IJPSR (2019), Volume 10, Issue 5 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 31 August 2018; received in revised form, 24 November 2018; accepted, 19 February 2019; published 01 May 2019

CANCER NANOTHERAPEUTICS - A REVIEW

Allakonda Rama, M. Anjaneyulu and P. Munija *

Department of Pharmaceutics, Vision College of Pharmaceutical Sciences and Research, Boduppal, Hyderabad - 500092, Telangana, India.

Keywords:

Nano-therapeutics, Micelles, Liposomes, Zeta potential, Cancer, Pathophysiology

Correspondence to Author:
P. Munija

Assistant Professor,
Department of Pharmaceutics,
Vision College of Pharmaceutical Sciences and Research, Boduppal,
Hyderabad - 500092, Telangana,
India.

E-mail: munijapharma@gmail.com

ABSTRACT: Present study explains the cancer nano-therapeutics which is rapidly progressing and are being implemented to solve several limitations of conventional drug delivery systems such as nonspecific biodistribution and targeting, lack of water solubility, poor oral bioavailability. To improve the bio-distribution of cancer drugs, nanoparticles have been designed with optimal size and surface characteristics to increase their circulation time in the bloodstream. They are also able to carry their loaded active drugs to cancer cells by selectively using the unique pathophysiology of tumors, such as their enhanced permeability and retention effect and the tumor microenvironment. In this review, we will address, first, the types and characteristics of nanoparticles; second, how nanoparticles are being used as drug delivery systems to kill cancer cells more effectively and also to reduce or overcome drug resistance; and third, how nanoparticles had been formulated and evaluated to improve their therapeutic action, efficacy, and functionality in future cancer treatments. Finally, nanoparticles have greater therapeutic action towards cancer treatment.

INTRODUCTION: Conventional chemotherapeutic agents are distributed non-specifically in the body where they affect both cancerous and normal cells, thereby limiting the dose achievable within the tumor and also resulting in suboptimal treatment due to excessive toxicities. Molecularly targeted therapy has emerged as one approach to overcome the lack of specificity of conventional chemotherapeutic agents [1]. However, the development of resistance in cancer cells can evade the cytotoxicity not only of conventional chemotherapeutics but also of this newer molecularly targeted therapeutics [2]. Nanoparticles, by using both passive and active targeting strategies, can enhance the intracellular concentration of drugs in cancer cells while avoiding toxicity in normal cells [15, 16].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(5).2133-42

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(5).2133-42

Furthermore, when nanoparticles bind to specific receptors and then enter the cell, they are usually enveloped by endosomes *via* receptor-mediated endocytosis, thereby bypassing the recognition of P-glycoprotein, one of the main drug resistance mechanisms [17]. In nanotechnology, a nanoparticle is defined as a small object that behaves as a whole unit concerning its transport and properties.

Particles are further classified according to diameter. Nanoparticles are particles between 1 and 100 nanometers (nm) in size with a surrounding interfacial layer and having a very large surface area compared to their volume, so they are often able to react very quickly. This makes them useful as catalysts to speed up reactions. Nowadays nanoparticles are playing crucial role in drug delivery and related pharmaceutical development in the context of nanomedicine. As science and technology of nanometer-scale complex systems (10-1000 nm) consisting of at least two components, one of which is a pharmaceutically active ingredient although nanoparticle formulations of the drug itself are also possible.

The whole system leads to a special function related to treating, preventing or diagnosing diseases sometimes called smart- drugs or theragnostics. The primary goals for research of nano-biotechnologies in drug delivery include:

- More specific drug targeting and delivery.
- Reduction in toxicity while maintaining therapeutic effects.
- Greater safety and biocompatibility.
- Faster development of new safe medicines.

Characteristics of Nanoparticles: The special characters of nanoparticles are their shape, size, surface, and inner structure. The nanoscale materials behave very differently compared to larger scales, and it is still very difficult to predict the physical and chemical properties of particles as they are a very small size.

To effectively deliver the drug to the targeted tumor tissue, nanoparticles must have the ability to remain in the bloodstream for a considerable time without being eliminated. Conventional surface non modified nanoparticles are usually caught in the circulation by the reticuloendothelial system, such as the liver and the spleen, depending on their size and surface characteristics. The fate of injected nanoparticles can be controlled by adjusting their size and surface characteristics.

Size: One of the main advantages of nanoparticles is their size is tunable. The size of nanoparticles used in a drug delivery system should be large enough to prevent their rapid leakage into blood capillaries but small enough to escape capture by fixed macrophages that are lodged in the reticuloendothelial system, such as the liver and spleen. The size of the sinusoid in the spleen and fenestra of the kuffer cells in the liver varies from 150 to 200 nm, and the size of gap junction between endothelial cells of the leaky tumor vasculature may vary from 100 to 600 nm. Consequently, the size of nanoparticles should be up to 100 nm to reach tumor tissues by passing through these two particular vascular structures.

Surface: In addition to their size, the surface characteristics of nanoparticles are also an important factor determining their life span and fate during circulation relating to their capture by macrophages. Nanoparticles should ideally have a hydrophilic surface to escape macrophage capture. This can be achieved in two ways: coating the surface of nanoparticles with a hydrophilic polymer, such as PEG (polyethylene glycol). Protect them from opsonization (antigen-bearing) by repelling plasma proteins; alternatively, nano-particles can be formed from block copolymers with hydrophilic and hydrophobic domains [15].

