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TUMOR TARGETING DRUG DELIVERY SYSTEM

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ABSTRACT
Nanotechnology has revolutionized fundamental opportunities for higher specific drug delivery with minimum side effects. Since its inception, the goal of nanotechnology has been to advance effective and reliable systems for precise anti-cancer therapy and diagnosis. Conventional chemotherapeutics possess some serious side effects including damage of the immune system and other organs with rapidly proliferating cells due to nonspecific targeting, lack of solubility, and inability to enter the core of the tumors resulting in impaired treatment with reduced dose and with low survival rate. There are some risk factor also consider which may leads to cancer. The conventional treatments are surgery, Radio-therapy and chemo therapy but the real fact is none of the above mentioned treatment is enough for procurement of cancer and that's why now scientist and researchers are thinking about nano-technology. Nano technology has provided the opportunity to get direct access of the cancerous cells selectively with increased drug localization and cellular uptake. Nano particles can be programmed for recognizing the cancerous cells and giving selective and accurate drug delivery avoiding interaction with the healthy cells.

KEYWORDS: nanotechnology, polymerization, emulsification, nanopercipitation, receptors, surfactant.

INTRODUCTION
Cancer is one of the most serious fatal diseases in today's world that kills millions of people every year. It is one of the major health concerns of the 21st century which does not have any boundary and can affect any organ of people from any place.[1] Cancer, the uncontrolled proliferation of cells where apoptosis is greatly disappeared, requires very complex process of treatment. Because of complexity in genetic and phenotypic levels, it shows clinical diversity and therapeutic resistance. A variety of approaches are being practiced for the treatment of cancer each of which has some significant limitations and side effects.[2-3] Cancer treatment includes surgical removal, chemotherapy, radiation, and hormone therapy. Chemotherapy, a very common treatment, delivers anticancer drugs systemically to patients forquenching the uncontrolled proliferation of cancerous cells.[4-5] Unfortunately, due to nonspecific targeting by anticancer agents, many side effects occur and poor drug delivery of those agents cannot bring out the desired outcome in most of the cases. Cancer drug development involves a very complex Procedure which is associated with advanced polymer chemistry and electronic engineering.[6] The main challenge of cancer therapeutics is to differentiate the cancerous cells and the normal body cells. That is why the main objective becomes engineering the drug in such a way as it can identify the cancer cells to diminish their growth and proliferation. Conventional chemotherapy fails to target the cancerous cells selectively without interacting with the normal body cells. Thus they cause serious side effects including organ damage resulting in impaired treatment with lower dose and ultimately low survival rate.[7-8]

Nanotechnology is a rapidly expanding field due to the multidisciplinary support from researchers in the academic, industry, and federal sectors. Nanotechnology plays an important role in therapies of the future as nanomedicines by enabling this situation to happen, thus lowering doses required for efficacy as well as increasing the therapeutic indices and safety profiles of new therapeutics.[9-12]

Fig no.1

ADVANTAGES: In comparison to conventional cancer treatments, the nano scale of these particulate systems also lowers the irritant reactions at the injection site.

1. Nanotechnology-based delivery systems can also protect drugs from degradation.
2. Due to decrease in the size the available enhanced product may vary in their physical properties.
3. Reduction in dose frequency.
4. Economic and Patient compliance.
5. Insoluble drugs can also be delivered using Nano-based delivery systems.
6. Nano-based systems can also incorporate previously rejected drugs or drugs with administration issues.
7. Due to specific pathophysiological feature of the diseased tissues, drug targeting is refined and improved.
8. An ideal targeting system should have longer circulating time and optimum concentration at target site.
9. Its pharmacological activity is not affected by longer circulating time.
10. Enhanced permeability and retention effect are characteristic features of tumor, aiding drug delivery.
11. Macrophages (liver and spleen) are passively targeted by drugs.
12. Blood Brain Barrier is the most efficient and challenging natural barrier for CNS targeting drugs which are Lipophilic. For such drugs nanotechnology is the simplest solution as such drugs reach the target site via ultra-filtration process due to its nano-size.
13. Enhance the oral bioavailability of the agents that are not effectively used orally.

