Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
7(3), 2018, 61-71

ISSN 2321 – 0958

Review Article

APPROCHES TO REDUCE TOXICITY OF ANTICANCER DRUG

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Abstract: Around the world, remarkable resource is being investigated for in prevention, diagnostic and treatment of cancer. Cancer is second leading cause of death. The current approach to treat cancer by mainly chemotherapy agent, radiation and surgery, but main obstacle is to lack of selectivity result in toxicity to non cancerous proliferative cell .conventional anticancer drug exhibit much toxic effect in the body. So in this review focus approaches to treat cancer with minimum adverse effect. The possible approaches regarding, site specific drug targeting by polymeric drug, ligand conjugated drug which directly binding to cancer cell by cancer targeting receptor. Also discuss about chemoprotective agent, dose reduction intermittent therapy and drug polymer which help to help reduce toxicity. Unique challenge and opportunity in these work help to anticancer drug development.

Keywords: Cancer, Polymeric Drug, Passive Targeting, Approaches, Toxicity

Introduction: The conventional old treatment for cancer therapy is associated with several toxic effects along with several limitations. Therefore searching and developing new method for cancer became important. This mini review was dedicated on the design and synthesis of nanoparticles of anticancer drug for cancer treatment [1, 2]. The approaches discussed include targeted anticancer nanoparticles which are depending on the presence of unique cellular condition at the desired target. Due to the presence of certain enzymes at target sites, antibody detected enzymes prodrug therapy (ADEPT) gene directed enzyme prodrug therapy (GDEPT), which is the important strategy to cancer therapy and reduce side effect associated with anti cancer drug [3,4,5]. In these approaches, a design of anticancer nanoparticles is capable using use of different drug polymer. Therefore it is a must to involve innovate approaches for the design of new anticancer drug with reduced toxicity & better therapeutic index [6, 7].

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Received on: May 2018
Accepted after revision: July 2018

Nanoparticles: Nanoparticles are customized drug delivery system capable of preferentially targeting large dose of chemotherapeutic agent or therapeutic genes into malignant cells. Nanoparticles hold great promise of significantly changing the face of oncology by their ability of target delivery, thereby overcoming limitation of conventional chemotherapy, which include undesirable biodistribution, cancer cell drug resistance, and severe systematic side effect [8,9]. There is numerous nanoparticles system currently being employed for cancer therapeutics. The property of this system has been modulate to enhance delivery of drug to the tumor [10].The therapeutic agent is either conjugated to the surface of the NPs, or encapsulated & protected inside the polymeric core [11]. By desirable quality of their unique, physicochemical properties nanoparticles have shown promise in delivering a range of molecule to desired site in the body. NPs technology may improve the therapeutic index of drug by enhancing their efficacy and or increasing their tolerability in the body. Nanoparticles could also improve the bioavailability of water insoluble drugs, carry large payloads, and protect the therapeutic drug from physiological barrier, as well as enable the development of novel classes of bioactive macromolecule (e.g.-DNA and SiRNA). Additionally, the incorporation of imaging contrast with agent within nanoparticles can allow us to visually the site of drug delivery or monitor the, in vivo efficiency of the therapeutic agent [12-15]. The nanoparticles can be encapsulate drugs with high loading efficiency and protect them from undesired effect of external condition [16]. Since, emerging in the early 1970, controlled drug delivery system (DDS), which are aimed to deliver drug at predetermined rates & predefined periods of time, have attracted increasing attention [17].

Types of nanoparticle

Inorganic nanoparticle: In the field of modern material science inorganic nanoparticles has been developed the role based upon their unique physical properties and particularly in biotechnology. Based upon these two factors of inorganic nanoparticles, they have certain physical properties that mainly include size dependent optical, magnetic, electronic, and catalyst properties. Biorelated application are involved for the preparation of these interesting nanoparticles like iron oxides, gold, silver, silicon, quantum dots, etc [18].

