Available online on 19.07.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Nanotechnology: Emerging Platform for Drug Based Delivery System in Cancer

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ABSTRACT

In present scenario cancer has become one of the most difficult global healthcare problems, despite of having library of anti-cancer drugs the problem remains the same due to no specificity, burst release, damaging of normal cells and numerous side effects. Nanotechnology the emerging field gained attention as it offers site specific treatment in various tumors with lesser side effect. Nano carriers, a transport module provide platform to circumvent the problems related with the delivery of anticancer drug in drug delivery systems. Nano carriers help to improve the bioavailability and therapeutic efficiency of antitumor drugs, while providing preferential accumulation at the target site. Various nanocarriers are clinically approved for the delivery of antitumor drugs for their intended actions at the targeted sites. This review illustrates about the various nanocarriers, their importance in the delivery of anticancer drugs, targeting mechanisms of nanoparticles, various method of preparations of nanoparticles and influence of nanotechnology on herbal drug.

Keywords: Nanocarrier, bioavailability, multi drug resistance,

Article Info: Received 21 May 2019; Review Completed 29 June 2019; Accepted 11 July 2019; Available online 19 July 2019

Cite this article as:

Misra C, Gaur M, Gupta LN, Nanotechnology: Emerging Platform for Drug Based Delivery System in Cancer, Journal of Drug Delivery and Therapeutics. 2019; 9(4):744-749 http://dx.doi.org/10.22270/jddt.v9i4.3152

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1. Introduction

Globally cancer has been the second leading cause of death, and is responsible for an estimated 9.6 million deaths in 2018.[1] Chemotherapy involves rapidly killing and blocking of growth of cells in the body. Chemotherapeutics encounters the faster growing cancer cells, than the healthy ones, however because there are healthy cells which are also fast-growing, the drugs used in chemotherapy also attack those fast-growing healthy cells. This unwanted attack results in the failure of conventional chemotherapy.[2] In addition; the major drawback to the success of chemotherapy is hindered due to multi drug resistance (MDR). [3] Prolong uses of these anticancer drug results in development of multi drug resistances. The limitations of conventional chemotherapy have led to the development to target the delivery of drugs specifically to cancer cells through directing the cellular events at nanometer scale. Where conventional therapies necessitate hundreds or thousands of cells to detect the presence of any tumor, nanotechnology based approaches could significantly lower this requirement, thus making possible much earlier diagnosis and treatment regimes.

Nanoparticles are materials with size ranging from 1 to 1000 nm. Nanoparticles proceed by active and passive targeting strategies for encountering cancerous cells that effectively enhance the intracellular concentration of therapeutic drugs in the cancerous cells while avoiding toxicity in normal cells.[4] There are a variety of NP based drug delivery systems currently being explored for cancer therapeutics.[5] Cancer related examples of nano-formulations include organic and inorganic nanoparticles. The aim of this paper is to review fabrication methods for the most common nanoparticle type, its importance and future prospect.

2. Nanocarriers based drug delivery systems

Nanocarrier-based drug delivery system enables effective delivery of anticancer drugs by hindering the environment of cancer cells and exploiting their pathophysiological conditions

2.1 Organic nanocarriers

1. **Solid lipid nanoparticles (SLNs)**

Solid lipid nanoparticles are particle with size range from 50 nm to 1000 nm. These carriers consist of monolayer phospholipid, dispersed in water or in aqueous surfactant

ensuring colloidal stability. Homogenization at high pressure and micro emulsification are the two most common effective methods used for the preparation of SLNs nanoparticles. Solid lipid like fatty acids, waxes, steroids provide a highly lipophilic lipid matrix for drugs when dissolved or are dispersed in surfactant.[6]

SLNs as nanocarriers has been used in incorporating drug as it has various major benefits like it increases the bioavailability of poorly soluble drugs, reduces toxicity, increases efficacy, enhances stability.