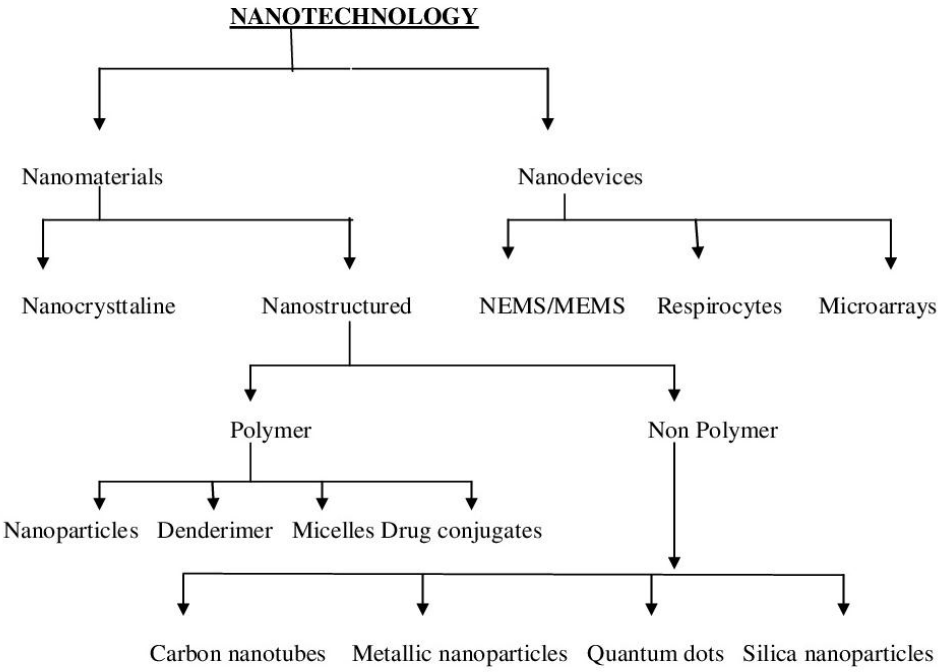

Fig No.2: Schematic Representation of Nano Technology.

MECHANISM OF ACTION: Targeting to Cancer Cell The delivery of nanoparticles to specific sites can be through size dependant passive targeting or by active targeting in which, passive targeting depends on both tumor structure and the structure of surrounding inflamed tissues (reference). The nanoparticulate delivery systems may exploit a characteristic of solid tumors by the enhanced permeability and retention (EPR) effect in which tumor tissues demonstrate several distinctive characteristics such as hyper vasculature, defective vascular architecture and a deficient lymphatic tissue/system.[13] Drainage leads to accumulation of macromolecules and retention in tumor cells for a longer period of time. Active targeting has been performed to achieve a high degree of selectivity to specialized tissues and to enhance the uptake of NP's into target areas.[14]

