silver nanoparticles. Their high aggregation in biological system is due to their high surface energy, poor solubility and poor biocompatibility. In the case of carbon nanotubes, it quickly scavenged by the RES system of the body, resulting in low biological half-life, high immunogenicity or foreignness, undefined and unpredictable safety issue, and acute and chronic toxicity due to large absorption.^{6,7}

Today, there are many applications of nanotechnology in our lives. Sunscreens containing nanoparticles of zinc oxide and titanium dioxide are the most used applications of nanotechnology on the market. They allow the normally white product to be more transparent when applied to the skin.

They provide more patient compliance, however studies have shown that with nanoparticles the reactive free radical levels will increase. As a result, there is a potential for serious cellular damage.⁸



Health implications of Nanoparticles

The common delivery vehicles are oral, injection, transdermal, inhaler, and transmucosal.⁹ So the main sites of clinical application are skin, intestinal and lung. We can summarize some of the health implications of nanoparticles as follows:

Skin

500–1000 nm Particles' size theoretically can penetrate and reach the lower levels of human skin. The smaller and nanoparticles are likely to move deeper into the skin. Therefore, TiO₂ nanoparticles sunscreens, which absorb UV light and protect skin against sunburn or genetic damage. It may be able to penetrate the surface through hair follicles or pores. Lademann et al., reported that micrometer-sized particles of TiO₂ get through the human stratum corneum and even into some hair follicles including their deeper parts.¹⁰

Intestine

At present, the nanoparticulate uptake within the intestine is still unclear and dependent on the used material as well as its particle properties (size, surface structure, chemical composition, etc.). For example; poor oral bioavailability of some charged particles, such as nanoparticles carboxylated polystyrene or those composed of positively charged polymers which exhibit electrostatic repulsion and mucous entrapment.¹¹

Generally, intestinal nanoparticle (~510-550 nm) absorption showed 15-250 folds higher in comparison to larger particles.¹² The intestinal epithelium uptake occur via manifold mechanisms such as: phagocytosis, or diffusion¹³, depending on both the material type and the exposed cell type. Also, the nanoparticle can enter via intracellular transport mechanism however; this mechanism seems of minor importance.¹⁴

Lung

Based on three particle-types titanium dioxide (TiO₂), carbon black, and diesel particles, exposure studies in rats demonstrate that very fine or nanoparticles entered to the lung lead to more potent adverse effects such as inflammation and susceptibility to tumors compared with larger sized particles of identical chemical composition at equivalent mass concentrations or intra tracheally-instilled doses. Surface properties, such as catalyst's activity and particle surface area, may play a significant role in nanoparticle particle toxicity.¹⁵⁻¹⁷

New pharmaceutical application of nanoparticles

Several nanoparticle technologies are currently in clinical trials and a few have progressed to clinical use. Despite no industry guidance exists and there is no approval pathway for manufacturers to follow. Currently, FDA approved some drug products employing this technology as represented in table 1.

The most recently application were the gold nanoparticle. It was used for cancer treatment, as anti-fouling polymers and therapeutics, targeting agents (introduced by Sigma Aldrich). It can also be used as a biosensor as it improves the performance for the detection of infectious diseases.¹⁸

Classification of Nanoparticles

Pharmaceutical nanotechnology provides two basic types of nanotools; nanomaterials and nanodevices, which play an important role in pharmaceutical nanotechnology and other related fields.¹⁹ A schematic diagram of various types of pharmaceutical nanosystems was represented in Figure 1.