The composition of SLNs containing lipid, drug and surfactant and their preparation method by hot or cold homogenization, drug can either be dispersed homogeneously in lipid matrix of SLNs (incorporated into the shell surrounding the lipid core (drug-enriched shell model) or incorporated into the core surrounded by a lipid shell (drug-enriched core model).SLNs have been used in effectively delivery of various anticancer drug like docetaxel[7],doxorubicin[8], paclitaxel[9], methotrexate[10] and 5-fluorouracil (5-FU)[11].

2. Liposomes

Liposomes are bilayer or multilayered phospholipid in spherical shaped vesicles with polar head groups oriented interiorly while non-polar head in the external phase. Liposomes have attained great attention because biocompatibility, biodegradability, low toxicity, and has property to trap both hydrophilic and lipophilic drugs[12] with less decomposition of the entrapped combinations, and release the entrapped at designated targets.

They showed a number of advantages over conventional systems which are, enhanced delivery of drug, protection of active drug from environmental factors, improved performance features of the product, preventing early degradation of the encapsulated drug, cost-effective formulations of expensive drugs and efficient treatment with reduced systemic toxicity.[13] Moreover, liposomes intact drugs have altered the pharmacokinetic properties compared to free form of drugs. Liposomes are commonly used as model cells or carriers for various bioactive agents including drugs, vaccines, cosmetics and nutraceuticals. The biodegradable and biocompatible composition of liposomes made them excellent therapeutic carriers and has increased their use in biomedicine formulations.[14]

3. Dendrimers

Dendrimers are nanocarriers associated with central core having branched macromolecules.[15] Usually, they are produced by using natural or synthetic components, which include sugars, nucleotides and amino acids. There unique size and well-arranged irregular branching patterns are obtained by polymerization process

Dendrimers are branched layer molecules containing numerous active terminals and initiator core with diameter 1.5-14.5 nm[16]. The synthesis process involves addition of new branch to the core is termed as generation. Numerous branches are added to the core to make the molecules a bulky thus increases helps to increase the linkages of drugs[17]. These nanocarriers usually intact drug molecules with hydrogen bonding or through chemical linkages other than this various ligand targeting drugs and surface functionalized drug are also attached to obtain specific objectives, which usually implicate precise contact at cell walls and biologically active sites. For preclinical study dendrimers came into light in forming dendrimer–drug conjugates. Recently, dendrimers have been extensively used in fields of biomedicine, including gene delivery, immunology, magnetic resonance imaging, vaccines and antiviral, antibacterial and anticancer drug delivery[18].

4. Polymeric Nanoparticles (PNPs)

Polymers nanoparticles are colloidal particles with size range of 10 to1000 nm. These particles are made up of biodegradable polymer and their structure can be categorized into nanospheres or nanocapsule particle[19]. Nanospheres are polymeric particle which can easily entrap drug inside the polymer matrix without any degradation[20] whereas in nanocapsule the drug is dissolved in liquid core and future is encapsulated by solid polymeric membrane [21]. Various number of methods like solvent evaporation, salting out, nanoprecipitation, dialysis, supercritical fluid technology, emulsification polymerization, miniemulsion polymerization, microemulsion polymerization have been reported for formation of these polymeric nanoparticles theses method also include successfully adsorption or chemical conjugation of drug on to the surface[22].

2.2 Inorganic nanocarriers

1. Carbon nanotubes (CNTs)

The discovery of carbon nanotubes came into lime light in 1991 by Iijima. These are hollow tube like structured formed by graphene sheet belong to family of fullerenes an allotropic form of carbon[23]. CNTs comprise of cross - sectional nanometer range dimensions and lengths that can extend over a thousand time their diameters. The range of these diameters ranges from 0.4–2 nm and 2–100 nm for single walled carbon nanotubes and multiwall carbon nanotubes respectively. The commonly used convenient techniques for the production of CNTs include arc discharge, laser ablation and thermal or plasma-enhanced chemical vapor deposition[24].