Nanocrystal: Nanocrystal having dimensioned smaller than 10mm are also described as Quantum Dots (QD) .Nanocrystal are aggregate of around hundred or thousand of molecules that combine in a crystalline form, composed of pure drug with only a thin coating comprised of surfactant or combination of surfactant [18].

Polymeric nanoparticle: Polymeric nanometre is solid colloidal particle with diameter ranging from 1 to 100 nm. They have been investigated especially in drug delivery and drug targeting due to their particle size and long circulation in the blood [19, 20]. They considered of macromolecular material and can be used therapeutically as adjuvant in vaccines or drug carriers in which the active ingredient is dissolved, entrapped, encapsulated, absorbed or chemically attached. Polymeric nanoparticles are biodegradable, biocompatible, after complete drug protection [21].

Dendrites: Dendrites are nano-sized, very symmetric molecule with well defined, homogenous, and monodisperse structure consisting of tree-like arms or branches. It has three main part core, branch and surface. A variety of dendrimess exist, and each has biological properties such as polyvalence, self assembly, electrostatic interaction, chemical stability, low cytotoxicity, and solubility [22, 23].

Nanosomes: Nanosomes are currently used for medicine application such as targeting diagnosis and therapy. Brain targeting- thus nanosomes are being developed for treatment of various tumors (CNS Tumors). E.g. Silica coated iron

oxide nanoparticles coated polyethylene glycol used to access specific areas of brain involved with tumor. Tumor targeting– nanosomal delivery with magnetic resonance imaging and laser assist in targeting the nanoparticles. Specifically to the tumor cells and destroy the cell loaded with these nanoparticles by the heat generated by iron oxide particle by absorbing the infrared light [24].

Nanosphere: Nanospheres are the spherical particles which have the size between 10-200nm in diameter and that exhibit some new enhanced size dependent properties in comparison of large spheres of the same material. Basically the drug is dissolved, entrapped, encapsulated or attached to the matrix of polymer. In the matrix system of polymer the drug is physically and uniformly dispersed. Nanospheres can be amorphous or crystalline in nature and also they have the ability to protect the drug from enzymatic and chemical degradation [25, 26].

Nanocapsule: Nanocapsule show promise as active vectors due to their capacity to release drugs, their sub cellular size allows relative higher intracellular uptake than other particulate system. They can improve the stability of active substances. Nano-encapsulated system as active substance carriers include high drug encapsulation efficiency due to optimized drug solubility in the core, low polymer content compared to other nanoparticulated system such as nanospheres. Drug polymeric shell protection against degradation factor like pH and light and the reduction of tissue irritation due to the polymeric shell [27].

Liposomes: Liposome, sphere-shaped vesicles consisting of one or more phospholipids bailayers, liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural non-toxic phospholipids. Due to their size and hydrophobic, hydrophilic character (besides biocompatibility), liposome's are promising system for drug delivery. So the liposomal drug gets accumulated into the tumour tissue passively to produce enhanced effects. Active targeting of the liposomal drug can be achieved by using immunoliposomes or ligand directed liposomes [28,29].

Nanotube: This nonmaterial's are allotropes of carbon, made of graphite, and have been constructed in cylindrical tubes with nanometre scale in diameter and several millimeters in length. Since the beginning of the 21st century, they have been introduced in pharmacy and medicine for drug delivery system in therapeutics. Carbon nanotube is able to absorb or conjugate with variety of therapeutic molecules (drugs, proteins, antibodies, DNA, enzymes, etc [30].