Shape: In addition to the surface, the shape of nanoparticles are also played key role, during circulation time, bio-distribution and cellular uptake, as well as enhance drug targeting in cancer cells. In recent, according to new research studies rod-shaped and worm-shaped nanoparticles are more effective to achieve optimal anticancer efficacy with minimal side effects in drug delivery, because of the reason this rod and worm-shaped nanoparticles penetrate through the nuclear-membrane and into the nucleus is important for increasing the toxicity of cancer. A successful nano-carrier must satisfy several design criteria including drug loading capacity, triggered (or appropriate) release, elements for successful systems for drug transport. As spherical shaped (micelles and vesicles) nanoparticles, appears to adhere more readily to the surface of endothelial cells that line inside the blood vessels. Hence, rod and worm-shaped nanoparticles are more effective in targeting drug delivery in cancer [16, 17].

Inner Structure: Inner structure of nanoparticles varies with the types of nanoparticles. As the internal structure of nanoparticles possesses a well-distinguished core-shell structure. Silver nanoparticles are made up of well crystallized FCC Al inner part (dark zone) embedded with an amorphous metal Al shell (grey zone) and coated by an alumina shell (bright zone). High-resolution transmission electron microscopy shows several layers inside the Al nanoparticles: oxide layer, amorphous Al, single crystal Al, and a cavity in the center. The particles are made up of a well crystallized FCC (face-centered cubic) Al inner part (dark zone) embedded with an amorphous metal Al shell (grey zone) and coated by an alumina shell (bright zone).

Delivery of Nano Drug Carriers: Anti-cancer drugs to be effective in cancer treatment, they should first, after administration, be able to reach

the desired tumor tissues through the penetration of barriers in the body with minimal loss of their volume or activity in the blood circulation.

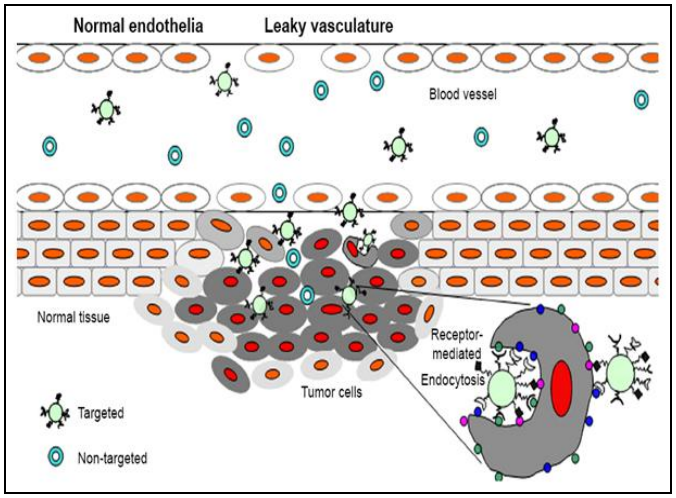

FIG. 1: SCHEMATIC REPRESENTATION OF THE ROLE OF ENHANCED PERMEABILITY AND RETENTION EFFECT (EPR) IN THE DRUG CARRIERS. Tumor targeting of both targeted and non-targeted nanoparticles is achieved by extravasation of nanoparticles through increased permeability of the tumor vasculature and ineffective lymphatic drainage (EPR), whereas ligand-targeted nanoparticles could bind, and enter the tumor cells *via* receptor-mediated internalization

Second, after reaching the tumor tissue, drugs should have the ability to selectively kill tumor cells without affecting normal cells with a controlled release mechanism of the active form. These two basic strategies are also associated with improvements in patient survival and quality of life by increasing the intracellular concentration of drugs and reducing dose-limiting toxicities.

Types of Nanoparticles: Nanocarrier-based drug delivery systems for chemotherapeutic drugs act efficiently on multiple malignant sites. The most common drug delivery approaches are based on organic and inorganic particles. The organic particles used for drug delivery application are micelles, liposomes, polymers, dendrimers, and nanogels. They have versatile surface building blocks for efficient endocytosis and loading. Whereas inorganic nanoparticles are gold, quantum dots, super-paramagnetic iron oxide nanoparticles, paramagnet lanthanide ions. These are applicable for molecular sensing devices and diagnostic imaging, they also exhibiting magnetic, electrical and optical properties that differed from their bulk counterpart **Fig. 2**.