CNTs have promising carrier characteristics which not only includes their hollow monolithic structure, but also their high mechanical strength, high electrical and thermal conductivities and their ability for surface modifications. The major drawback with CNTs as a drug carrier are their poor water solubility and toxicity which can be overcome by surface functionalized, which make them water soluble, biocompatible, non/less toxic and as a serum-stable carrier.

2. Mesoporous silica nanoparticles (MSNs)

Mesoporous silica nanoparticles are comb like structure which gain interest by researcher due to their massive availability of silica as a material and simple synthesis procedures. MSNs ranges from 2 to 50 nm in diameter they are versatile of loading hydrophilic as well as lipophilic drug and also possess s good biocompatibility, large specific surface area and pore volume, high loading capacity[25] In addition, MSNs enables targeted drug delivery with increase therapeutic efficacy .Their surface can easily undergo functionalization for controlled drug delivery and reduce toxicity. Many anticancer drugs like paclitaxel[26], camptothecin[27], doxorubicin[28] and methotrexate[29] have been loaded in large amount with nanoscale particle range in tumor tissue by active as well as passive mechanism and as show fruitful result in effective delivery.

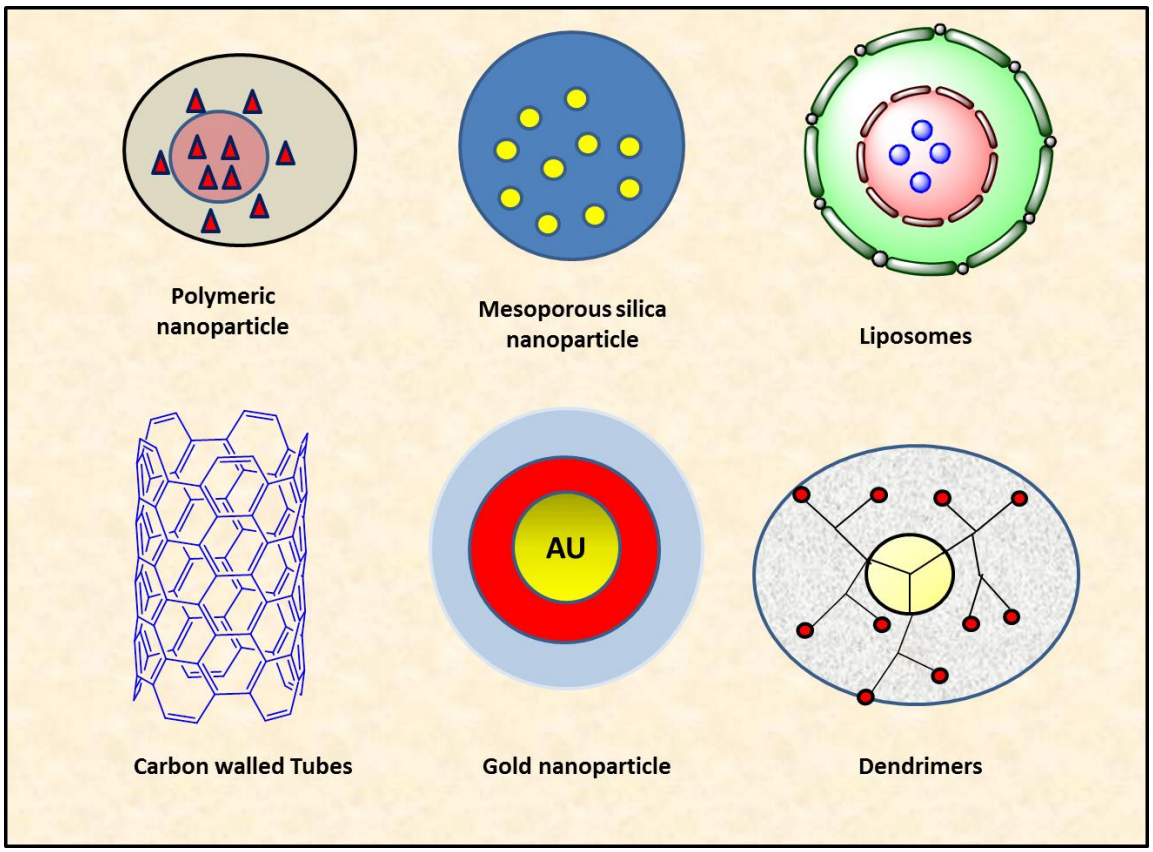

Fig 1 .Types of nanocarriers for novel drug delivery system

3. Targeting of nanoparticles on cancer cells

3.1 Passive Targeting

The abnormal growth of cancer cells increases the demand of oxygen and nutrients than that of normal cells through blood vessels, which result in forming wide and leaky blood vessels around the cells induced by angiogenesis. The reduction in number of perivascular lining rapidly proliferate