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# NANOTECHNOLOGY: A PHARMACEUTICAL APPROACH

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## ABSTRACT

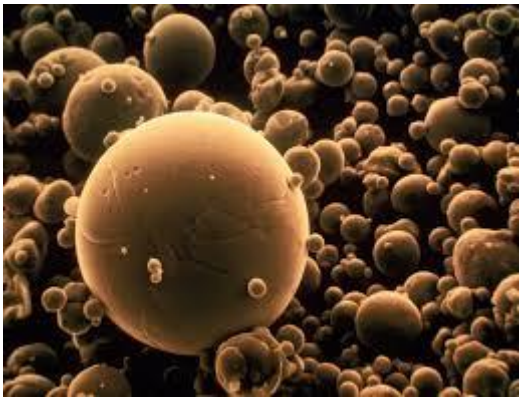
Nanotechnology defined as a tiny science. By Nanotechnology we can achieve better therapeutic action, better bioavailability and better patient compliance. Pharmaceutical nanoparticles (nps) are defined as particulate dispersions or solid, submicron-sized(less than 100 nm in diameter) drug carrier that may or may not be biodegradable. Basically, nanoparticles have been prepared by using various techniques as such solvent evaporation method, spontaneous emulsification or solvent diffusion method, salting out method, nano precipitation method, polymerization method, coacervation or ionic gelation method, supercritical fluid technology. Nanoparticles have been evaluated by using parameters such as drug entrapment efficiency, particle shape, particle size, zeta potential, stability of nanoparticles *in-vitro* release study, applications of nanoparticles as such Tumor targeting using nanoparticulate delivery system, nanoparticles for gene delivery, tissue repair.

**KEYWORDS:** Nanotechnology nano coacervation nanoparticulate tissue repair.

## INTRODUCTION

Nanotechnology defined as design characterization, production and applications of structures, devices and systems by controlling shape and size at nanometer scale. The prefix “nano” comes from the ancient Greek *vavoc* through the Latin *nanus* meaning *very small*. According to International System of Units (SI) nanotechnology is typically measured in nanometers scale of 1 billionth of a meter (1nm corresponding to 10-9 m) referred as “the tiny science”. Pharmaceutical nanoparticles (NPs) are defined as particulate dispersions or solid, submicron-sized(less than 100 nm in diameter) drug carrier that may or may not be biodegradable. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. The term nanoparticle is a combined name for both nanospheres and nanocapsules.

Drug is confined to a cavity surrounded by a unique polymer membrane called nanocapsules, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed.[1-2]



**Advantages of nanoparticles**

Nanoparticles offer numerous advantages in drug delivery system. These advantages include, but are not limited:

1. Nanoparticles have many significant advantages over conventional and traditional drug delivery system.
2. Nanoparticles are control and sustain release form at the site of localization, they alter organ distribution of drug compound. They enhance drug circulation in blood, bioavailability, and therapeutic efficacy.
3. Nanoparticles can be administered by various routes including oral, nasal, parenteral, intra-ocular etc.
4. In the tiny areas of body nanoparticles shows better drug delivery as compare to other dosage form and target to a particular cell type or receptor.
5. Due to small particle size nanoparticles overcome resistance by physiological barriers in the body and easily penetrate to cell walls, blood vessels, stomach epithelium and blood–brain barrier.
6. Nanoparticle enhances the aqueous solubility of poorly soluble drug, which improves bioavailability of drug.
7. As a targeted drug carrier nanoparticles reduce drug toxicity and enhance efficient drug distribution.[3]
8. By using polymers drug release form nanoparticles can be modified which makes polymeric nanoparticle an ideal drug delivery system for cancer therapy, vaccines, contraceptives and antibiotics.[4]

9. Useful to diagnose various diseases
10. Enhanced stability of ingredients
11. Prolonged shelf life

**Limitations**

1. Smaller the particles size greater the surface area and this property makes nanoparticles very reactive in the cellular environment.
2. Altered physical properties which lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms due to smaller size and larger surface area.
3. Smaller particles size results in limited drug loading and burst release.[5]