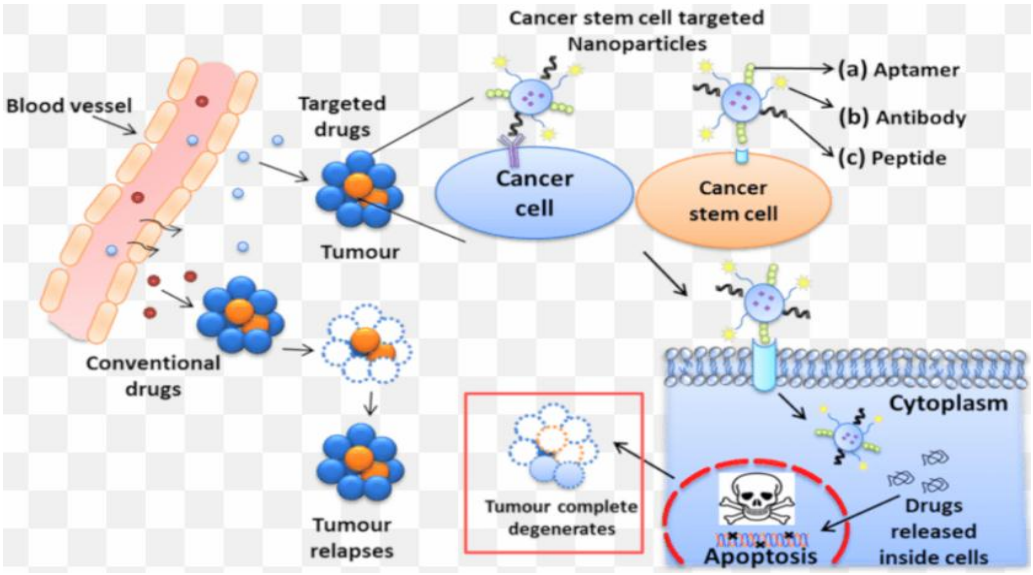

Fig no. 3.

Such as cancer cells and angiogenic micro capillaries growing around malignant cells. Nano particles are modified to target basic characteristics of cancer cells such as accelerated proliferation and particular antigen presentation.[15] Nano-particulate delivery systems utilize specific targeting agents for cancer cells and minimize the uptake of the anticancer agents with the help of normal cells, enhance the entry and release of the agent in tumor cells. These delivery systems include the anticancer agent, a targeting moiety, and a carrier and penetration enhancer.[16-19] The types of molecules which are capable of specifically recognizing and binding to other biological molecules are antibodies, enzymes, receptor ligands, and receptors. In all cancer therapies, targeting over surface modification provides numerous approaches for increasing treatment specificity and accuracy while reducing toxicity to healthy cells.[20] Passive targeting- The combination of leaky vasculature and poor lymphatic drainage results in the well-known Enhanced Permeability and Retention (EPR) effect Active targeting involves drug delivery to a specific site based on molecular recognition. One approach is to couple a ligand to nanoparticles which can interact with its receptor at the target cell site. Ligands that Binds to the Cancer Cell Receptors Cancer cells have many types of receptors and they are used for targeting purpose. These receptors and their ligands are given below. Some agents are used as theragnostic agents, for therapeutic and diagnostic purpose, which are targeted to the specific cell by bonded ligand.[21-24]

METHODS OF PREPARATION: Conventionally, two approaches are employed in synthesis of NPs: Pre-formed polymers dispersion method; and Monomer polymerization.[25]

Pre-formed polymer dispersion method Many approaches have been suggested to prepare biodegradable NPs from polymers (PLA, PLG, PLGA and poly) E-caprolactone)) by dispersing the preformed polymers .Abstract Polymeric nanoparticles are nano scale drug carrier. It can be modified by various surface modification reactions and the surface properties can be changed by covalent binding as well as adsorption of various agents which mimics ligand for specific receptors of cell.[26-27] In addition, these ligands are used for target specific drug delivery and for diagnostic purpose, termed as theragnostic agent. According to polymer properties, we can deliver hydrophobic or hydrophilic drug to a specific target. This review focuses on various techniques of targeting the nanoparticles to a specific site, along with this various preparation techniques, patent invention and their future prospects.[28-32]

Solvent evaporation method: This method involves, formation of an emulsion, using aqueous and organic phase. The polymer is completely dissolved in the organic solvent (e.g., Dichloromethane, chloroform, ethyl acetate). The drug is dispersed into the above preformed polymer solution. The aqueous solution is

added to make an emulsion making an O/W (oil/water) emulsion. To prevent phase separation surfactant/ emulsifying agents (gelatin, poly(vinly alcohol], polysorbate-80,) are added.[33] The end step is to evaporate the organic phase either by temperature and pressure or by continuous stirring.