Nanomaterials

Nanomaterials are mainly used as biomaterials, for example in; orthopedic or dental implants or as tissue-engineered products. Their coatings or surface modifications might enhance the biocompatibility by enhancing the interaction between the living cells with the biomaterial.²⁰

Nanodevices

Nanodevices are mini nature device in the nano scale. Most animal cells are 10,000 to 20,000 nanometers in diameter. This means that nanoscale devices (less than 100 nanometers) can enter cells and the organelles inside them to interact with DNA and proteins and to be effective in detection or imaging. Tools developed through nanotechnology may be able to detect disease in a very small amount of cells or tissue.²¹

Some of which include nano- and micro-electromechanical systems, micro fluidics (control and manipulation of micro or nano liter of fluids), and microarrays (different kind of biological analyses, e.g. DNA, protein, cell, and antibody).²²

They have the ability to directly interact with biologically significant molecules, and to convert those interactions into directly significantly amplified electrical or electromagnetic signals. It enabled a new generation of early-stage diagnostic techniques. Detection of cancer at early stages is a critical step in improving cancer treatment.

Despite the enormous advantages of nanotechnology, still many important concerns must be addressed including the toxicological effects of the *in vivo* use of the relevant nanomaterials. The identification of appropriate target molecules and biomarkers to be screened was mainly for making proper protocols for sample preparation, and for complete the interpretation of diagnostic results obtained from both animal models and human trials.²³

A brief discussion of some pharmaceutical nanosystems will be presented below:



Pharmaceutical nanosystems

Carbon nanotubes (CNTs)

Carbon nanotubes are hexagonal networks of carbon atoms, 1 nm in diameter and 1–100 nm in length, as a graphite layer rolled up into a cylinder. They are existing in two forms: single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs) as represented in Figure 2.²⁴

Both forms were differed in their graphene cylinder arrangement. They are small macromolecules have unique size, shape, and have significant physical properties. Nanotubes offer some distinct advantages over other drug delivery and diagnostic systems due to their interesting physicochemical properties such as ordered structure with high characteristic ratio, ultra-light weight, high mechanical strength, high thermal and electrical conductivity, high surface area and metallic or semi-metallic manners. Also they are resistant to temperature changes as their characters do not change in extreme cold or in extreme heat.²⁵

CNTs are used for thermal treatment of cancer and drug delivery agents; however, toxicity of pure CNTs represents a major challenge for clinical application. In general, it has been observed that the CNTs will interact with cell proteins' and interfere with their structure, possibly causing cell death.²⁶ Coating will result in the complete disappearance of the CNTs' toxicity.²⁷ One of the most common approaches to coat the CNT surface and reduce its toxicity is coated with polyethylene glycol (PEG). PEG is biocompatible polymer, which can reduce *in vivo* CNTs toxicity.²⁸

Polymeric nanoparticles

Polymeric nanoparticles are the most used nanoparticles in drug synthesis. That was due to its biocompatibility like properties, non immunogenicity, non toxicity and biodegradability. They are also act as a colloidal carrier with 10 nm -1 μ m size (Figure 3 adopted from Senthil kumar et al., 2007)²⁹ consisting of synthetic or natural polymers. In polymeric nanoparticles the drug is dissolved, encapsulated (nanocapsules) and entrapped in matrix systems (nanospheres). Nanocapsules are systems in which the drug enclosed and surrounded by a polymeric membrane while nanospheres are matrix systems in which the drug is physically and uniformly dispersed (Figure 3B).³⁰

Various natural polymers like albumin, gelatin and alginate are used to prepare the nanoparticles; however, they have certain disadvantages like poor batch-to-batch variability, highly degradable and potential antigenicity.³¹

Synthetic polymers are more preferable. They used for nanoparticles preparation to be in the form of preformed polymer, e.g. polyesters like polycaprolactone (PCL), poly lactic acid (PLA) or monomers that can be polymerized in situ, e.g. polyalkyl cyanoacrylate. Their composition can be adjusted to achieve an optimal complexation of the

loaded drug and to control their physicochemical properties such as hydrophobicity/ hydrophilicity.³²

Polymeric nanoparticulate systems are attractive modules for intracellular and site specific delivery. Nanoparticles can be made to reach a target site by asset their size and surface modification with a specific identification of the used ligand. Their surface can be easily modified and functioned.³³

Metallic nanoparticles

Metallic nanoparticles are emerging as a good delivery carrier for drug and biosensor. They're used for diagnostic use or treatment use as they provide a quick, highly defined snapshot of the living system. The main metallic nanoparticles of various metals have been made yet were silver and gold nanoparticles. They have a prime importance for biomedical use, especially in cancer treatment (tumor targeting ligands). Their large surface area to volume ratio provides an opportunity for surface modification. Various ligends have been linked to nanoparticles to decorate the surface, including sugars, peptide, protein and DNA. Therefore, they have been used as an active bioactive delivery and in drug discovery, bioassays, imaging, detection and many other applications.³⁴

The most common applications of the metallic nanoparticles were silver nanoparticle and gold nanoparticles.

