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A Review on Nanopartilces And Methods of Preparation

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Abstract- Nanoparticles in the size range 1–100 nm are developing as a class of therapeutics for cancer. Early clinical outcomes propose that nanoparticles therapeutics can show enhanced effectiveness, while concurrently reducing side effects, owing to properties such as more targeted localization in tumours and active cellular uptake. Here, we high point the features of nanoparticles therapeutics that discriminate them from previous anticancer therapies, and describe how these features provide the potential for therapeutic effects that are not achievable with other modalities. While large numbers of preclinical studies have been published, the emphasis here is placed on preclinical and clinical studies that are likely to affect clinical inquiries and their implications for proceeding the treatment of patients with cancer.

Key words-Cancer, Targeted, Discriminate, Preclinical, Pub-med, Research paper.

Historical Perspective- Nanoparticles have been in use in ceramic and medicine since ancient times. Historical indications propose that Gold nanoparticles were used as drug by Chinese during 2500 BC. Red colloidal gold is still in use under the name of Swarna Bhasma and Makaradhwaja" in old-style medicine organisation of India called Ayurveda, which dates back to 1st millennium BC Recent scientific study of the a vessel of Roman period (4th century AD) called "Lycurgus Cup," kept in British Museum, London demonstrations the use of Nanoparticles of Gold-Silver alloy for its trimming (Freestone et al. 2007). Similarly, churches of Middle Ages used gold in colloidal state surrounded within the matrix of glass to make aesthetically agreeable ruby coloured glasses of different types and colours (due to the formation of nanoparticle of different sizes). In 16th Century Europe an aqueous form of colloidal gold called "Aurum Potabile (drinkable gold)" was thought to have remedial properties for many diseases (Caseri 2000). In 1857 Michael Faraday described methods for fusion of stable aqueous dispersions and optical properties of gold nanoparticles (Faraday 1857). In 1915, in his famous book "The World of Neglected Dimensions", Wolfgang Ostwald recognized colloidal particles as unique state of matter, whose particles "*are so small that they can no longer be recognized microscopically, while they are still too large to be called molecules.*" During this period work in groups of Turkovich, Frens, Stöber, Iijima, Bawendi and others has resulted into development of synthetic methods to produce unchanging nanostructures of gold, silica, carbon, cadmium etc. with sizes in the range of 1 to 100 nm (Jaiswal & Simon 2004). During the same period

development of technique like Atomic Force Microscopy, Scanning Tunneling Electron Microscopy, Dynamic light scattering have enabled detailed study and manipulation of materials at nanoscale. This has set the stage for a burst of research activities involving study, manipulation and application of nanoparticles. Originally nanomaterial's research was mainly focused in the area of materials science, mainly in development of microelectronic and optoelectronic device.