Spontaneous emulsification/solvent diffusion technique: This is an upgraded approach of the conventional solvent techniques (evaporation), in which the oil phase consists of a water-soluble organic solvent (acetone, methanol) and water insoluble solvent (dichloromethane, chloroform) as oil phase.[34] Aqua is used as the aqueous phase. Upon mixing the water soluble organic phase spontaneously diffuse into the water and thus precipitating out the water insoluble organic phase contain the drug as polymeric nano-particles.[35] The remaining aqueous phase is then subjected to evaporation resulting in polymeric NP. The formation of NP's depends upon the Oil-to-polymer ratio and offers advantages over the conventional methods.

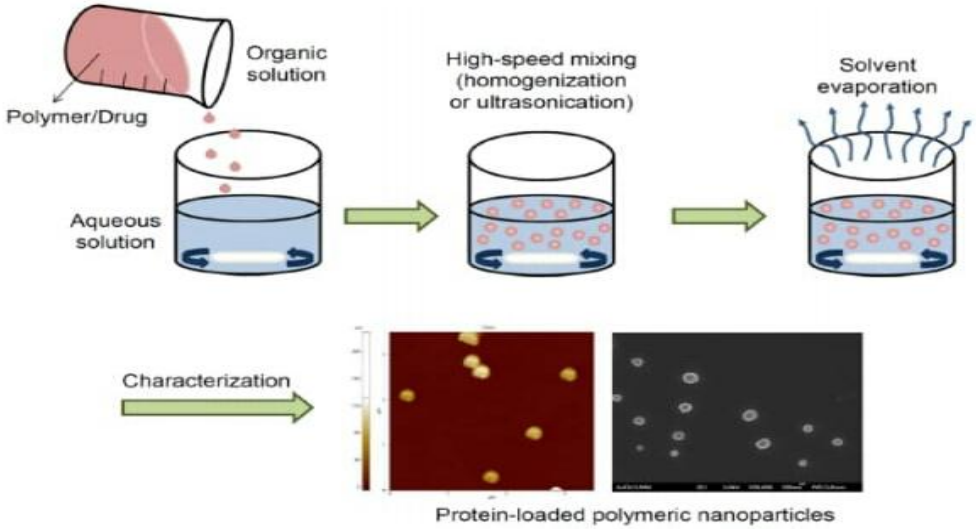

Fig no.4

Salting out/emulsification–diffusion method: Bindschaedler et al. first disclosed a modified version of emulsion process that results in a salting-out process which avoids surfactants and chlorinated solvents. Polymer and drug are firstly dissolved in a water-miscible solvent such as acetone, it is then emulsified more like Ouzo effect, into aqueous gel containing a salting agent (electrolyte: MgCl2, CaCl2; non-electrolyte: Sucrose). Dilute it with sufficient water to facilitate the acetone diffusion into aqueous phase resulting in salting out as nanosphere/particles.[36-40] Both the solvent and salting agent are removed via cross-flow filtration. The selection of appropriate salting agent is vital as it plays an important role in the encapsulation process of making the nanoparticles.

Nanoprecipitation: This approach is also known as solvent displacement method. The preformed polymer dis-solved into the organic layer is precipitated out by diffusion of organic solvent into the aqueous medium by either using surfactant.[41] The polymer (PLA), is dissolved in a water-miscible solvent of intermediate polarity, it's diffusion into aqueous phase leading to the precipitation of nanoparticles.