Silver nanoparticles (AgNPs) have antibacterial properties due to the presence of silver ions. They may enter the living organism's body in food, and also through the skin or the respiratory system^{35, 36} and even pass the blood-brain barrier.³⁷ AgNPs has a typically cytotoxic effect. As they enhanced the antioxidative defense proteins of genes coding expression which is a typical feature of the response to oxidative stress.³⁸

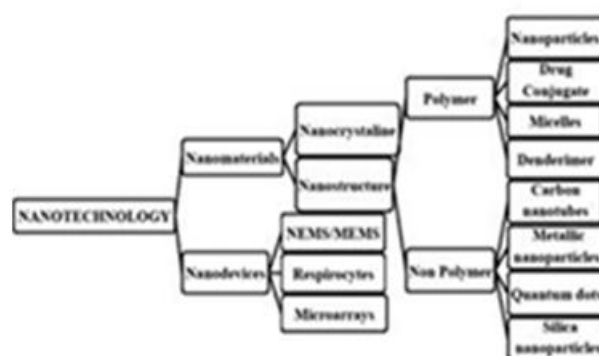


Figure 1: Schematic diagram of various types of pharmaceutical nanosystems

Gold nanoparticles (AuNPs) exhibit a combination of physical, chemical, optical and electronic properties unique from other biomedical nanotechnologies. They provide a highly multifunctional platform to image and diagnose diseases,³⁹⁻⁴⁰ to deliver therapeutic agents

selectively⁴¹, to sensitize cells and tissues to treatment regimens,^{42,43} to monitor and guide surgical procedures,^{44,45} to preferentially administer electromagnetic radiation⁴⁶ to disease sites, and to deliver compounds that are intrinsically susceptible to enzymatic degradation, as well as those that exhibit poor intracellular penetration (e.g., siRNA).⁴⁷

Also, AuNPs can be coated with polyethylene glycol chains via Au-S bonds to reduce their uptake by the liver

and spleen and prolong their half-life in blood.⁴⁸ Other biomolecules such as peptides⁴⁹, small-molecular-weight compounds⁵⁰, aptamers⁵¹, and monoclonal antibodies⁵² have also been attached to the surface of AuNPs to increase the particles' tumor-targeting potential. That means the multi-functionality of AuNPs, give future advances in AuNP-mediated cancer therapy which could include chemo therapy and chemo radiotherapy.⁵³

Table 1: FDA-approved products utilizing nanotechnology (Some product)

Agent	Sponsor	Uses	Technology	Approval date	Mode of application
SilvaGard	AcryMed, Inc	Antimicrobial	Metalic nanoparticle	May 2005	Transdermal batch
Doxil	Alza Corporation	Ovarian Cancer	Liposome	February 2005	Injection
Tricor	Abbott Laboratories	Cholesterol lowering	Polymeric encapsulated	December 2004	Oral capsule
Abraxane	APP	Breast cancer	Drug conjugated with albumin	January 2005	Injection
Estrasorb	Novavax Allergan	Reduction of vasomotor symptoms, such as hot flushes and night sweats in menopausal women	micellar nanoparticles (emulsion)	October 2003	Transdermal
Amphotec of	Sequus	Invasive aspergillosis in patients who are refractory to or intolerant of conventional Amphotericin B	lipid-based	November 1996	Subcutaneous suspension
Megace	Elan Corp Par Pharma	Anorexia	Nanocrystalline	September 1993	Oral suspension