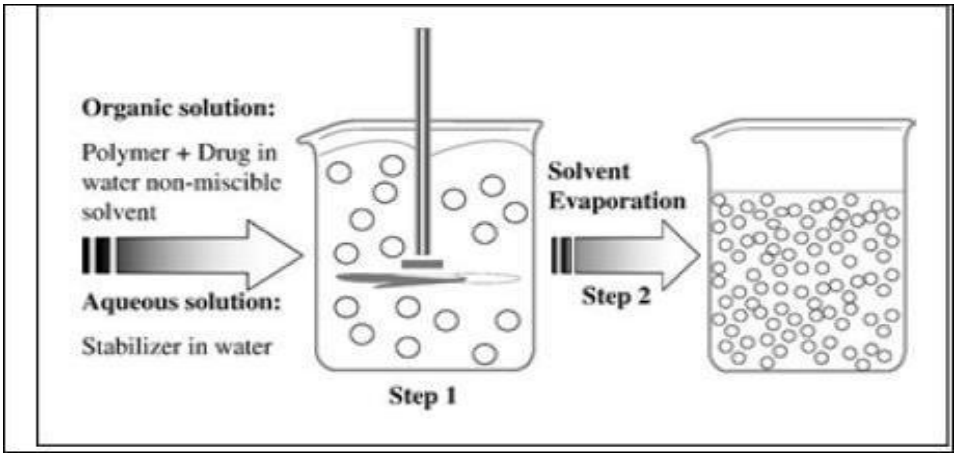
Introduction-The development of drug delivery systems that are able to modify the bio distribution, tissue uptake and pharmacokinetics of therapeutic agents is considered of great importance in biomedical research. Controlled release in drug delivery can significantly enhance the therapeutic effect of a drug. Among drug delivery systems, nano carriers are the smallest devices for transport of drugs, and they includes a variety of the type of nanoparticles developed for cancer, including liposomes, nanoshells, nanocapsules, dendrites, polymer drug conjugates, polymeric nano gels and micelles, and polynucleotide nanoparticles. The attractive properties of nano medicines include their ability of controlled release of drugs, the targeting of specific tissues and the biocompatibility. Because of their size, nanocarriers can be occupied up, in many cases, very professionally by cells, internalized and stored into cytoplasm or different organelles. Nanocarrier uptake into a cell depends on the cell-type, since some cells are more susceptible to include no functionalized systems via their design. The single attributes of tumours support extravasation of polymeric nanomedicines through large pores on the endothelial layer and via the disordered neoplastic tissue architecture. Thus, nanoparticles target the tumour passively via the EPR effect if their size is smaller than 100nm. Therefore, current research involves novel strategies to attach targeting ligands with high affinity for receptors overexpressed on tumours or ways to utilize the tumour's own microenvironment as a stimulus for drug release. An active targeting strategy can improve the efficacy of the therapy and lessen side effects associated with drugs, since not all nanocarriers can overcome the cell membrane barrier without a targeting motif. Nanoparticle systems are able to target various portions of the tumour using specific targeting moieties and evade the problems associated with multi-drug resistance. Thus, to increase the delivery of a given drug to a specific target site, targeting ligands are conjugated to carriers. The presence of reactive pendant groups in nanogels make easy their factorization forward specific cell motif by binding of ligands. Furthermore, it is an important fact that targeting ligands lead to macrophage recognition and faster clearance compared to the non-targeted nanoparticles. Various molecules, that include folates, transferrin, antibody and antibody fragments, peptides, small molecules, and carbohydrates, have been used to target nanocarriers to specific receptors on humoral cell surfaces. In many cases, ligand-targeted nanoparticles demonstrate better internalization by cancer cells and more effective intracellular drug delivery than other preparations. Cancer is one of the most challenging diseases to cure and the second leading cause of death in developed countries. Over the past few decades, it continues to be a worldwide health

problem in spite of the rising number of nanoscaled technologies. (1) Chemotherapy is the major therapeutic approach for the treatment of localized and metastasize cancers. Even though the development of both diagnostic and therapeutic tools is on the rise, nonselective distribution of drugs, enhanced drug toxicity, and undesirable side effects to normal tissues aggravate the challenges for chemotherapy. To prevail over this, carrier-mediated drug delivery offers a number of design opportunities for engineering the delivery of a particular drug, with enhanced therapeutic effect. (2) The search for more molecular targets will advance the ability to improve delivery at the tumour level while decreasing toxicity to normal tissue. As a result, moieties-targeted drug-loaded nanoparticles, searching for new tumour targets, novel ligands, new strategies for targeting, and particle stabilization, are generally considered as promising candidates for cancer chemotherapy and we can expect their extensive clinical evaluation in the near future. The substances, which size ranges from 1 to 1000 nanometers, are called nanoparticles. Micro- and nano- particles with a diameter of less than 10 μm, particles can penetrate the mucus layer more deeply. The formation of nano particles and physiochemical parameters such as pH, monomer concentration, ionic strength as well as surface charge, particle size and molecular weight are important for drug delivery. Further, these nanoparticles have the capability to reverse multi drug resistance, a major problem in chemotherapy. (3) Nanoparticulate delivery systems are extensively investigated as a drug delivery strategy in the pharmaceutical research. In general, nanocarriers may protect a drug from degradation, enhance drug absorption by facilitating diffusion through epithelium, modify harmacokinetic and drug tissue delivery profile and/or recover intracellular diffusion and distribution. Furthermore, by modulating the surface properties, composition and milieu, the desired release pattern of the drug and its bio distribution can be achieved.