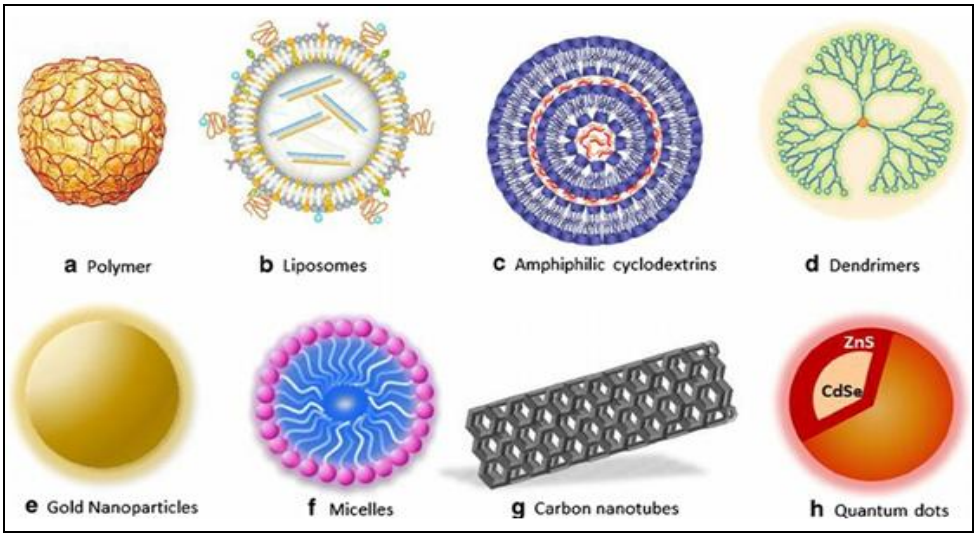

FIG. 2: TYPES OF NANOPARTICLES

Nanoparticles applied as drug delivery systems are submicron-sized particles (3-200 nm). These are classified as:

1. Polymer-Based Drug Carriers
2. Lipid-Based Drug Carriers
3. Viral Nanoparticles
4. Carbon Nano-Tubes
5. Gold Nanoparticles
6. Quantum Dots

1. Polymer-Based Drug Carriers:

Polymeric Nanoparticles (Polymer-Drug Conjugates):

Natural: Polymers such as albumin, chitosan and heparin occur naturally and choice for the delivery of oligonucleotides, DNA, and protein, as well as drugs. Recently, a nanoparticle formulation of paclitaxel, in which serum albumin is included as a carrier nanometer-sized albumin-bound paclitaxel

(Abraxane); has been applied in the clinic for the treatment of metastatic breast cancer. Besides metastatic breast cancer, abraxane has also been evaluated in clinical trials involving many other cancers including non-small-cell lung cancer (phase II trial) and advanced non-hematologic malignancies (phase I and pharmacokinetics trial).

Synthetic: Among synthetic polymers such as N-(2- hydroxypropyl)- methacryl amide copolymer (HPMA), polystyrene-maleic anhydride copolymer, polyethylene glycol (PEG), and poly-L-glutamic acid (PGA), PGA was the first biodegradable polymer to be used for conjugate synthesis **Fig. 2a**. HPMA (hexamethylphosphoramide) and PEG are the most widely used non-biodegradable synthetic polymers. PK1, which is a conjugate of HPMA with doxorubicin, was the synthetic polymer-drug conjugate to be evaluated in clinical trials as an anticancer agent. A phase I clinical trial has been completed in patients with a variety of tumors that were refractory or resistant to prior therapy such as chemotherapy and/or radiation. PK1 should be further evaluated in the next level of clinical trials.

Polymeric Micelles (Amphiphilic Block Co-polymers): The functional properties of micelles are based on amphiphilic block co-polymers **Fig. 2f**, which assemble to form a nanosized core/shell structure in aqueous media. The hydrophobic core region serves as a reservoir for hydrophobic drugs, whereas the hydrophilic shell region stabilizes the hydrophobic core and renders the polymers water-soluble making the particle an appropriate candidate for IV administration. The drug can be loaded into a polymeric micelle in two ways: physical encapsulation or chemical covalent attachment. The first polymeric micelle formulation of paclitaxel, genexol-PM (PEG-poly (D, L-lactide)- paclitaxel), is a cremophor free polymeric micelle-formulated paclitaxel. A phase I and pharmacokinetic study have been conducted in patients with advanced refractory malignancies. Multifunctional polymeric micelles containing targeting ligands and imaging and therapeutic agents are being actively developed and will become the mainstream among several models of the micellar formulation.

Dendrimers: A dendrimer is a synthetic polymeric macromolecule of nanometer dimensions, composed of multiple highly branched monomers that emerge radially from the central core **Fig. 2d**. Properties associated with these dendrimers such as their mono disperse size (1.5-10 nm), modifiable surface; multi-valency, water solubility, and available internal cavity make them attractive for drug delivery. Polyamidoamine dendrimer, the dendrimer most widely used as a scaffold, was conjugated with cisplatin. The easily modifiable surface characteristic of dendrimers enables them to be simultaneously conjugated with several molecules such as imaging contrast agents, targeting ligands, or therapeutic drugs, yielding a dendrimer-based multifunctional drug delivery system.

2. Lipid-Based Drug Carriers:

Liposomes: Liposomes are self-assembling closed colloidal structures composed of lipid bilayers and have a spherical shape in which an outer lipid bilayer surrounds a central aqueous space. Similarly, several kinds of cancer drugs have been applied to this lipid-based system using a variety of preparation methods. Among them, liposomal formulations of the anthracyclines doxorubicin (Doxil, Myocet) and daunorubicin (Dauno Xome) are approved for the treatment of metastatic breast cancer and AIDS-related Kaposi's sarcoma. Besides these approved agents, many liposomal chemo-therapeutics are currently being evaluated in clinical trials. The next generation of liposomal drugs may be immunoliposomes, which selectively deliver the drug to the desired sites of action.