endothelial cells resulting in large pores of 100 nm to 780 nm with leaky blood vessels[30]. Nanoparticles containing drug can easily enter the interstitial area in the tumor. This feature is called the enhanced permeability and retention (EPR) effect and facilitates tumor interstitial drug accumulation. Nanoparticles can easily accumulate selectively by enhanced permeability and retention effect and then diffuse into the cells[31]

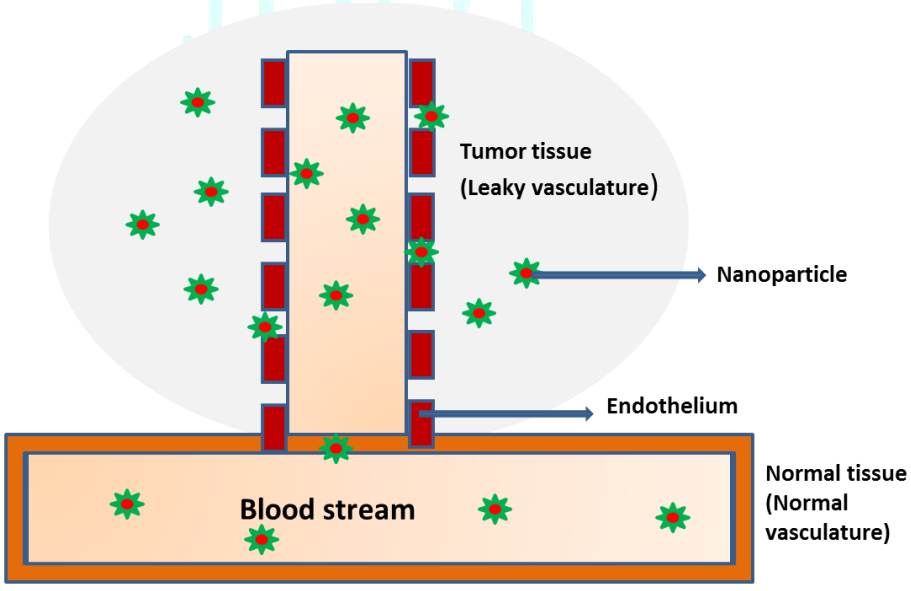

Fig 2. Shows Passive targeting and EPR effect of nanoparticles in tumors cells

3.2.2. Active Targeting

Nanoparticle with chemotherapeutic agents is designed to actively target the cancerous cells. This active targeting is based on modification in surface of nanoparticle, ligand receptor interaction or antibody-antigen recognition. Active targeting is based on molecular recognition usually targeting agents are attached with the surface of nanoparticles for molecular recognition. Nanotechnology based targeted delivery mainly influence by mainly three targeting mechanism apoptosis inducing agent, a targeting moiety-penetration enhancer and a carrier. Particles containing chemotherapeutic agents are engulfed by phagocytes and rapidly cleared by the reticuloendothelial system (RES)[32]. Nanoparticles can also be sustained in blood stream with hydrophilic coated polymer that can sufficiently target cancerous cells. Nanoparticle mostly target cancerous cells as some receptors are over expressed on the surface of them that make the distinguishing feature[33]. Cancerous cells are targeted by attachment of complementary ligands on the surface of nanoparticles. After the binding of nanoparticles with the receptor it undergoes receptor-mediated endocytosis or phagocytosis by cells, resulting in cell internalization of the encapsulated drug.