Methods of Preparation-

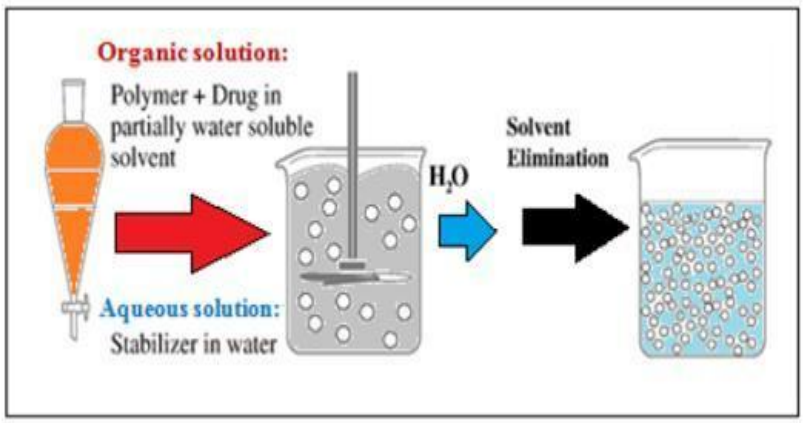
1. Solvent evaporation- Solvent evaporation was the first method industrialized to prepare PNPs from a. In this method, polymer solutions are prepared in volatile solvents and emulsions are formulated. In the past, dichloromethane and chloroform preformed polymer were widely used, but are now substituted with ethyl acetate which has a better toxicological profile. The emulsion is converted into a nanoparticle suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. In the conventional methods, two main plans are being used for the formation of emulsions, the preparation of single-emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in-water, (w/o)/w. These methods utilize high-speed homogenization or ultrasonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure. Afterwards, the solidified nanoparticles can be collected by ultracentrifugation and washed with distilled water to remove aromas such as surfactants. Finally, the product is lyophilized.(6,7) prepared PLGA

nanoparticles of about 200nm by utilizing dichloromethane 1.0% (w/v) as the solvent and PVA or Span 40 as the stabilizing agent.



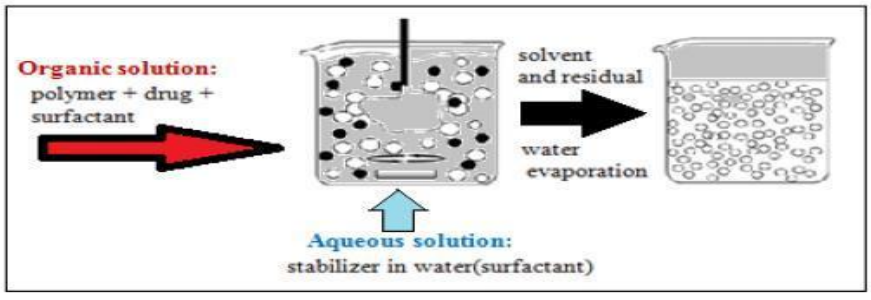
2. Emulsification/solvent diffusion (ESD) - This is a modified version of solvent evaporation method. The encapsulating polymer is dissolved in a partially water soluble solvent such as propylene carbonate and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. In fact, to produce the precipitation of the polymer and the consequent formation of nanoparticles, it is necessary to promote the diffusion of the solvent of the dispersed phase by dilution with an excess of water when the organic solvent is partly miscible with water or with another organic solvent in the opposite case. Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer, leading to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules, according to the oil-to-polymer ratio. Finally, the solvent is eliminated byevaporation or filtration, according to its boiling point. This technique presents several advantages, such as high encapsulation efficiencies (generally >70%), no need for homogenization, high batch-to-batch reproducibility, ease of scale-up, simplicity, and narrow size distribution. Disadvantages are the high volumes of water to be eliminated from the suspension and the leakage of water-soluble drug into the saturated-aqueous external phase during emulsification, reducing encapsulation efficiency.

3. **Emulsion polymerization-** The polymerization process can be initiated by different mechanisms. Initiation occurs when a monomer molecule dissolved in the continuous phase collides with an initiator molecule that might be an ion or a free radical. Alternatively, the monomer molecule can be transformed into an initiating radical by high-energy radiation, including g-radiation, or ultraviolet or strong visible light. Chain growth starts when initiated monomer ions or monomer radicals collide with other monomer molecules according to an anionic polymerization mechanism. Phase separation and formation of solid particles can take place before or after termination of the polymerization reaction.