Liposomes

The name liposome is derived from two Greek words: 'Lipos' meaning fat and 'Soma' meaning body. Structurally, liposomes are formed from an aqueous volume is enclosed by a lipid bilayer as represented in fig 4. Liposomes are the most developed nanocarriers for novel and targeted drug delivery such as in anticancer therapy⁵⁴, vaccination, gene therapy⁵⁵, and diagnostics⁵⁶ due to their ability to simulate the behavior of natural cell membranes.⁵⁷ They also, have a great potential for applications in both food and pharmaceutical industries. Furthermore, their structure can protect the incorporated compounds in their aqueous interior core or within their bilayer membrane from external destructive conditions such as light, pH or enzymes, allowing them to be released at designated targets.⁵⁸

Liposomes exist in two basic types based on their size and number of layers. Multilamellar vesicles (MLVs) consist of several lipid bilayers separated from one another by aqueous spaces. They are heterogeneous in size and have different ranges from a few hundreds to thousands of nanometers in diameter (figure 5A). Alternatively, small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) aqueous space entrapped and surrounding with a

single bilayer (figure 5b). SUVs size is less than 100 nm while LUVs have diameters size larger than 100 nm.⁵⁹

Multilayer liposome is mainly thickness-dependant and the capsule surface can be engineered in order to (1) target specific cell populations, (2) activate certain cell functions upon binding of it to the cell surface or upon intracellular uptake, (3) release the content at the required moment when reaching the target site or (4) upon a well-defined stimulus.⁶⁰

It has the possibility of delivering different dosages from different areas of its layers. The drugs molecules encapsulated within multilayer patterns of phospholipids for delivery to cells. Lipids have negligible solubility in water, so their use has the potential to solve the cross-contamination problem which occurs in other small-molecules.⁶¹

Polymeric micelles

Polymeric micelles are usually <100 nm in size. They are generally arranged in a spherical structure with hydrophobic cores shielded from water by a mantle of hydrophilic groups (Figure 6).⁶² The hydrophilic shell of the micelle provides a steric stability and avoids rapid uptake by the reticulo endothelial system (RES), resulting in prolonged circulation time in the body.⁶³ The interior

core has the capacity to hold drugs which are poorly soluble in aqueous solution.

One of the main advantages of polymeric micelles is the incorporation of chemotherapeutic agents into nanosized drug carriers. They have several advantages compared to systemic chemotherapy. First, loading them in nanoparticles lead to increase their bioavailability and be rapidly eliminated by liver and/or kidneys. Second, they are passively targeted to the tumors. As, they are nanosized drug carriers with small size so enhancing the permeability and retention (EPR) effect, leading to a higher drug concentration at the tumor site and decreased toxicity compared with systemic administration. Third, hydrophobic drugs can only be administered intravenously (i.v.) after addition of Solubilizing adjuvants like ethanol or Cremophor EL, which is often accompanied with toxic side effects. Incorporation of these drugs in micelles avoids the use of adjuvants.⁶⁴⁻⁶⁷

Polymer drug conjugate

The conjugation of the drugs with polymer improves therapeutic properties of the drug. The drug conjugates with peptides, proteins, small molecules or oligonucleotides (figure 7). Polymer-conjugated drugs commonly reveal prolonged half-life, stability, high aqueous solubility, low immunogenicity and antigenicity and precise targeting to tissues or cells. The polymer-drug conjugate consider the early steps of polymer therapeutics towards cancer therapy. They also can create a multimodal platform, which can be used not only for therapeutic (drug delivery) but also in diagnostic (imaging) applications.⁶⁸⁻⁷⁰

Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) are a class of particulate drug carriers ranging from 50 to 1000 nm⁴⁰. They mainly composed of physiological lipid, dispersed in water or in aqueous surfactant solution, but the liquid lipid of the emulsion has been replaced by a lipid remain in the solid state at room and body temperatures. The hydrophobic chains of phospholipids are embedded in the fat matrix (figure 7).^{71, 72}