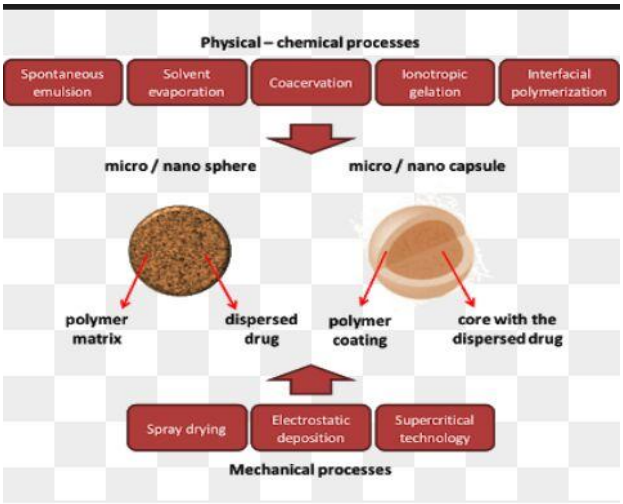

Fig no.5

Production of NPs using supercritical fluid technology: Conventional methods (solvent evaporation, coacervation and in situ polymerization) involve the use of toxic solvents and/or surfactants. The current green approach is the use of Super-critical fluids. This method utilizes CO2 in its supercritical state where it provided the ad-vantage of both liquid and gas, and above all is environment safe.[42] Easy regulation of temperature, pressure, higher purity of NP's and minimum-to-no

solvent residue are the attractive features of this approach.

The NP's are prepared via two methods, RESS (Rapid Expansion Supercritical Solution), RESOLV, SAS (solvent anti solvent). RESS method is a simple approach which utilizes Supercritical CO2 as a solvent. The material of interest is completely dissolved into it, and drawn out of a nozzle by varying its temperature/pressure, thus precipitating out the NP's and CO2 released as a gas. This is a clean technique as no residue of solvent remains. It is highly favourable for bio-erodible drug loaded polymers. The major drawback of this technique is the limited molecular mass (10, 000) and solubility in SCCO2.[43-47] RAS, a simple, but significant modification to RESS involves spreading of the supercritical solvent into a liquid solvent and also termed as RESOLV. The liquid solvent apparently suppresses the particle growth in the expansion jet, thus making it possible to obtain primarily nano-sized particles. In SAS method, is widely accepted for the drug-polymer which cannot be dissolved into SC-CO2. The drug-polymer is dissolved in a solvent which favours the SC-CO2. When the SC-CO2 is introduced into the solvent-drug-polymer mixture, at high pressures, enough antisolvent will enter into the liquid phase so that the solvent power will be lowered and the solute precipitates. After precipitation, when the final operating pressure is reached, the anti-solvent flows through the vessel so as to strip the residual solvent. This method, also called as gas antisolvent (GAS) technique.[48]