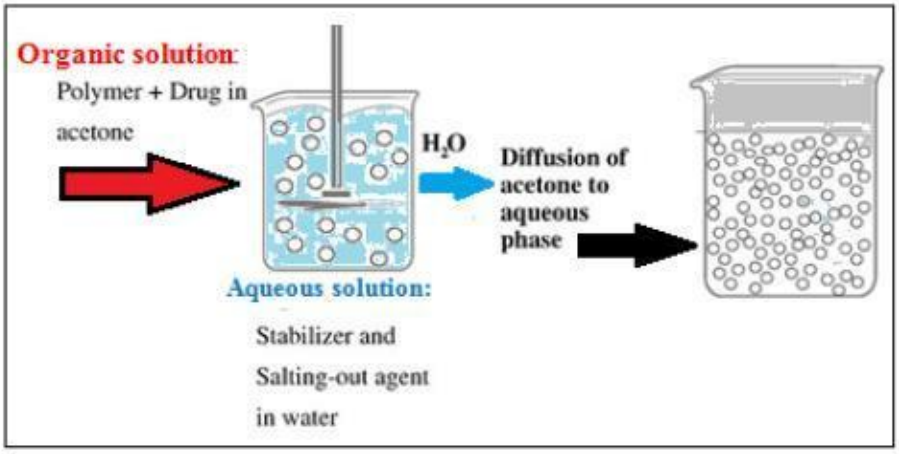
4. Emulsion droplet coalescence-The nanoparticles are formed within the emulsion-droplets. Decreasing chitosan deacetylation degree was shown to increase particle size and to reduce nanoparticle capacity for drug association, as a consequence of the diminished capacity of ion-pair formation and de-swelling. It was also found that varying chitosan concentration between 0.5 and 2.5% did not affect 5-fluorouracil encapsulation efficiency (around 70%) or release profile, which extended over 13 hours. To our knowledge, no other works report the application of this method to produce chitosan nanoparticles.

5. Nanoprecipitation-Nanoprecipitation is also called solvent displacement method. It involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium in the presence or absence of a surfactant. The polymer generally PLA, is dissolved in a water- miscible solvent of intermediate polarity, leading to the precipitation of nanospheres. This phase is injected into a stirred aqueous solution containing a stabilizer as a surfactant. Polymer deposition on the interface between the water and the organic solvent, caused by fast diffusion of the solvent, leads to the instantaneous formation of a colloidal suspension.

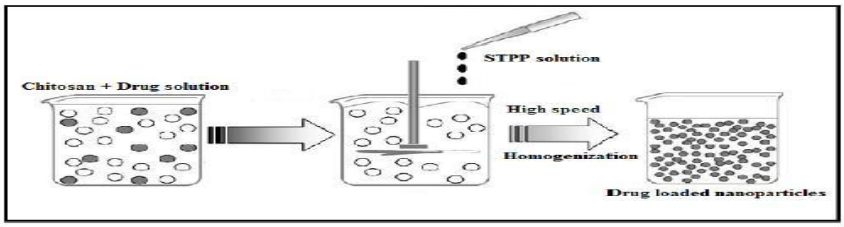


6. Salting out -Salting out is based on the separation of a water miscible solvent from aqueous solution via a salting out effect. The salting out procedure can be considered as a modification of the emulsification/solvent diffusion. Polymer and drug are initially dissolved in a solvent such as acetone, which is subsequently emulsified into an aqueous gel containing the salting-out agent

(electrolytes, such as magnesium chloride, calcium chloride, and magnesium acetate, or non-electrolytes such as sucrose) and a colloidal stabilizer such as polyvinylpyrrolidone or hydroxyethylcellulose. This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of acetone into the aqueous phase, thus inducing the formation of nanospheres.



9. Ionic gelation or coacervation of hydrophilic polymers-Polymeric nanoparticles is prepared by 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(13,14).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 poly anion 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.



Ionic gelation or coacervation of hydrophilic polymers

Advantage of nanoparticle-

1. Controlled and sustained release of the drug during the transportation and at the site of localization, altering organ distribution of drug and subsequence clearance of the drug so as to achieve increase in drug therapeutic efficiency and reduction in side effects.

2. Drug can be incorporated in to the system without any chemical reaction; this is an important factor for preserving the drug.

3. Controlled release and drug degradation characteristics can be readily modulated.

4. There is no wastage of drug and thus enhanced bioavailability of drug at specific site in right proportion for prolonged period of time.