**Preparation of Nanoparticles**

The preparation of nanoparticles can be classified as:

A) Dispersion of preformed polymers

1. Solvent evaporation method
2. Spontaneous emulsification solvent diffusion method
3. Salting out method
4. Solvent displacement/Nanoprecipitation

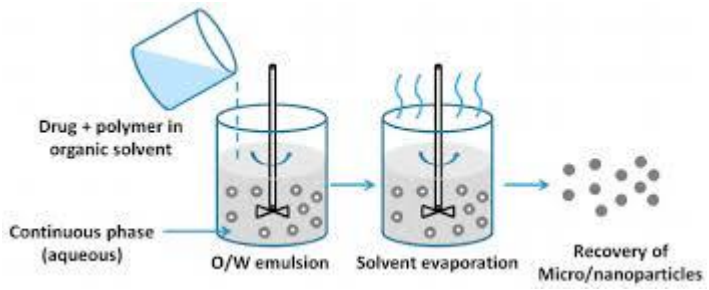
B) Polymerization method

C) Ionic gelation or co-acervation of hydrophilic polymers

D) Supercritical fluid technology

**Solvent evaporation method**

Solvent evaporation method first developed for preparation of nanoparticles.[1] In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate which is also used as the solvent for dissolving the hydrophobic drug. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form oil in water (o/w) emulsion. After the formation of stable emulsion, the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration.[6] In order to produce small particle size, often a high-speed homogenization or ultrasonication may be employed.[7]




**Spontaneous emulsification or solvent diffusion method**

This is a modification of Solvent evaporation method. In this method, the water miscible solvent along with a small amount of the water immiscible organic solvent is used as an oil phase. Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to the formation of small particles. As the concentration of water miscible solvent increases, a decrease in the size of particle can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase.[5]

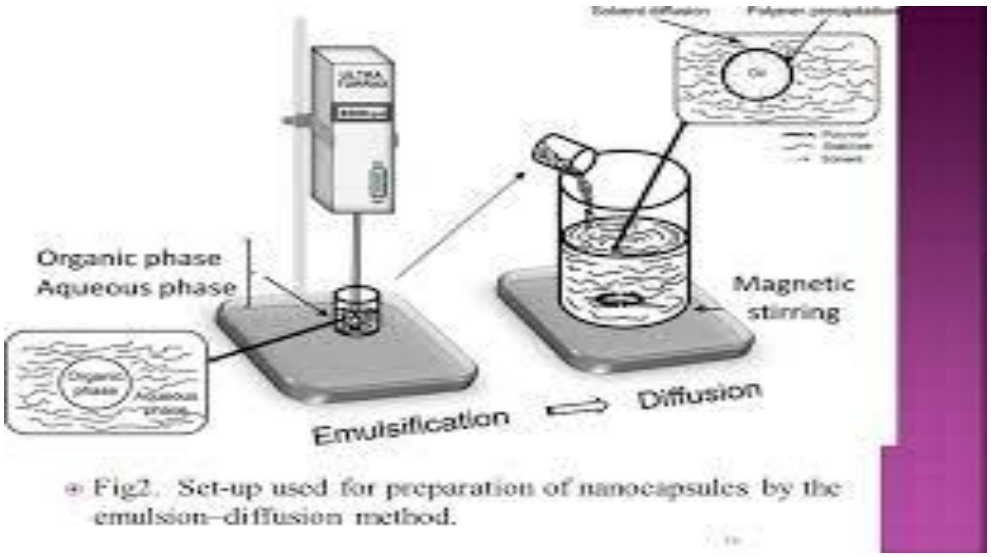
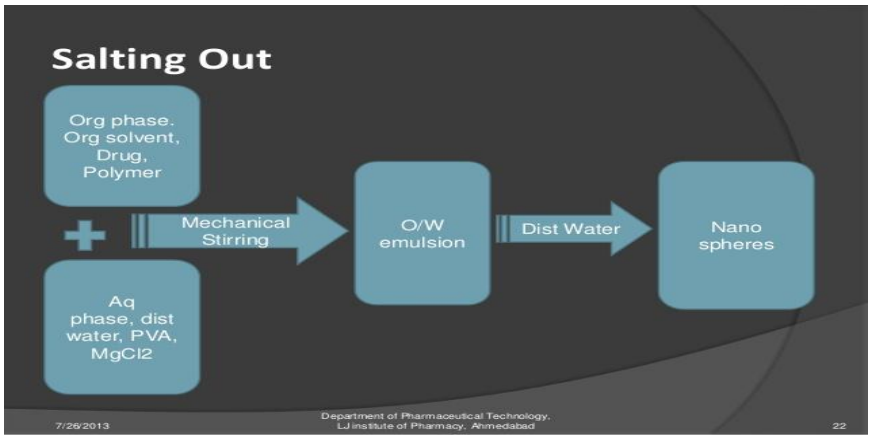