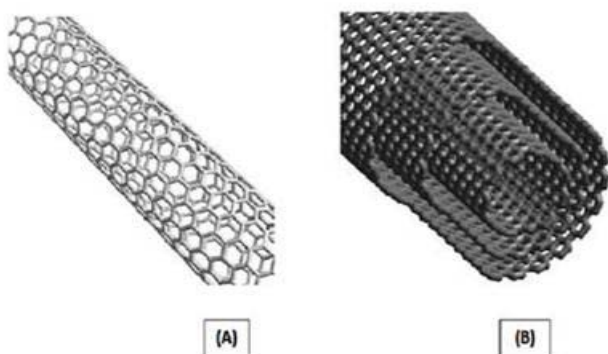


Figure 2: Carbon nanotubes (a) Single walled (SWNTs) (b) Multi walled (MWNTs)

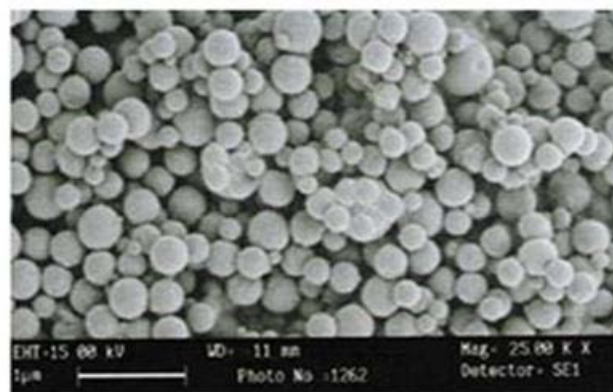


Figure 3A

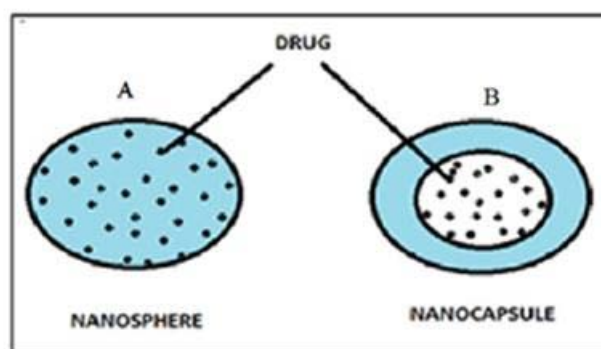


Figure 3B

Figure 3A: Scanning electron microscopy image of polymer nanoparticles; **Figure 3B:** Schematic diagram represented: a) nanoparticles nanospheres (matrix systems) b) encapsulated nanoparticles.

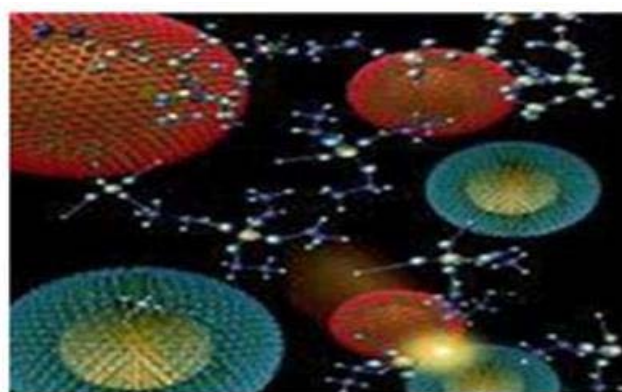


Figure 4: Surface functionalized gold nanoparticles

Many biocompatible/biodegradable lipids including: fatty acids, steroids, waxes, mono-, di-, or triglyceride mixtures were used. A wide variety of biocompatible surfactants are used to stabilize SLN (cationic, non-ionic, anionic, and polymeric).⁷³ Therefore, SLNs offer many other advantages such as physical stability with low toxicity.