3. Viral Nanoparticles: A variety of viruses including cowpea mosaic virus, cowpea chlorotic mottle virus, canine parvovirus, and bacteriophages have been developed for biomedical and nanotechnology applications that include tissue targeting and drug delivery. Several targeting molecules and peptides can be displayed in a biologically functional form on their capsid surface using chemical or genetic means. Therefore, several ligands or antibodies including transferrin, folic acid, and single-chain antibodies have been conjugated to viruses for specific tumor targeting *in -vivo*. Besides this artificial targeting, a subset of viruses, such as canine parvovirus, have a natural affinity for receptors such as transferrin receptors that are up-regulated on a variety of tumor cells. By targeting heat shock protein, a dual-function

protein cage with specific targeting and doxorubicin encapsulation has been developed.

4. Carbon Nanotubes: Carbon nanotubes are carbon cylinders composed of benzene rings that have been applied in biology as sensors for detecting DNA and protein, diagnostic devices for the discrimination of different proteins from serum samples, and carriers to deliver vaccine or protein. Carbon nanotubes are completely insoluble in all solvents, generating some health concerns and toxicity problems. However, the introduction of chemical modification to carbon nanotubes can render them water-soluble and functionalized so that they can be linked to a wide variety of active molecules such as peptides, proteins, nucleic acids, and therapeutic agents. Antifungal agents (amphotericin B) or anticancer drugs (methotrexate) have been covalently linked to carbon nanotubes with a fluorescent agent (FITC).

5. Gold Nanoparticles: Gold nanoparticles are known to be non-toxic and non-immunogenic [21, 22] and effectively employed as drug delivery vehicles in targeting tumors simultaneously improving the chemotherapy of drugs known to be limited by severe dose-limiting side effects. Nanoscale, gold nanoparticles are being used to connect resistors, conductors, and other elements of an electronic chip.

Photodynamic Therapy - Near- IR absorbing gold a nanoparticles (including gold nano shells and nanorods) produce heat when excited by light at wavelengths from 700 to 800 nm. Gold nano-particles have used in the fabrication of cancer targeting multimodal drug delivery system and in tumor imaging, because of their electrical and optical properties and low toxicity, easy of synthesis [23, 24]. These are potentially biodegradable *in-vivo*. Also, ultra-small gold NPs (their diameter can be controlled by variation of different chemical and physical parameters) exhibits uniform distribution within the tumor tissues due to their ability to diffuse through tissues, but the uptake is poor [6]. The optical and electronic properties of gold nanoparticles are tunable by changing the size, shape, surface chemistry, or aggregation state. One of the unique properties exhibited by GNPs is surface plasmon resonance enhanced light scattering and absorption, which can be customized by varying the size or shape of the nanoparticles for different applications. Although several chemical methods have been successfully employed for the synthesis of various gold nanostructures, their toxicity limits their application in medicine [28]. Gold nanoparticles stabilized with a monolayer of L-aspartate in combination with conventional anti-cancer drugs doxorubicin, cisplatin, and capecitabine were successfully used as a tumor-targeting drug delivery agents [29].

6. Quantum Dots: Quantum dot itself (the semiconductor nanoparticle) and it is toxic **Fig. 2h**. Therefore some of the typical modifications had made for it to become biocompatible. The core consists of semiconductor material that emits light. The shell consists of an insulator material that protects light-emitting properties of the quantum dots, and it (shell) had a biocompatible material (such as PEG) or lipid layer. These Semiconductor quantum dots and nanoparticles composed of metals, lipids or polymers have emerged with promising applications for early detection and therapy of cancer. Quantum dots with unique optical properties are commonly composed of cadmium contained semiconductors. Cadmium is potentially hazardous, and toxicity of such quantum dots to living cells, and humans is not yet systematically investigated.

Cancer treatment requires high accuracy in delivering ionizing radiation to reduce toxicity to surrounding tissues. Recently some research has been focused on developing photosensitizing quantum dots for production of radicals upon absorption of visible light. Even though visible light is safe, this approach is suitable to treat only superficial tumors. Ionizing radiation (X-rays and gamma rays) penetrate much deeper thus offering a big advantage in treating patients with tumor in internal organs. Such a concept of using quantum dots and nanoparticles to yield electrons and radicals in photodynamic and radiation therapies.

Formulation Methods of Nanoparticles:

1. Solvent Evaporation Method
2. Double Emulsification method
3. Emulsions - Diffusion Method
4. Nano-Precipitation Method
5. Coacervation Method

6. Salting Out Method
7. Dialysis
8. Supercritical Fluid Technology

1. Solvent Evaporation Method: Solvent evaporation method first developed for the preparation of nanoparticles. In this method firstly nano-emulsion formulation prepared. Polymer dissolved in organic solvents (dichloromethane, chloroform or ethyl acetate). The drug is dispersed in this solution. Then this mixture emulsified in an aqueous phase containing surfactant (polysorbates, poloxamers sodium dodecyl sulfates polyvinyl alcohol, gelatin) makes oil in water emulsion by using mechanical stirring, sonication, or micro fluidization (high-pressure homogenization through narrow channels). After the formation of emulsion, the organic solvent evaporates by increased the temperature and reduced pressure with continuous stirring.