Fig2. Set-up used for preparation of nanocapsules by the emulsion–diffusion method.

**Salting Out Method**

This technique was introduced and patented by Bindschaedler *et al.* and Ibrahim *et al*. Salting out method is very close to solvent-diffusion method. This technique based on the separation of water-miscible solvent from aqueous solution by salting out effect (Catarina PR et al., 2006). In this method toxic solvents are not used. Generally acetone is used because it is totally miscible with water and easily removed. Polymer and drug / emulsion stabilizer/ viscosity increasing agent such as polyvinylpyrrolidone or hydroxyethylcellulose, PVA,

Poly(ethylene oxide), PLGA and poly(trimethylene carbonate). After preparation of o/w emulsion diluted with addition of sufficient water to allow the complete diffusion of acetone into the aqueous phase, thus inducing the formation of nanospheres. This technique does not require an increase in temperature dissolved in a solvent which emulsified into a aqueous solution containing salting out agent (electrolytes, such as magnesium chloride and calcium chloride, or non-electrolytes such as sucrose) but salting out can also be produced by saturation of the aqueous phase using colloidal stabilizerand stirring energy required for lower particle size. Disadvantage of this technique is exclusive application to lipophilic drug and the extensive nanoparticles washing steps.[1,8,9]



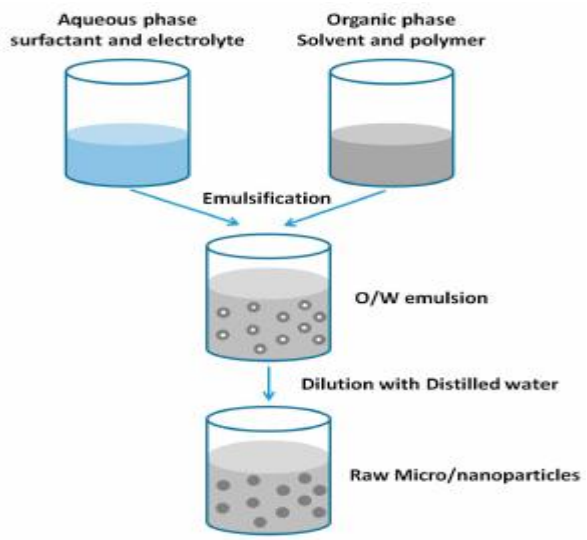

**Nanoprecipitation method**

Briefly, about 250 mg of cationic copolymer Eudragit E 100 was dissolved in 6 mL of ethanol, which was diluted with 4 mL of distilled water under the influence of sonication (40 kHz, Lark, India). Prepared organic phase was loaded in to a syringe equipped with needle (with inner diameter of 0.30 x 8 mm). The loaded organic phase was injected at the rate of 2 mL per minute by inserting the needle (submerged position) in to 20 mL of aqueous phase containing 250 mg of poloxamer 188 under the influence of sonication (40 kHz, Lark, India). Subsequently, nanoparticles were formed and turned the aqueous phase slightly milky with bluish opalescence. However, sonication process was continued up to 60 minutes to aid size reduction and to evaporate residual solvent present in the nanoformulation