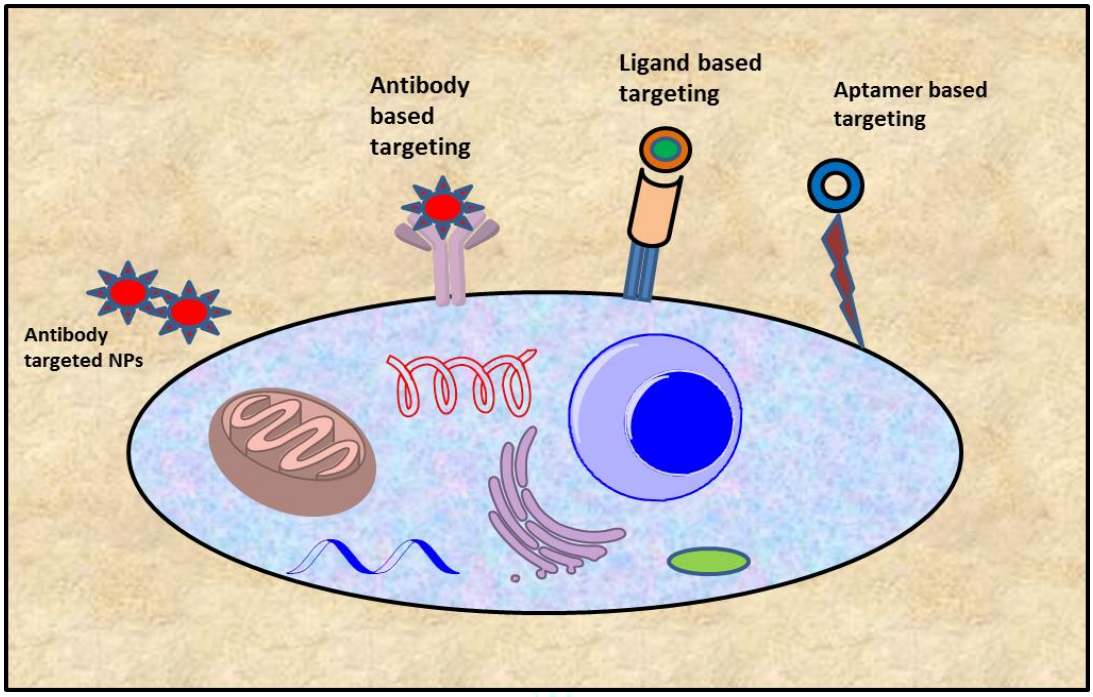

Fig 3: Shows active targeting of nanoparticle through drug delivery system

4. Preparation techniques of nanoparticles

4.1 Solvent Evaporation

In this process the polymer is dissolved in organic solvent (dichloromethane, chloroform or ethyl acetate) and drug is dispersed in solution drop wise. Then this mixture is added in an aqueous phase containing surfactant (polysorbates, poloxamers sodium dodecyl sulfates polyvinyl alcohol, gelatin) to make an emulsion by using mechanical stirring, sonication, or homogenizer. After formation of emulsion the organic solvent evaporates with continuous stirring[34]. This procedure is known as single emulsion solvent evaporation method. For double emulsion method the mixture is emulsified in aqueous phase containing surfactant (w/o) then pour in surfactant having different concentration (w/o/w) stir overnight for evaporation of organic solvent and centrifuge after 5 hours.