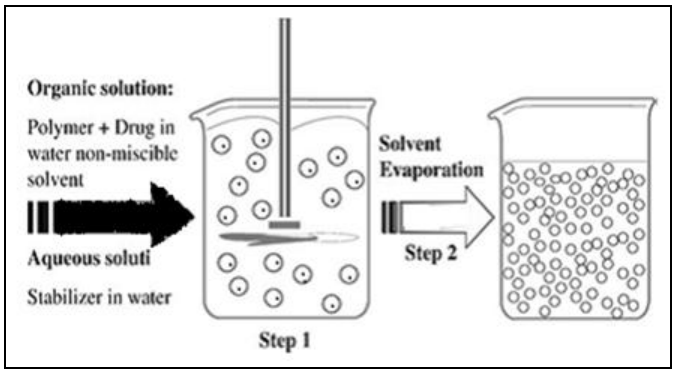

FIG. 3: REPRESENTATION OF THE SOLVENT-EVAPORATION TECHNIQUE

2. Double Emulsification Method: Emulsification and evaporation method have a limitation of poor entrapment of hydrophilic drugs; hence, double emulsification technique is used. Firstly w/o emulsion prepared by addition of aqueous drug solution to organic polymer solution with continuous stirring. This prepared emulsion another aqueous phase with vigorous stirring, resultant w/o/w emulsion prepared. Then organic solvent removed by high centrifugation.

3. Emulsions - Diffusion Method: This method patent by Leroux *et al*., it is a modified form of salting out method. Polymer dissolved in water-miscible-solvent (propylene carbonate, benzyl alcohol), this solution saturated with water. Polymer-water saturated solvent phase is emulsified in an aqueous solution containing a stabilizer. Then solvent removed by evaporation or filtration.

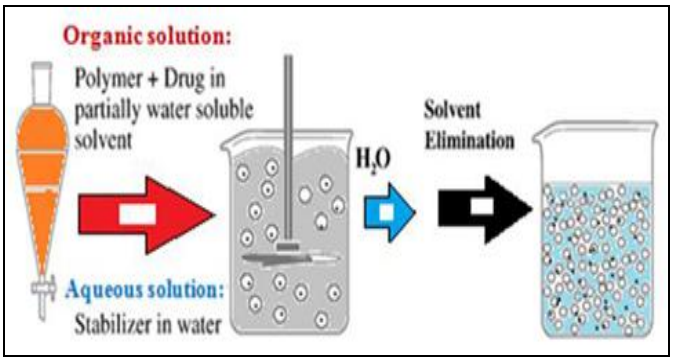

FIG. 4: REPRESENTATION OF THE EMULSIFICATION -DIFFUSION TECHNIQUE

4. Nano-precipitation Method: The other name of this method is called the solvent displacement method. This technique was first described by Fessi *et al*., 1989. In this method precipitation of polymer and drug obtained from the organic solvent and the organic solvent diffused into the aqueous medium with or without the presence of surfactant. Tamizhrasi *et al*., prepared lamivudine loaded nanoparticles. Firstly drug was dissolved in water, and then co-solvent (acetone used to making inner phase more homogeneous) was added into this solution.

Then another solution of polymer (ethyl cellulose, eudragit) and propylene glycol with chloroform prepared, and this solution was dispersed to the drug solution. This dispersion was slowly added to 10 ml of 70% aqueous ethanol solution. After 5 min of mixing, the organic solvents were removed by evaporation at 35 °C under normal pressure, nanoparticles were separated by using cooling centrifuge (10000 rpm for 20 min), the supernatant was removed, and nanoparticles washed with water and dried at room temperature in a desiccator.

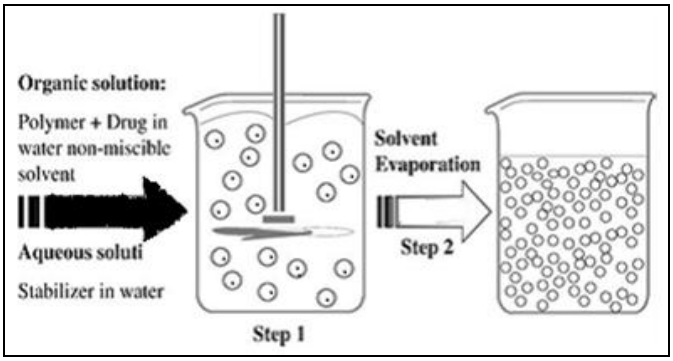

FIG. 5: REPRESENTATION OF THE NANO-PRECIPITATION TECHNIQUE

5. Coacervation Method: By using biodegradable hydrophilic polymers (such as chitosan, gelatin and sodium alginate, *etc*.) nanoparticle prepared by Coacervation method. Calvo *et al*., prepared nanoparticles by ionic gelation method which involves two aqueous phases. The first phase contains polymers like chitosan, a di-block copolymer like ethylene oxide or propylene oxide (PEO-PPO). The second phase contains polyanion sodium tripolyphosphate. Between these two phases, electrostatic interaction occurs which forms coacervates.