**Polymerization method[11, 12, 13]**

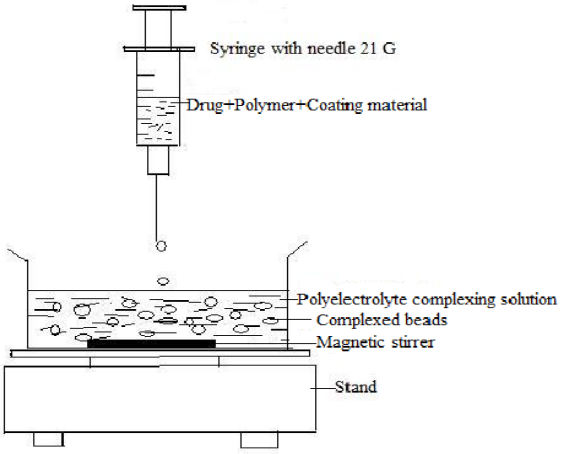
In this method, monomers are polymerized to form nanoparticle in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption onto

the nanoparticles after polymerization completed. The nanoparticle suspension is then purified to remove various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles.




**Coacervation or ionic gelation method**

The preparation of nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate, calvo and co-workers developed a method for preparing hydrophilic chitosan nanoparticles by ionic gelation.[14,15] The method involves a mixture of two aqueous phases, of which one is the polymer chitosan, a di-block co-polymer ethylene oxide or propylene oxide (peo-ppo) and the other is a polyanion sodium tripolyphosphate. 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, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature.




**Supercritical fluid technology**

Supercritical fluid technology method is alternative method because in this method organic solvents are not used which are hazardous to the environment as well as to physiological systems. Supercritical fluid defines as a solvent at a temperature above its critical temperature at which the fluid remains a single phase regardless of pressure. Supercritical CO2 is the most widely used supercritical fluid because of its mild critical conditions (*T*c = 31.1 °C, *P*c = 73.8 bars) it is non-toxicity, non-flammability and low price.

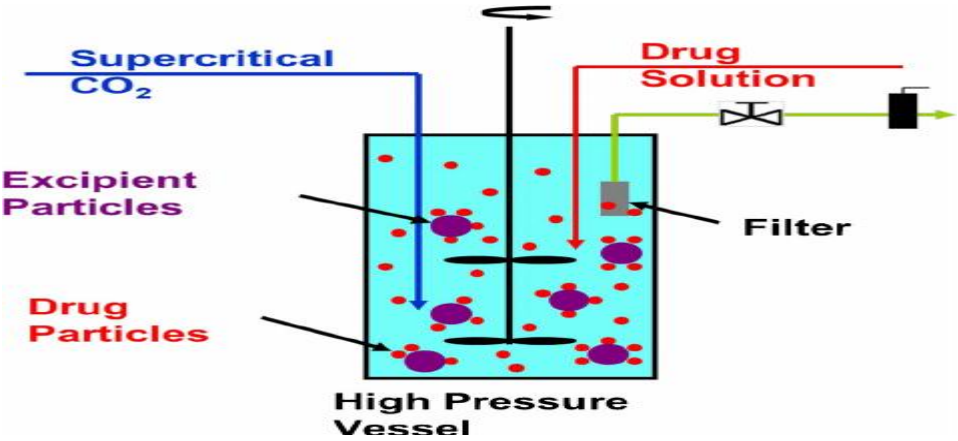
Mainly supercritical fluid used in two main techniques:

1) Supercritical anti-solvent (SAS)

2) Rapid expansion of critical solution (RESS).

In SAS process liquid solvents are used, which should completely miscible with the supercritical fluid. The process of SAS employs a liquid solvent, e.g. methanol, which is completely miscible with the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, it results the formation of nanoparticles.[5]

In RESS high degree of super saturation occur by dissolving solute in a supercritical fluid to form a solution, followed by the rapid expansion of the solution across an orifice or a capillary nozzle into ambient air by the rapid pressure reduction in the expansion which results in homogenous nucleation and thereby, the formation of well-dispersed particles.[4]




**Evaluation of Nanoparticles**

**Drug Entrapment Efficiency[16]**

The nanoparticles were separated from the aqueous medium by ultracentrifugation at 10,000 rpm for 30 min at 5□c. Then the resulting supernatant solution was decanted and dispersed into phosphate buffer saline pH 7.4. Thus the procedure was repeated twice to remove the unentrapped drug molecules completely. The amount of drug entrapped in the nanoparticles was determined as the difference between the total amount of drug used to prepare the nanoparticles and the amount of drug present in the aqueous medium.