Polymeric drug conjugate: Polymeric anticancer drugs are generally less toxic, when composed with free drug so far require significantly higher concentration inside the tumor to kill. The same amount of cancer cells as low molecular drugs. This decrease in drug efficacy can be compensated by targeting a polymeric drug to the specific organ, tissue and cells [31, 32]. Polymeric NPs are defined by their morphology and composition in the core and periphery. The therapeutic agent is either conjugated to the surface of the NPs or encapsulated and protected inside the polymeric core [33]. There are numerous NPs currently being employed for cancer therapeutics. The properties of this system have been molecular to enhance deliver to tumor for instant, hydrophilic surface provide the NPs with stealth property for longer circulations time, and positive change surface can enhance internalization into the cancer cell. The broad scope for chemically modifying the polymeric system facilitates its wide utility for large therapeutic aspect in the field of oncology. Polymeric drug conjugate have shown enhance tumor accumulation, increase therapeutic index and circulation accompany by sustained release of the bound drug [34].

Polymer for anticancer nanodrug: These are some important polymer used for help reducing toxicity of anticancer drug- such as

Poly (ethylene Glycol) PEG: PEG is most commonly used non-ionic polymer in the field of polymer based drug delivery. Due to high aqueous solubility PEG polymer is considered as a adaptable candidate for the prodrug conjugation. Ringworm was the first propose the rational model for pharmacologically active polymer in 1975 [35]. PEG in its most common form is a linear or branched polyether terminated with hydroxyl group. PEG is synthesized by anionic polymerization of ethylene oxide initiated by nucleophilic attack of a hydroxide ion on the epoxide ring. Most useful for polypeptide medication is monomethoxy PEG (mPEG). Successful conjugation of PEG with biomolecule depends upon the chemical structure, molecular weight, strict, hindrance, and the relativity of the bimolecular as well polymer. In order to synthesize a bioconjugate both chemical entities (i.e. the bioactive as well as polymer) need to possess a reactive or functional group such as –COOH, -OH, -SH, or -NH, before the synthetic methodology to form a conjugation involve either protection or deprotection of the group. PEG is the most widely used polymer in delivering anticancer drug clinically. PEGylation(i.e. the conventional attachment) of protein drug and bioactive is known to enhance the aqueous solubility of drugs, PEG nanodrug have prolong circulation time, minimize non specific cellular uptake, and achieve specific tumor targetibility through the Enhanced Permeability and Retention Effect. Numerous PEG based therapeutic have been develop and several have received market approval [36, 37].

N-(2-hydroxypropyl) methacrylamide (HPMA): N-(-Hydroxypropyl) methacrylamide or HPMA is water soluble (highly water soluble) non immunogenic and non toxic and long blood circulation. So it can be used as macromolecular carrier for low molecular weight drug (especially for anticancer drug) to enhance therapeutic efficacy and reduce toxic effect. Poly (HPMA) - drug conjugate accumulate at cancer cell by passive targeting mechanism Enhance Permeation and Retention Effect. So it's diverse property it can be applied for nanomedicine [38].

Beta cyclodextrin: Cyclodextrin (CDS) is cyclic compound consisting of six to eight glucose units, which are termed α, β, and γ respectively. These cyclic oligosaccharides contain a some, what lyphophilic outer surface, because of their chair conformation of glucopyrahose units, the CDs are shaped like reduced unit rather than perfect cylinders. CDs are able to form dynamic molecular inclusion complex with many drug incorporating the dry molecule, or commonly a lipophilic moiety of molecular into central cavity (39, 40). They are also beneficial in improving the aqueous solubility of poorly water-soluble molecule, to pocket degradable substance, to obtain sustained delivery or design innovative drug carrier [41].

POLY (lactic-co-glycolic acid) PLGA: PLGA has attracted considerable interest as a base material for biomedical application due to its biocompatibility, failure biodegradation rate depending on the molecular weight and copolymer ratio. Approval for clinical use in human by U.S food and drug administration. Potential to modify surface property to provide better interaction with biological material. PLGA based material with suitable properties and shape for specific biomedical application. Unlike pure polylactic and polyglycolic acid show poor solubility in. tetrahydrofuron of its ester linkage through bulk or heterogeneous erosion, in aqueous environment [42,43,44].