Saikat Das *et al*., prepared dug loaded albumin nanoparticle by coacervation method. Drug and protein solution (2% w/v) incubated for one hour at room temperature and pH adjusted to 5.5 by using 1M HCl. In this solution, ethanol was added in 2:1 ratio (v/v) in a controlled rate of 1 ml/min. Resultant coacervate hardened with 25% glutaraldehyde (1.56 µg/mg of protein) for 2 h which allow cross-linking of protein. Rotary vacuum evaporation at reduced pressure organic solvents was removed then nanoparticle was collected and purified by centrifugation at four-degree centigrade. Pellets of nanoparticles were then suspended in phosphate buffer (pH 7.4; 0.1M) and lyophilized with mannitol (2% w/v) at –48 ºC and 28 × 10^{-3} M Bar pressure for 24 h.

6. Salting Out Method: Salting out method is very close to the 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 miscible with water and easily removed. Polymer and drug 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 stabilizer/ emulsion stabilizer/ viscosity increasing agent such as polyvinyl pyrrolidone or hydroxyethylcellulose, PVA, Poly (ethylene oxide), PLGA and poly (trimethylene carbonate). After preparation of o/w emulsion diluted with the addition of sufficient water to allow the complete diffusion of acetone into the aqueous phase, thus inducing the formation of nano-spheres. This technique does not require an increase in temperature and stirring energy required for lower particle size. The disadvantage of this technique is an exclusive application to lipophilic drug and the extensive nanoparticles washing steps.

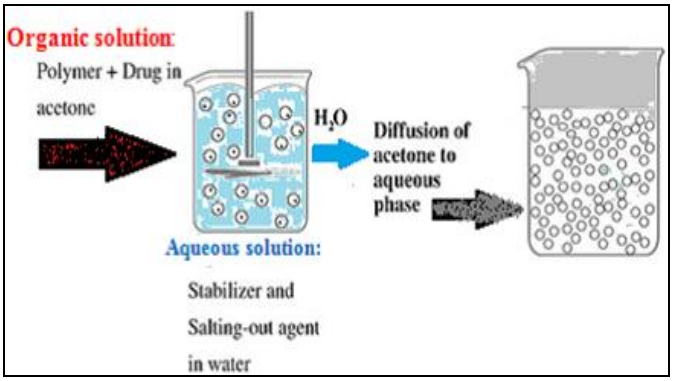

FIG. 6: REPRESENTATION OF THE SALTING OUT TECHNIQUE

7. Dialysis: Dialysis is an effective method for the preparation of nanoparticles. In this method firstly polymer {such as poly (benzyl-l-glutamate)-b-poly (ethylene oxide), poly (lactide)-b-poly (ethylene oxide)} and drug dissolved in an organic solvent. This solution added to a dialysis tube and dialysis performed against a non-solvent miscible with the former miscible. The displacement of the solvent inside the membrane is followed by the progressive aggregation of the polymer due to a loss of solubility and the formation of homogeneous suspensions of nanoparticles. Dialysis mechanism for the formation of the nanoparticle is not fully understood at present. It may be based on a mechanism similar to that of nano-precipitation.

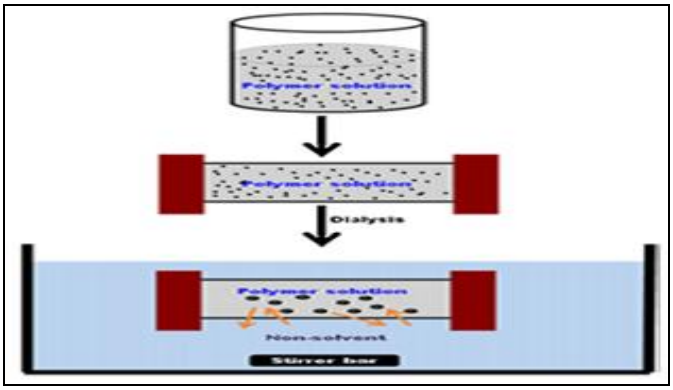

FIG. 7: REPRESENTATION OF OSMOSIS BASED METHOD FOR PREPARATION OF NANO-PARTICLES

8. Supercritical Fluid Technology: Supercritical fluid technology method is an 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 defined 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 (Tc = 31.1 °C, Pc = 73.8 bars) it is nontoxicity, non-flammability, and low price.

The mainly supercritical fluid used in two main techniques:

- Supercritical anti-solvent (SAS)
- The rapid expansion of critical solution (RESS).

In the SAS process, liquid solvents are used, which should completely miscible with the supercritical fluid. The process of SAS as 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 in the formation of nanoparticles.

In RESS high degree of supersaturation 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.

Evaluation of Nanoparticles:

Particle Size and Zeta Potential: Particle size and zeta Potential of nanoparticles are determined by using Malvern Zetasizer.

Surface Morphology: Surface morphology study is carried out by Scanning Electron Microscopy (SEM).

Polydispersity Index: Polydispersity index of nanoparticles is carried out by using Malvern Zetasizer.

Percentage Yield: The yield of nanoparticles was determined by comparing the whole weight of nanoparticles formed against the combined weight of the copolymer and drug using the following formula:

Yield % = Amount of nanoparticles / Amount of drug + polymer × 100

Encapsulation Efficiency: For the determination of encapsulation efficiency accurately weighed NPs (10 mg) were added to 10 ml of distilled water and after the equilibrium solubility was attained, clear supernatant after centrifugation was filtered and 1 ml of the filtrate was mixed with 4 ml of methanolic HCl. The resulting sample was analyzed on UV visible spectrophotometer.