4.3 Nanoprecipitation method

This method was first described by Fessi at al. 1989[35] also known as solvent displacement method. This technique included precipitation of polymer and drug. Firstly drug was dissolved in water, then the inner phase was formed by addition of solvent into this solution. The drug solution was dispersed with another solution prepared with polymer such as ethyl cellulose and propylene glycol mixed in chloroform .This dispersion was slowly added to 10 ml of 70% aqueous ethanol solution mixed for 5 minutes. The solution was kept at 35 degree C under normal pressure for removal of the organic solvents. Then the solution was centrifuge at 10000 rpm for 4 degree C for 20 min supernatant were removed and nanoparticles washed with water and dried at room temperature in a desicator[36].

4.4 Ionic gelation method

Ionic gelation method involves two aqueous phases First phase contain biodegradable hydrophilic polymers like chitosan, gelatin and sodium alginate and second phase contain poly anion sodium tripolyphosphate the electrostatic interaction between these two phases result in formation of forms coacervates[38]. Various nanoparticles using drugs like Prednisone, Acyclovir have been prepared using chitosan, pectin- calcium chloride and sodium alginate, calcium chloride have been prepared for control drug release and gastroretentive drug delivery beads respectively[39]. Insulin loaded nanoparticle using arabic gum were prepared for diabetes patients. Chitosan was dissolved in 1.0% acetic acid under stirring at room temperature. For preparation of nanoparticle arabic gum was added dropwise with the help of syringe to chitosan solution containing insulin under gentle magnetic stirring at room temperature. The nanoparticle suspension was centrifuged for 15 min at 14,000 rpm at 4°C[39].