SLNs are becoming increasingly used for the protection of labile drugs from degradation in the body and for controlling the sustained release.⁷⁴ They have potential to carry lipophilic or hydrophilic drugs, small size, large surface area, high drug loading and improve performance

of pharmaceutical preparation, good biocompatibility and low toxicity.⁷⁵

The application of SLN formulations in anticancer drug delivery has overcome many obstacles commonly seen in conventional cancer chemotherapy. Various anticancer drugs, including: etoposide⁷⁶, methotrexate⁷⁷, and idarubicin⁷⁸ have been incorporated into SLN and evaluated by different research groups. Also, loading the drugs in SLN helps in accessing the solid tumors which have shown relatively low drug uptake. The high drug-loaded SLN, and reduced circulation time, due to slow clearance increase the specific targeting effect of the drugs.⁷⁹

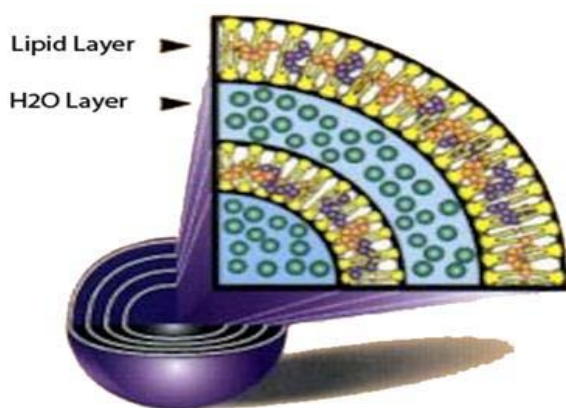


Figure 5A

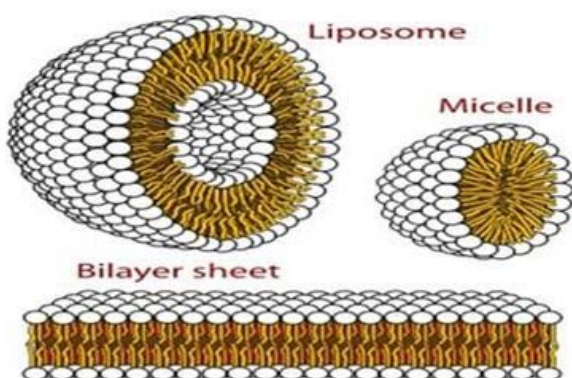


Figure 5B

Figure 5: Structure of Liposomes: a) Multilamellar vesicles (MLVs); b) Unilamellar vesicles (UVs)

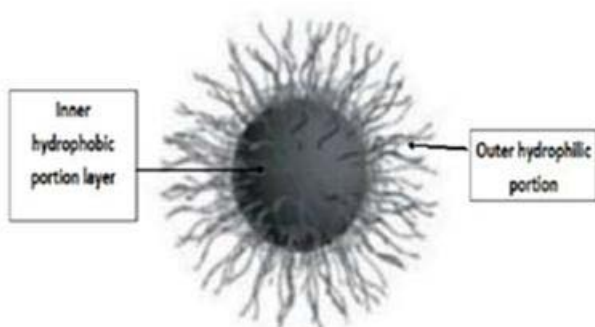


Figure 6: Structure of block copolymer micelles

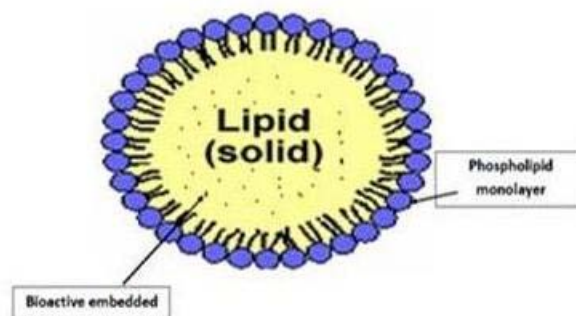


Figure 7: Structure of solid lipid nanoparticle (SLN)