The encapsulation efficiency was determined by using the following formula [23]:

Encapsulation efficiency (%) = [1-(Drug in supernatant liquid / Total drug added)] × 100

Drug Loading Capacity: For the determination of drug loading capacity, NPs (5 mg) were dissolved in 5 ml of methanolic HCl, and the solution was filtered through 0.2 µm filter (Axiva syringe filter) then, concentration in the sample was determined using UV visible spectrophotometer.

The percentage drug loading capacity was determined using the following formula [24]:

% Drug loading = (Mass of a drug in NP / Mass of NP recovered) × 100

***In-vitro* Release Study:** *In-vitro* drug release studies were performed in USP Type II dissolution apparatus at a rotation speed of 50 rpm. The prepared nanoparticles are immersed in 900 ml of phosphate buffer solution in a vessel, and the temperature was maintained at 37 ± 0.20 °C. Required quantity 5 ml 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.

Kinetic Study: For estimation of the kinetic and mechanism of drug release, the result of in vitro drug release study of nanoparticles were fitted with various kinetic equation like zero order (cumulative % release *vs.* time), first order (log % drug remaining *vs.* time), Higuchi‟s model (cumulative % drug release *vs.* square root of time). R^2 and k values were calculated for the linear curve obtained by regression analysis of the above plots.

Stability of Nanoparticles: Stability studies of prepared nanoparticles determined by storing optimized formulation at 4 °C ± 1 °C and 30 °C ± 2°C in the stability chamber for 90 days. The samples were analyzed after some time like at 0, 1, 2, and 3 months for their drug content, drug release rate (t_{50}%) as well as any changes in their physical appearance (ICH Q1A (R2) 2003).

Advantages of Nanoparticles: Nanoparticles offers numerous advantages in drug delivery system.

- Nanoparticles are controlled and sustain release forms at the site of localization; they alter the organ distribution of drug compound.
- They enhance drug circulation in blood, bioavailability, therapeutic efficacy and reduce side effects.
- Nanoparticles can be administered by various routes including oral, nasal, parenteral, intra-ocular, *etc*. In the tiny areas of the body, nano-particles shows better drug delivery as compared to other dosage form and target to a particular cell type or receptor. Due to small particle size nanoparticles overcome resistance by physiological barriers in the body.
- Easily penetrates to cell walls, blood vessels, stomach epithelium, and blood-brain barrier.
- Nanoparticle enhances the aqueous solubility of the poorly soluble drug, which improves the bioavailability of the drug.
- As targeted drug carrier nanoparticles reduce drug toxicity and enhance efficient drug distribution.
- By using polymers, drug release from nanoparticles can be modified which makes polymeric nanoparticle an ideal drug delivery system for cancer therapy, vaccines, contraceptives, and antibiotics.

Disadvantages of Nanoparticles:

- There are many limitations to be solved such as
- Poor oral bioavailability
- Instability in circulation
- Inadequate tissue distribution and toxicity.

Applications of Nanoparticles:

- Biodegradable chitosan nanoparticles encapsulating quantum dots were prepared by D. K. Chatterjee and Y. Zhang, with suitable surface modification to immobilize both tumor targeting agent and chemokine on their surfaces. The interactions between immune cells and tumor cells were visualized using an optical microscope. Use of quantum dots in the treatment of cancer is a great advancement in this area. Quantum dots glow when exposed to UV light. When injected they seep into the cancer tumor and the surgeon can see the glowing tumor.
- Nanotechnology had developed very helpfully in regenerating the injured nerves.
- In a recent study, antibody-conjugated magnetic poly-(D, L-lactide-co-glycolide acid) (PLGA) nanoparticle with doxorubicin (DOX) was synthesized for the simultaneous targeted detection and treatment of breast cancer. DOX and magnetic nanoparticles were incorporated into PLGA nanoparticles with DOX serving as an anticancer drug and Fe_2O_3 nanoparticles used as an imaging agent. They also used antibody herceptin 1 for targeting breast cancer.
- Molecular imaging techniques, such as optical imaging (OI), magnetic resonance imaging (MRI), ultrasound imaging (USI), positron-emission tomography (PET), and others, have been reported for imaging of *in-vitro* and *in-vivo* biological specimens.

CONCLUSION: Nanotechnology is opening a prospective future in pharmaceutics. A nanoparticle is a novel approach for drug delivery which we can achieve better therapeutic action, better bio-availability, reduce toxicity. Today nanoparticles are successfully used in brain targeting, in cancer therapy, *etc*. nanoparticles allows us to enhance patient compliance for better therapy. A real therapeutic breakthrough can be achieved solely by carrying out painstaking studies in the field of nano-therapy. Using nanosystems in therapies of diseases may contribute to achieving an effective cancer treatment.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Cho K, Wang X and Nie S: Clinical cancer research, therapeutic nanoparticles for drug delivery in cancer. Clin Cancer Res 2008; 14: 1310-16.