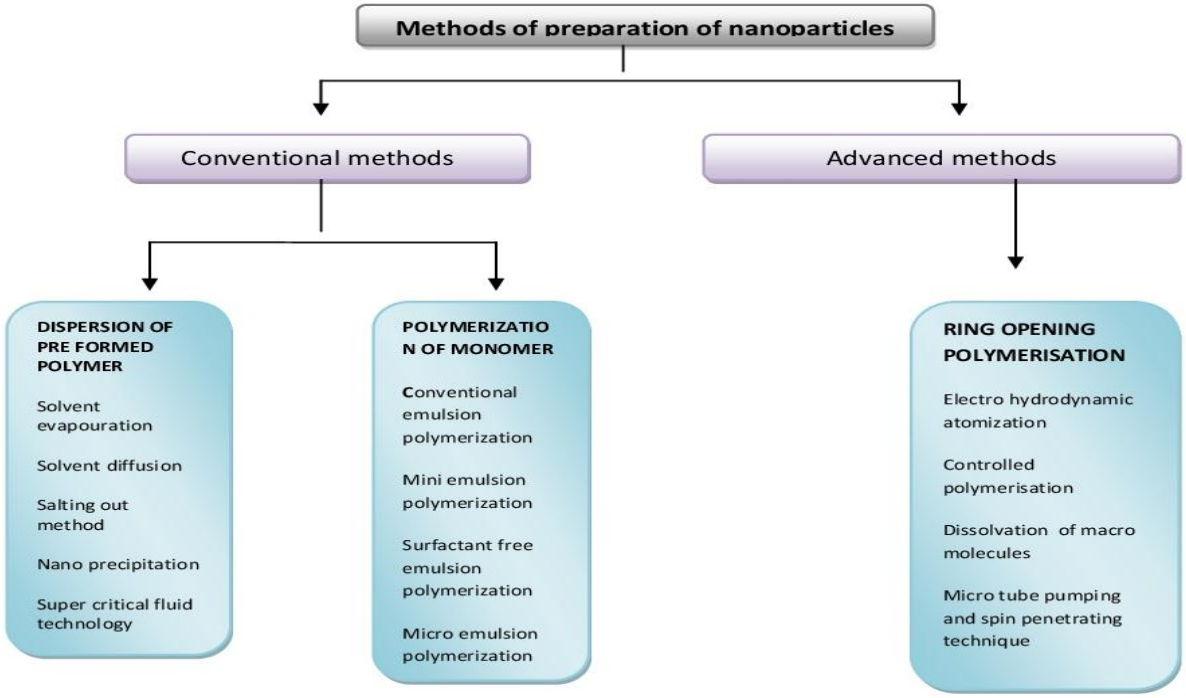

Fig.no:6

Polymerization of monomers

Conventional emulsion polymerization: In this conventional system, the ingredients are comprised of surfactant, water, a monomer of low water solubility, and a water-soluble initiator. Colloidal stabilizers may be electrosteric, electrostatic, steric or exhibiting both stabilizing mechanisms. Initiation appears when a monomer molecule dissolved in the continuous aqueous phase of collides with an initiator molecule that might be a free radical or ions. Alternatively, through high-energy radiation the monomer molecule can be changed into an initiatingradical.[49-52] Formation of solid particles and phase separation can occur before or after the termination of the polymerization reaction.

Surfactant-free emulsion polymerization: The varying quantities of surfactants are being utilized in the process of conventional emulsion polymerization systems, but there is need to eliminate those surfactants from the final product. Removal of surfactants increases the cost of production and is a slow process. Moreover, increasing energy and environmental concerns cannot be effectively addressed be-cause of these drawbacks.[53] As a substitute, emulsion polymerization has been performed in the absence of added emulsifier, often referred to as emulsifier-free, surfactant-free, or soap-less emulsion polymerization. This technique has received considerable attention, to be used as a simple, reen process for PNP production without the addition of stabilizing surfactant as well as for its subsequent removal.[54]