Preparation of Nanoparticles

Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticles.⁸⁰

The selection of the base polymer mainly differs according to the used design and the application properties. Many other factors also have a great effect such as the required particle size and the drug's physico-chemical properties. The surface structure and functionality, biodegradability and biocompatibility degree, and the drug release profile of the final product also should take into consideration.⁸¹

Solvent evaporation

Solvent evaporation method was the first method developed to prepare NPs. In this method, emulsions are formulated using polymer solutions in volatile solvents. After the solvents of the polymer were evaporated, the emulsion was converted into a nanoparticle which was allowed to diffuse through the continuous phase of the emulsion. This method required high-speed homogenization or ultra-sonication and stabilizer. Particle size was found to be affected by the type of stabilizer and its concentrations, homogenizer speed and also the polymer concentration.⁸²

Nanoprecipitation

Nanoprecipitation is also called a solvent displacement method. It involves the precipitation of a used polymer from an organic solution. Precipitation was by diffusion of the organic solvent in the aqueous medium in the presence or absence of a surfactant. Polymer was deposited on the interface between the water and the organic solvent. This method is basically applicable to lipophilic drugs.⁸³

Salting out

It depends on the separation of a water-miscible solvent from an aqueous solution via a salting-out effect. Polymer and drug are initially dissolved in a solvent, which is subsequently emulsified into an aqueous gel containing the salting-out agent. Both the solvent and the salting-out agent are eliminated by cross-flow filtration. Salting out does not require an increase of temperature and therefore, it may be useful with sensitive substances.⁸⁴

Dialysis

The polymer is dissolved in an organic solvent and placed inside a dialysis tube with proper molecular weight cutoff. Dialysis is performed against a non-solvent miscible with the former miscible. Dialysis offers a simple and effective method for the preparation of small, narrow-distributed PN.⁸⁵

Emulsification/solvent diffusion (ESD)

It is considered a modification of solvent evaporation method. The polymer is dissolved using organic solvent partially miscible with water. In order to precipitate polymer and the formation of nanoparticles, an excess amount of water is necessary to promote the diffusion of the solvent containing the dispersed polymer. The polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer. Finally, the solvent is eliminated by evaporation or filtration. However the high volumes of water elimination lead to reducing the encapsulation efficiency.⁸⁶

Supercritical fluid technology

It was an environmentally safe method by using more environmentally friendly solvents, to produce NPs with high purity without any traces of organic solvent. Supercritical fluid generally defined as a solvent at a temperature above its critical temperature, the fluid remains a single phase regardless of the pressure used.⁸⁷

Polymerization method: monomers are polymerized to form nanoparticles in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption onto the nanoparticles after polymerization completed. The concentration of surfactant and the stabilizer determines the final size of the NPs formed.⁸⁸

Emulsion polymerization

The method's classification based on the use of an organic or aqueous continuous phase. Surfactants or protective soluble polymers were used to prevent aggregation in the early stages of polymerization. The polymerization process can be initiated by different mechanisms; an ion or a free radical by high-energy radiation, including γ -radiation, or ultraviolet or strong visible light. Phase separation and formation of solid particles can take place before or after termination of the polymerization reaction.⁸⁹

Mini emulsion

Mini emulsions are special classes of emulsions that are stabilized. It consists of water, co-stabilizer, surfactant, monomer mixture, and initiator. The main difference between emulsion polymerization and mini-emulsion polymerization is; the mini emulsions are produced by high-energy homogenization to reach a steady state and have an interfacial tension much greater than zero.⁹⁰

Micro-emulsion polymerization

Micro-emulsion polymerization is similar to emulsion polymerization. They are entirely different when compared kinetically. In micro-emulsion polymerization is a thermodynamically stable micro-emulsion containing swollen micelles and thermodynamically stable and a high quantity of surfactant systems. The types and concentration of initiator, monomer, surfactant, and reaction temperature are some of the critical factors affecting the micro-emulsion polymerization kinetics and the properties of NP.⁹¹

Interfacial polymerization

It involves polymerization of two reactive monomers or agents, which are dissolved respectively in two phases (i.e., continuous and dispersed-phase). Polymer formation takes place at or near the liquid-liquid interface when the two solutions are brought in contact or stirred together.⁹²