2. Nasimi P and Haidari M: Medical use of nanoparticle drug delivery and diagnosis diseases. International Journal of Green Nanotechnology 2013; 1: 1-5.
3. Tiriuwa R: Nanoparticle-preparation and evaluation parameters. Indian Journal of Pharmaceutical and Biological Research (IJPBR) 2015; 4(2): 27-31
4. Singh SK and Lillard Jr JW: Drug delivery approaches for breast cancer. International Journal of Nanomedicine 2017; 12: 6205-6218
5. What is cancer? Cancer.gov. National cancer institute Retrieved 28 march 2018
6. "Cancer Glossary." Cancer.org. American Cancer Society. Archived from the original on 1 September 2013. Retrieved 11 September 2013.
7. Kuper H, Adami HO and Boffetta P: Tobacco use, cancer causation and public health impact. Journal of Internal Medicine 2002; 251 (6): 455-66. doi:10.1046/j.1365-2796. 2002.00993.x. PMID 12028500
8. Paper no. 08 novel drug delivery system. no. 16 Formulation techniques of nanoparticles; pharmaceutical sciences
9. Pal SL, Jana U, Manna PK, and Mohanta GP: Nanoparticles: An overview of preparation and characterization. Journal of Applied Pharmaceutical Sciences 2011; 1(6): 228-34.
10. Tamizhrasi S, Shukla A and Shivkumar T: Formulation and evaluation of lamivudine loaded polymethacrylic acid nanoparticles. International Journal of Pharma Tech Research IJPRIF 2009; 1(3): 411-15.
11. Sonker P, Tewari AK, Chaube SK, Kumar R, Sharma VP, Sonker A and Yadav P: A study on cancer and its drugs with their molecular structure and mechanism of action: A Review. World J Pharm Sci 2018; 6(7): 13-34.
12. Shinde AKJ and Harinath N: Formulation, development and characterization of simvastatine nanoparticles by solvent displacement method. Der pharmacia Letter 2014; 6(2): 145-55
13. Ross JS, Schenkein DP and Pietrusko R: Targeted therapies for cancer 2004. Am J Clin Pathol 2004; 122: 598-09.
14. Morgillo F and Lee HY: Resistance to epidermal growth factor receptor-targeted therapy. Drug Resist Updat 2005; 8: 298-10.
15. Maeda H: The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. Adv Enzyme Regul 2001; 41: 189-07.
16. Allen TM: Ligand-targeted therapeutics in anticancer therapy. Nat Rev Cancer 2002; 2: 750-63.
17. Larsen AK, Escargueil AE and Skladanowski A: Resistance mechanisms associated with altered intracellular distribution of anticancer agents. Pharmacol Ther 2000; 85: 217-29.
18. Mitragotri S: In drug delivery, shape does matter. Pharm Res 2009; 26(1): 232-4
19. Champion JA, Katare YK and Mitragotri S: Particle shape: a new design parameter for micro- and nanoscale drug delivery carriers. J Control Release 2007; 121: 3-9
20. Venkataraman S, Hedrick JL and Ong ZY: The effects of polymeric nanostructure shape on drug delivery. Adv Drug Deliv Rev 2011; 63: 122846
21. Huang X, Jain PK, El-Sayed IH and El-Sayed MA: Gold nanoparticles: interesting optical properties and recent applications in cancer diagnostics and therapy. Nanomedicine (Lond) 2007; 2: 681-93.
22. Jain PK, Huang X, El-Sayed IH and El-Sayed MA: Noble metals on the nanoscale: optical and photothermal properties and some applications in imaging, sensing, biology, and medicine. Acc Chem Res 2008; 41: 1578-86.
23. Turkevich J, Stevenson PC and Hillier J: A study of the nucleation and growth processes in the synthesis of colloidal gold. Disc Farad Soc 1951; 11: 55-75.
24. Stern ST, Hall JB, Yu LL, Wood LJ, Paciotti GF and Tamarkin L: Translational considerations for cancer nanomedicine. J Controlled Release 2010; 146: 164-74. [PMC free article] [PubMed]
25. Libutti S, Paciotti G, Myer L, Haynes R, Gannon W and Walker M: Results of a completed phase I clinical trial of CYT- 6091: a pegylated colloidal gold-TNF. Nanomedicine 2009; 27: 3586.
26. Schiller JH, Storer BE, Witt PL, Alberti D, Tombes MB and Arzoomanian R: Biological and clinical effects of intravenous tumor necrosis factor-alpha administered three times weekly. Cancer Res 1991; 51: 1651-8 [PubMed]
27. Paciotti GF, Myer L, Weinreich D, Goia D, Pavel N and McLaughlin RE: Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery. Drug Deliv 2004; 11: 16983. [PubMed]
28. Libutti S, Paciotti G, Myer L, Haynes R, Gannon W and Walker M: Results of a completed phase I clinical trial of CYT- 6091: a pegylated colloidal gold-TNF. Nanomedicine 2009; 27: 3586.
29. Lakshmana Prabu S, Shirwaikar AA, Shirwaikar A and Kumar A: Formulation and evaluation of sustained release microspheres of rosin containing aceclofenac. Ars Pharm 2009; 50(2): 51- 62.

How to cite this article:
Rama A, Anjaneyulu M and Munija P: Cancer nanotherapeutics - a review. Int J Pharm Sci & Res 2019; 10(5): 2133-42. doi: 10.13040/ IJPSR.0975-8232.10(5).2133-42.