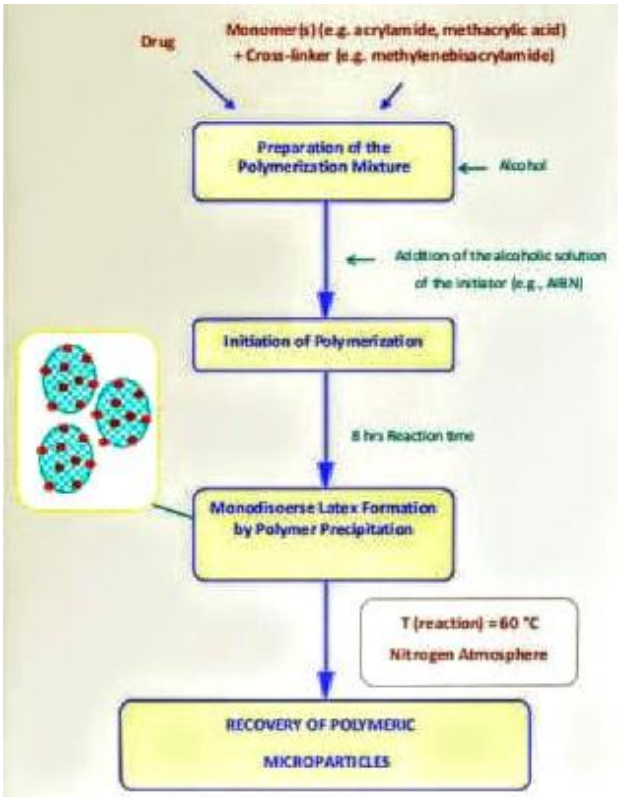

Fig no.7

Mini-emulsion polymerization: A distinctive formulation used in mini-emulsion polymerization consists of monomer mixture water, initiator co-stabilizer, and surfactant. A low molecular mass compound acts as the co-stabilizer and also the use of a high-shear device (ultrasound, etc.) is the main difference between mini-emulsion polymerization and emulsion polymerization. The critically stabilized Mini-emulsions require a high-shear to reach a steady state and have an interfacial tension much greater than zero.[55-59] With various co-stabilizers and initiator combi-nations versatile PNPs are well developed in the present era.

Micro-emulsion polymerization: The new and effective approach that has attracted significant attention for preparing nano sized polymer particles is a micro-emulsion polymerization. Although microemulsion polymerization and emulsion appear similar the reason being both methods can produce colloidal polymer particles with high molar mass but they are entirely different when compared kinetically.[60] Micro-emulsion polymerization exhibits two reaction rate intervals, whereas in emulsion polymerization three are detected. Both the average number of chains per particle and particle size are considerably smaller in micro-emulsion polymerization. In the pro-cess of micro-emulsion polymerization a water soluble initiator is added to the aqueous phase of swollen micelles that are thermodynamically stable micro emulsions.[61-64] The polymerization starts with the spontaneous formation of thermodynamically stable state and relies on high quantities of surfactant systems, which possess an interfacial tension, close to zero at the oil/water interface.[65]

Interfacial polymerization: The Interfacial polymerization is one of the well-established methods used for the preparation of polymeric nano-particles. It involves step i.e., polymerization of two reactive monomers or agents, which are dissolved respectively in two phases (i.e., dispersed-phase and a continuous phase), and the reaction takes place at the interface of the two liquids. Preparation of nanoparticles can also be done by polymerization of monomers.[66] Poly (alkylcyanoacrylates), PACA, being biodegradable is used to formulate nanoparticles by polymerization method. Here, the cyanoacrylic monomer under vigorous and continuous stir-ring is added to an aqueous solution of surface-active agents (polymerization medium) at ambient temperature to polymerize the alkyl cyanoacrylate. Drug is then dissolved in the polymerization medium either before the addition of the monomer or at the finish of the polymerization reaction. The NP suspension is then purified by ultracentrifugation or by re-suspending the particles in an isotonic surfactant free medium.[67-71]

Different Methods for Preparation of Nanoparticles

Drug loading into the NPs is achieved by two methods: firstly, by adsorbing the drug after the formation of NPs by incubating them in the drug solution or secondly, by incorporating the drug at the time of NP production.[72] It is thus evident that a large amount of drug can be entrapped by the process of incorporation when compared to the adsorption. The kind of surface-active materials and stabilizers has an effect on drug loading.[73] Beside adsorption and incorporation, a novel method of drug loading for the water-soluble drugs was proposed by Yoo et al. In this method, drug was chemically conjugated into NPs, spontaneous emulsion solvent diffusion method was used to prepare conjugates of doxorubicin-PLGA and doxorubicin-loaded PLGA nanoparticles and found to have good encapsulation efficiency of 96.6% as well as 3.5% loading of nano-particles.[74] Using the ring opening polymerisation technique, studies show the preparation of H2N-PEG-PLA, which uses H2N-PEG as micro initiator.[75]

Electro hydrodynamic atomization: This new method was first utilised by Xie et al. who developed nanoparticles by electro hydrodynamic atomization (EHDA) of a PLGA solution using acetonitrile. This basic phenomenon has been laid by sir Raileigh who described the possibility to diffuse the fluid in small formation of polymeric nanoparticles with reduced particle size and narrow size distribution.[76-79] Among the available controlled/living radical polymerization methods, mainly three approaches are presently successful and extensively studied viz. nitroxide-mediated polymerization (NMP), atom transfer radical polymerization (ATRP) and reversible addition and fragmentation transfer chain polymerization (RAFT).[80]