Controlled/Living Radical Polymerization in Nano reactors

Controlled/living radical polymerization enables precise synthesis of polymer of controlled structure and well-defined molecular weight. It causes dispersion in aqueous systems (emulsion, miniemulsion, etc.) and enables the synthesis of polymeric nanoparticles of various morphologies comprising well-defined polymer with a number of potential applications. The recent emergence of many so-called controlled or 'living' radical polymerization (C/LRP) processes have opened a new area using an old polymerization technique.⁹³

Ionic gelation or coacervation of hydrophilic polymers

Polymeric nanoparticles are prepared by using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. The method involves a mixture of two aqueous phases. In this method, positively charged amino group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, while, the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature was an ionic gelation.⁹⁴

Characterization of Nanoparticles

Characterization refers to study of the material's facial appearance such as its composition, structure, and various properties like physical, electrical, magnetic, etc.⁹⁵

Structural characterization

It is a determination of nanoparticles characters like shape, size, surface morphology, structural arrangement spatial distribution, density, geometric feature, etc.⁹⁶

- a) Scanning electron microscopy (SEM) generates the images by scanning the surface of the sample. It produces the image down to length scales of 10 nm provides valuable information regarding a structural

arrangement, spatial distribution as well as the surface morphology of nanoparticles.⁹⁷

- b) Transmission electron microscopy: gives more detailed geometrical features and information like crystal structure, quality, and orientation of nanoparticles.⁹⁸

Particle Size and Particle Size Distribution (It means the homogeneity of particle size. It measured by measuring the polydispersity index):

They determine the *in vivo* distribution, toxicity and the targeting ability of nanoparticle systems. They can also influence the drug release and loading and also the stability of nanoparticles. They determined by dynamic light scattering, which is used to measure particles ranging from a few nanometers to about 3 μm , or laser diffraction is used to detect microparticles or possible aggregates of drug nanoparticles.^{99, 100}

Particle Charge / Zeta Potential

Zeta potential is used to determine the charge on the particle surface. The zeta potential can also be used to optimize formulation parameters as a charged active material is encapsulated within the center of the nanocapsule. It can make predictions regarding the adsorbed surface and the storage stability of the colloidal dispersion. Currently, the principal technique involved in zeta potential determination is laser doppler anemometry.¹⁰¹

Crystalline Status

Differential scanning calorimetry, X ray diffraction and other analytical methods are used to assess any possible changes brought about in the physical form of the drug during processing.¹⁰²

Release profile

In-vitro release characteristic under physiologic & sink condition. Drug release rate depends on: solubility of drug, drug diffusion through the nanoparticle matrix, nanoparticle matrix erosion/degradation; and particle size and particle size distribution of nanoparticles.¹⁰³

Drug stability

Bioassay of drug extracted from nanoparticle, chemical analysis of drug.¹⁰⁴

Toxicity Evaluation

The toxicities of nanosystems are evaluated using well defined and established protocols available in the literature. Ex vivo toxicity evaluation generally carried out in various cell lines and MTT assay is used to determine the cell viability. In vivo acute and chronic toxicities are determined in various animal models.^{105, 95}

Summary

The main goal of this review is explained what nanotechnology means. It shows that nano particulate

systems have great importance. It's the solve of many problems such as; convert poorly soluble, poorly absorbed and less biologically active substance into a promising drug delivery system. Its greater surface area is optimizing the drug delivery and absorption and targeting the drug to specific site. There were different preparation techniques available for production of polymeric nanoparticles. We should use a suitable simple and safe technique among the various possible methods in preparing nano systems. It always depends on the drug's physicochemical characters. It is possible to choose the most desired method of preparation and the polymer to produce nanoparticles with desired size range with a good entrapment efficiency of the drug. Release assessments and sample size specific nanoparticle release data, and other evaluation methods can be a result of optimizing nanoparticles system.

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