Chitosan: Chitosan is a naturally occurring linear polysaccharide composed primarily of repeating units of D- Glucosamine. It is structurally similar to the cellulose and the presence of highly reactive amine group renders the polymer a net positive charge. Chitosan is the most common polymer currently used for drug/gene delivery because of excellent properties such as good biocompatibility and natural antibacterial, anti-inflammatory and neuroprotective behaviours, which ensure same

therapies. It can be enzymatically degraded in *vivo* by enzymes such as lysozoyme and chitosanase, into oligomers and finally to N-glucosamine, which is endogenously present in the human body [45].

Polyphosphester: PPEs form another interesting class of biomaterial that is composed of phosphorus incorporated monomer. These polymers consist of phosphate with two R groups (one in the backbone and one side group) and can be synthesized by a number of routes including ring opening polymerization, poly condensation and polyaddition originally developed in 1970 [46]. Polymer with repeating phosphester bond in the backbone is structurally versatile and biodegradable through hydrolysis, and possible enzymatic digestion at the phosphoester linkage under physiological condition. These biodegradable polyphosphoester are appearing for biological and pharmaceutical application because of their potential biocompatibility and similar to biomacromolecule such as nucleic acid [47].

Polymer drug preparation method: The selection of appropriate method for the nanoparticles depends on the physicochemical character of the polymer and drug to be loaded. Method include-

- Solvent evaporation method
- Emulsion diffusion method
- Solvent displacement method
- Polymerization method
- Salting out method
- Coacervation method
- Ionic gelation method

Solvent evaporation method: In this method polymeric drug solution in a volatile solvent such as dichloromethane is prepared and emulsified into nonaqueous phase. It mainly involve in two steps. First step require emulsification of the polymer drug, solvent is evaporated, inducing, polymer precipitation as nanosphere [48]. Nanoparticles are collected by ultracentrifugation and washed with distilled water to remove stabilizer residue or any free drug and lyophilized for storage. Modification of this method is known high pressure emulsificaion and solvent evaporation method. This method involve preparation of emulsion which then subjected to homogenization under high pressure follow by overall stirring to remove organic solvent the size can be control by adjusting stirring rate, type and amount of dispersing agent, viscosity of organic and aqueous phase and temperature. However this method can be applied to lipophilic drugs [48].

Linker: Molecules that bind were another (usually longer) molecule. Chemical linkers are used to conjugate drug polymer by formation at covalent bond. The molecule of antibody drug conjugates currently in clinical development use only limited number of chemical linker. This linker exploits difference in intracellular PH, reduction potential or enzyme concentration to trigger the release of the cytotoxin in the cell. One of the unique features of antibody conjugate drug (ACD) is that they offer a unique target therapeutic strategy, by combining the best feature of both antibodies and small molecules drug to create a single moiety that is highly specific and intracellular release. Some chemical linkers and their release mechanisms are. Hydrozone - Design for serum stability and degradation in acidic compartment within the cytoplasm [1]. Peptide- Designed to be enzymatically hydrolyzed by lysosomal protease such as cathepsin B.

Disulfide - Designed to be cleaved through Disulfide exchange with an intracellular thiol, such as glutathione. Thioether – Nonreducible and designed for intracellular proteolytic degradation [49, 50]. Peptides ligand has shown significant targeting potential because of their small size, high stability, and relative easiness of large scale synthesis with excellent quality control [117, 118]. Peptide conjugate nanoparticles have been widely used for targeting cancer cell and tumor vasculature [51, 52]. The peptide Arg-Gly-Asp and Gly-Pro-Leu-Gly are generally used for as peptide linker. [53].

Approaches to reduce toxicity of anticancer drug: Uses of chemoprotective agent in the treatment of cancer, chemoprotective agent are drug which protect the healthy tissue from the toxic effect of anticancer drug, Amifostatine, Mesna, Acetylcycstine, Dexrazoxane are chemoprotective agent (54).