EVALUATION

Evaluation of therapeutic Efficacy: The tumor size was measured twice weekly with a vernier calipers in two dimensions. Individual tumor volumes (V) were calculated using the formula V = [length £ (width)2]/2 where length (L) is the longest diameter and width (W) is the shortest diameter perpendicular to length Growth curves for groups of tumors are presented as the mean volume relative to the values on the Wrst day of the treatment [TV).[47] RTV = (*Vx*¡*V*0)/*V*0, where *Vx* is the volume at day *x* and *V*0 is the volume on the day of treatment (day 0) . The time taken for a tumor to triple its initial volume (43 § 1 to 129 §3 mm3) was determined.[81-84] Bn The diVerence between mean values of this parameter for individual tumors in treatment and control groups was deWned as the tumor growth delay (GD) achieved as a result of therapy. Tumor volume doubling time (DT) calculations were determined by the equation *V*F= *V*i e*Kt*, where *V*F is Wnal tumor volume, *V*i is the initial tumor volume and *t* is the number of days between *V*F and *V*i measurements. According to the formula, DT (in days) equals 0.693/*K*, where *K* = In (*V*F/ Vi).[85] At each time point, treated versus control tumor volume ratio values were calculated as percentage for each experimental group. The lowest values obtained within 4 weeks after treatment were used for evaluating the eYcacy of the compounds.[86-91] At the end of the experiment the animals were sacri Wced by cervical dislocation and the tumor mass was harvested and weighed. Evaluation of safety*:* For safety evaluation of the control and Nanoparticulate formulations, the body weight.[92] of each mouse was determined twice weekly and related to the Wrst day as percent change in body weight. In addition, blood samples were withdrawn from the retro-orbital venous plexus at day 25 after treatment and blood parameters (white blood cells and platelet counts) were determined.[93-98]

Biological Evaluation of the Thiolated Analogs The antiproliferative activities of analogs 3 – 6 were evaluated against the A2780 human ovarian cancer cell line. Analogs 3, 4, and 6 were slightly more potent than native paclitaxel, but analog 5 was significantly less potent. These differences are presumably due to the lability of analogs 3, 4, and 6 as compared with the stability of analog 5 in buffer.[99] The antiproliferative activities of nanoconstructs CYT-20203 and CYT-21625 were also determined. As with the unbound analogs, CYT-20203 had similar activity to native paclitaxel, but CYT-21625 was almost four-fold less potent, consistent with its greater stability.[100-102]

These results taken together indicate that although analogs 3, 4, and 6 are most probably not suitable for use as AuNP drug candidates, because of their potential lability at physiological pH, analog 5 does have the right combination of stability in buffer and lability in the presence of DTT to serve as a drug candidate.[103-108]

CONCLUSION

Nanotechnology has great potential to make an important role in prevention of cancer, detection, diagnosis, imaging and treatment. Nanoparticles are important because of their nanoscaled structure but nanoparticles in cancer are still bigger than many anticancer drugs. Due to their multifunctional character, nanoparticles have great interest of scientist. The drug delivery nanoparticles are the latest achievement in the treatment of cancer. Drug carriers include micro and nanocapsules, micro and nanoparticles, lipoproteins, liposomes and micelles. Drug carrier can be engineered to slowly degrade, react to stimuli and be site-specific.

Predicting the future of nanotechnology in drug delivery systems is not simple because the technology is moving fast and dynamically changing, and we are in the middle of such changes. As our understanding on nano drug delivery vehicles improves, the system will become simpler and simpler, that is probably the only way to bring the nanovehicles into clinical applications. The future of nanotechnology in drug delivery is very bright, as combined efforts of scientist in different disciplines are bound to make nanotechnology practical.

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