5. It improve the solubility of poorly water soluble drugs, prolong half life of drug systemic circulation by reducing immunogenicity, release drug at sustained rate and lower the frequency of administration .

It provides comfort and compliance to the patient and yet improves the therapeutic performance of the drug over conventional systems.

Toxicological hazards of nanoparticles- To use the potential of Nanotechnology in Nanomedicine, full attention are needed to safety and toxicological issues. For pharmaceuticals specific drug delivery formulations may be used to increase the so called therapeutic ratio or index being the margin between the dose needed for clinical efficacy and the dose inducing adverse side effects (toxicity). However, also for these specific formulations a toxicological evaluation is needed. This is particularly true for the applications of nanoparticles for drug delivery. In these applications particles are brought intentionally into the human body and environment, and some of these new applications are envisaged an important improvement of health care.

1- Nanomaterial's are developed for their unique (surface) properties in comparison to bulk materials. Since surface is the contact layer with the body tissue, and a crucial determinant of particle response, these unique properties need to be investigated from a toxicological standpoint. When nanoparticles are used for their unique reactive characteristics it may be expected that these same characteristics also have an impact on the toxicity of such particles. Although current tests and procedures in drug and device evaluation may be appropriate to detect many risks associated with the use of these nanoparticles, it cannot be assumed that these assays will detect all potential risks. So, additional assays may be needed.

2-Nanoparticles are attributed qualitatively different physico-chemical characteristics from micron-sized particles, which may result in changed body distribution, passage of the blood brain barrier, and triggering of blood coagulation pathways. In view of these characteristics specific emphasis should be on investigations in pharmacokinetics and distribution studies of nanoparticles (17). What is currently lacking is a basic understanding of the biological behavior of nanoparticles in terms of distribution in vivo both at the organ and cellular level.

3-Effects of combustion derived nanoparticles in environmentally exposed populations mainly occur in diseased individuals. Typical pre-clinical screening is almost always done in healthy animals and volunteers and risks of particles may therefore be detected at a very late stage. It may be argued that

some if not all of these specific effects will be detected during routine testing and post marketing evaluation after clinical use. (18)All would depend on the types of assays used in the preclinical evaluation, which should be considered in the light of the use of the final products. In addition, one cannot rely on the toxicological profile of the bulk material when that material is used in a nanoformulation. The use of nanoparticles as drug carrier may reduce the toxicity of the incorporated drug. In general the toxicity of the whole formulation is investigated while results of the nanoparticles itself are not described. So, discrimination between drug and nanoparticle toxicity cannot be made. So, there should be a specific emphasis on the toxicity of the "empty" non-drug loaded particles. This is especially important when slowly or nondegradable particles are used for drug delivery which may show persistence and accumulation on the site of the drug delivery, eventually resulting in chronic inflammatory reactions.

Conclusion- It can be believed that if applied properly, nanoparticles can be a good friend, but if used randomly, they can become a mighty foe. Hence, this current review accomplishes with a confidence and prayer that there would be devices devised to nullify any toxicity caused by nanoparticles to humans and the situation so that the unique properties of this substance can be put to great use for human betterment without any controversies. Hence, care has to be taken to utilize this marvel well and in a virtuous, actual, and well-organized way, sympathetic its boundaries and taking extreme care that it does not cause any harm to an individual or the drug delivery. Nanoparticles are one of the most important nanoparticles because of their applications. These nanoparticles have many important applications that include: pyrotechnic, propellant, explosive industries, rocket fuel, igniter, smokes, tracers, alloy powder metallurgy parts for automobiles and aircrafts, heat shielding coatings of aircrafts, corrosion, resistant, conductive and heat reflecting paints, conductive and decorative plastics, soldering and termite welding. Application of nanoparticles in these fields is reliant on the capability to manufacture particles with different chemical composition, shape, size, and monodispersity. Generally, there are various methods to synthesize nanoparticles. The methods for synthesizing aluminum nanoparticles can be divided into solid phase, liquid-phase and gas-phase processes. Nevertheless high cleanliness powders and nanopowders of dynamic metals are not easily synthesized in as much as their rapid oxidation occurs easily. The small sizes of aluminium nanoparticles make them predominantly prone to excessive oxidation while being stored prior to use. As a result, much attention has been devoted to modifying the aluminum nanoparticles in order passivity the surface against the formation of an oxide over layer, and thereby obtains longer shelf lives and better burn possessions.

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