Countering the toxicity: Alternate / intermittent therapy is a new way, in anticancer drug therapy, Dose reduction, Folic acid rescue-Leucovorin reduced folate is co-administer with anticancer drug. Folic acid is used to rescue bone marrow and GIT muscular cells, and is directed converted to THFA. Use as advance drug delivery system. Uses of suitable polymer for alter the physiochemical properties of drug *i.e.* the cationic polymers are more interaction due to negative charge of cancer cell and drug can internalize more in cancer cell (55).

Approaches for targeting delivery of Nanoparticles: The delivery of an anticancer drug to target tissue can be achieved by NPs primarily in two ways: Passive targeting mean by Enhanced Permeation and Retention (EPR) effect. Active targeting by ligand based targeting. Tumour cell targeting i.e. Transferring receptors, foliate receptors, epidermal growth factor receptors, Glycoproteins, Matrix metalloproteinase's. By charges of cancers cells.

By Active and passive targeting: NPs have prolonged circulation time, minimize non specific cellular uptake and achieve specific tumour targeting therapy EPRE. The rational of using NPs for tumor targeting is based on one of the most efficiency at NPs is delivering drug in the area of the tumor target via the Enhance Permeability and Relation Effect. This can be also be achieved by active targeting of ligand at surface at NPs. NPs limit the drug distribution to target organ, hence reduce the drug exposure against healthy tissue. It was reported poly (isohexyl cyanoacrylate) hemisphere showed higher concentration at doxorubicin in the liver, spleen, and lungs then in using make doxorubicin. Active targetting is used to describe specific interaction between drug and drug carrier and target cells, usually through specific ligand interaction. Ligand – receptor interaction are possible any when compound are in close proximity (<0.5nm) [56, 57, 58].

Passive targeting: Passive targeting is based on drug accumulation in the area around the tumor with leaky vasculature commonly referred as the Enhanced Permeation and Retention Effect [59].

Enhance permeation and reaction effect: Blood vessel increase their permeability when affected by solid tumor or by inflammatory or infection Process. The vessel becomes leaky, this allowing particle to cross the wall and permeate the intestinal space. The size of the particle can vary from 10-500 nm, thus the nature of the disease affect the porosity of the vasculature, allowing for control over diffusion of the drug. The choice of properly sized carrier would allow the drug to extravasate from the blood vessel. Moreover tumor cell lack an effective lymphatic drainage system. Both aspects facilitate structure with a size up to approximately 200 nm to accumulate in tumor tissue [60].

General character of nanoparticles Size: The basic physiological parameters such as hepatic filtration, tissue extravasations / diffusion and kidney excretion. It is clear the particle size play a key factor in the long circulation and biodistribution of NPs. NPs smaller than 10 nm can be rapidly cleared by the kindly or though extravasations while longer NPs they have higher tendency to cleared by cell of the mononuclear phagocyte system MPS also referred as reticuloendothelial system [61]. For example in *vivo* distribution result of polystyrene NPs, with consistently composition and raring particle size of 50 to 500 NPs show higher level of agglomeration in the liver [62]. Another study compared different size range of PEGylated spherical NPs (<100nm, 100-200nm, and >200nm) for protein absorption nanoparticles uptake by immuring macrophages, and blood cleared kinetic [63].

NPs size have key for for EPRE. Several studies have studied to determine the gap size in the leaky vasculature, so the size range 10-25 nm had clearly undergone EPRE [64-68].

Surface charge: It has been established that the surface charge of NPs also could after their uptake by the mononuclear phagocyte system cell. The neutrally charged NPs have more circulation time then change particle [69.70]. Positive charge NPs have generated more immune response compliment activation and conjugated activation compare to neutral charge particle. For example the molecule having amine at the surface higher rate of nonspecific uptake than molecular heaving hydroxyl sulphate or carboxyl group. So the NPs having charge between -10 to +10 mv have reduced nonspecific cellular uptake and interaction [71, 72].