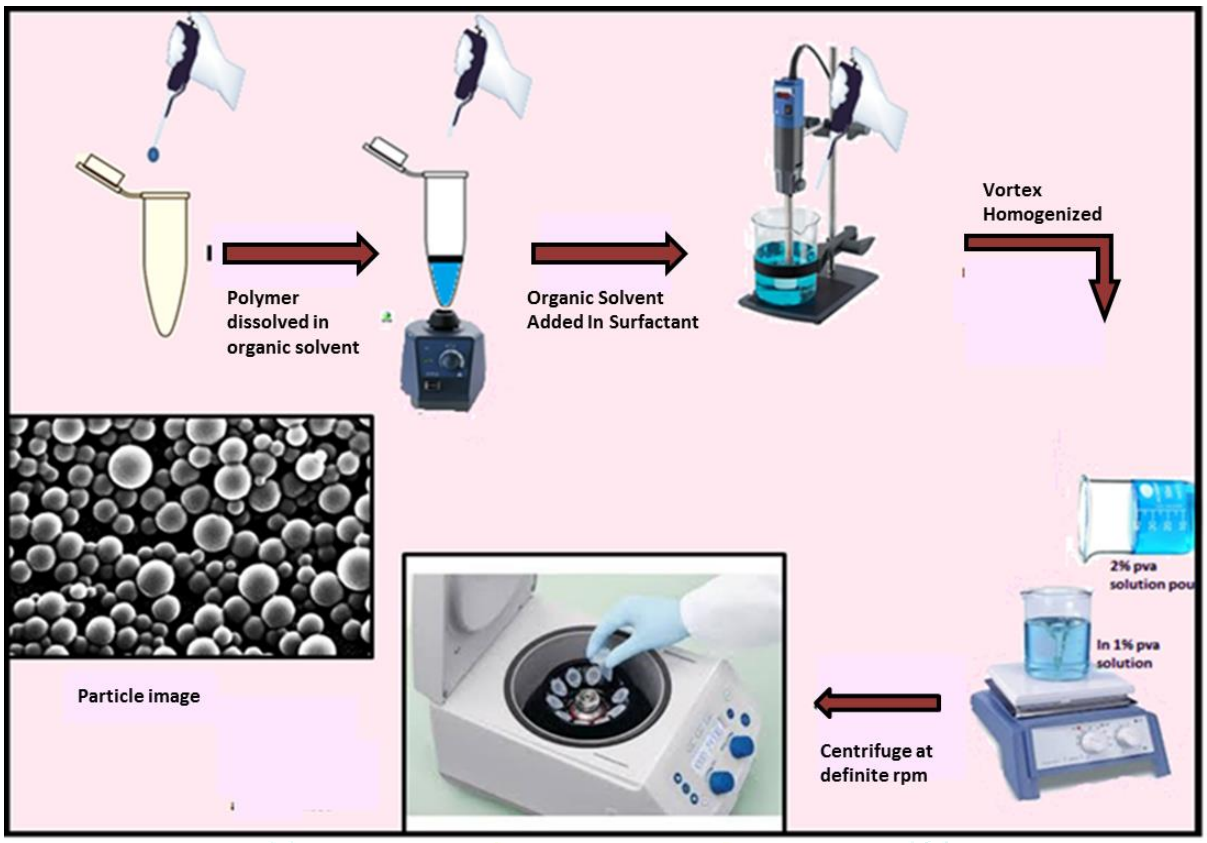

Fig: 4 Representation of double emulsion solvent evaporation method

4.5 Salting Out Method

This technique involves preparation of nanoparticles by addition of polymer and drug in a solvent usually acetone emulsified into a aqueous solution containing salting out agent such as magnesium chloride and calcium chloride. After the formation of emulsion water is added for complete diffusion of acetone which results in forming nanosphere. The technique of separating water miscible solvent from aqueous solution is known salting out effect[40]. Poly vinyl alcohol, polyvinyl pyrrolidone or hydroxyethyl cellulose are also used as colloidal, emulsion stabilizer for production of salting out effect by saturation of aqueous phase. The technique does not require any stirring energy or temperature for lowering particle size. The technique does not show effective response lipophilic drug.

5. Influence of nanotechnology on herbal drugs

Nanotechnology has shown tremendous success over synthetic drug through nanocarriers for targeted drug delivery system. Recently pharmaceutical scientists have focused on delivery of herbal drug through nanocarriers using a scientific approach. Various traditional Chinese and Indian medicines came into limelight during the study for treatment of various diseases such as cancer .The most commonly used traditional Chinese medicine Cuscuta chinensis nourish the liver and kidney but due to the poor water solubility of its major constituents such as flavonoids and lignans, limits its absorption by oral route. Thus nanoparticles for the same were developed to overcome the limitation and successful administration of drug through oral route without hindering the absorption of constituents[41]. In recent years various experimental studies have been taken for study of herbal drug with and without nanocarriers. Cucurbitacins and Curcuminoids lipophilic anticancer herbal drug were encapsulated with polylactic acid using a precipitation for effective delivery to cancer[42]. Traditional Chinese medicines have been encapsulated in nano formulation form and have been characterized for their targeted delivery and increased bioavailability and efficacy. In the recent years, Triptolide an herbal medicine was encapsulated in form of polymeric nanoparticles to enhance the solubility and reduce the toxicity for treatment of antineoplastic activity other than this curcumin a natural polyphenol encapsulated in form polymeric nanoparticle to bioavailability and solubility for antitumor activity.

6. Conclusions and future perspectives

Nanotechnology is assumed to be a fundamental setting in drug delivery system and human therapeutics. Nanocarriers have shown wonder in herbal and synthetic drugs delivery system especially in anticancer activity. Various limitations associated with conventional chemotherapy have been overcome by use of nanocarrier-based drug delivery systems. Nano carriers help to improve the bioavailability and therapeutic efficiency of antitumor drugs, while providing preferential accumulation at the target site. However, clinical practices are yet a challenge yet to be achieved. Human trials need to be conducted to establish effectiveness in clinical applications as an improved therapeutic modality for treatment of different disease

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