Drug Entrapment efficiency (%) = Amount of released from the lysed nanoparticle X 100

Amount of drug initially taken to prepare the nanoparticles

**Particle Shape[17]**

The nanoparticles were subjected to microscopic examination (SEM) for characterization size. The nanosuspension was characterized by SEM before going for evaluation; the nanosuspension was lyophilized to form solid particles. The solid particles were coated with platinum alloy using a sputter coater.

**Particle size[18]**

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the in vivo distribution, biological fate, toxicity and targeting ability of nanoparticle system. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Currently, the faster and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).

**Zeta potential**[19]

The Zeta potential of a nanoparticle is commonly used to characterized the surface charge property of nanoparticles. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (±) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles.

**Stability of Nanoparticles**

Stability studies of prepared nanoparticles determined by storing optimized formulation at 4°C ±1°C and 30°C ± 2°C in stability chamber for 90 days. The samples were analyzed after a time period like at 0, 1, 2 and 3 months for their drug content, drug release rate (t50%) as well as any changes in their physical appearance (ICH Q1A (*R*2) 2003).[20]

***In-vitro* release Study**

*In-vitro* drug release studies were performed in USP Type II dissolution apparatus at rotation speed of 50 rpm. The prepared immersed in 900ml of phosphate buffer solution in a vessel, and temperature was maintained at 37±0.20°C. Required quantity 5ml of the medium was withdrawn at specific time periods and the same volume of dissolution medium was replaced in the flask to maintain a constant volume. The withdrawn samples were analyzed using UV spectrophotometer.[21]

**Applications of Nanoparticles**

**Tumor targeting using Nanoparticulate delivery system**[22]

The rational of using nanoparticles for tumor targeting is based on (1) nanoparticles will be able to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active nanoparticles. (2) Nanoparticles will reduce the drug exposure of health tissues by limiting drug distribution to target organ. Verdun et al demonstrated in mice treated with doxorubicin incorporated into poly (isohexylcynoacrylate) nanospheres that higher concentration of doxorubicin manifested in the liver, spleen and lungs than in mice treated with free doxorubicin.

**Nanoparticles for Gene delivery**[23]

Polynucleotide vaccines work by delivering genes encoding relevant antigens to host cells where they are expressed, producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response. Such vaccines produce both humoral

and cell-mediated immunity because intracellular production of protein, as opposed to extracellular deposition, stimulates both arms of the immune system.

**Tissue repair**

Tissue repair using iron oxide nanoparticle is accomplished either through welding, apposing two tissue surfaces then heating the tissue sufficiently to join them or through soldering, where protein or synthetic polymer-coated nanoparticles are placed between two tissue surfaces to enhance joining of the tissue. Temperatures greater than 50°C are known to induce tissue union induced by the denaturation of proteins and the subsequent entanglement of adjacent protein chains.[24] This is believed to be nanoparticles that strongly absorb light corresponding to the output of a laser are also useful for tissue-repairing procedures. Specifically, gold or silica-coated iron oxide nanoparticles have been designed to strongly absorb light.[25] The nanoparticles are coated onto the surface of two pieces of tissue at the site where joining was desired. This technique afforded methods to minimize tissue damage by using the least harmful wavelengths of light and/or lower powered light sources. Stem cells are the body's master cells and have a unique ability to renew them and give rise to other specialized cell types.

## CONCLUSION

Nanoparticles present a highly attractive platform for a diverse array of biological applications. Nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biological active substance into promising deliverable drugs. Nanoparticle is novel approach for drug delivery which we can achieve better therapeutic action, better bioavailability, reduce toxicity. Today nanoparticles are successfully used in gene delivery etc. nanoparticles gives us an opportunity to enhance patient compliance for better therapy.

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