Characterization of Nanoparticals (NPs): To understand synthesis and application of NPs, characterization of NP is necessary [73]. Size determination is the primary parameter for characterization of NPs.

Scanning Electron Microscopy (SEM): SEM also used a high energy electron beam but the beam is scanned over the surface and the back scattering of the electron is looked at. The sample must again be under a vacuum and SEM electrically conductive at the surface. SEM is giving morphological examination with direct visualization. For SEM characterization, NP solution should be first converted into dry powder, which is then mounted and a sample holder followed by coating with a conductive metal. The sample is then scanned with for used fine beam of electron. The surface characteristics of the sample are obtained from secondary electron emitted from the sample surface. The mean beam size obtained by SEM is comparable with result obtained by dynamic high scattering. This techniques is time consuming and expensive (74, 75).

Transmission Electron Microscopy (TEM): TEM use an electron beam to interact with a sample to from an image on a photograph plate or specialist camera. The sample must there able to withstand the electron beam and also the high vacuum chamber that sample is put into. The sample preparation can be difficult as a thin sample and a supported grid must be prepared the proceeds can be also be time consume and this, along with cost are main disadvantages. This given higher resolution when is benefit when study of the sample to also it require understanding of the sample to allow interpretation of the results [76].

Conclusion: The aim of this review have been overview the design of anticancer drug which target the cancer cell the approaches which used follow active and passive targeting Enhance Permeation and Retention Effect. Their unique ideas about anticancer drug formulation to clinician offer them. New concept of the treatment to improve the therapeutic effectiveness thereby providing hope for new treatment option in the future. However new developed nanomedicine, whether it is carrier for drug, therapeutic agent or imaging agent, will need to be thoroughly characterized physiochemical. Pharmacologically and immunological before they Can be used for human. Acute and chronic toxicity determination by cell line or animal model is compulsory for safety of human. Nanotechnology provides hope in developing new way to diagnose, treat cancer in current trend.

References:

[1] Schrama, D.Reidfield, R.A., Becker, J.C. (2006).Antibody targeted drug as cancer therapeutics. Nature review Drug discovery, 5(2): 147-159

[2] Zhang, Q.Chen, G.Liu.X &Q.(2007).Monoclonal antibodies as therapeutic agent in oncology and antibody gene therapy.Cell research,17(2 :89-99)

[3] Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Jarvinen, T., & Savolainen, J. (2008). Prodrugs: design and clinical applications. Nature Reviews Drug Discovery, 7(3): 255-270.

[4] Singh, Y., Palombo, M., & Sinko, P. J. (2008). Recent trends in targeted anticancer prodrug and conjugate design. Current medicinal chemistry, 15(18): 1802.
[5] Niculescu-Duvaz, D.friedlos, F. Spooner, R. Martin, J.Marais,R.Springer, C.J(1999).Self-immolaive anthracycline prodrug for sucide gene therapy. Jounral of medicinal cheistry,42(13):2185-2489
[6] Singh, Y.Murat,P&defrancq,E.(2010).Recent developments in oligonucleotide conjigation.Chemical Society Review,39(6):2054-2070
[7] Abu-Jaish,A.Mecca,G.Gumma,S.Thawabeth,A.Karaman,R(2015) Metefenamic acid Prodrug amd Codrugs-two decades of development.World journal of Pharamaceutical Research 4(6):2408-2429
[8] Sinha R, Kim GJ, Nie S, Shin DM. Nanotechnology in cancer therapeutics; bioconjugated nanoparticles for drug delivery.Mol cancer ther. 2006;5(8):1909-1907
[9] Gu FX,Karnik R,WangAZ,et al.Targeted nanoparticle for cancer therapy.Nano Today.2007;2(3):14-21
[10] HaleyB,FrenkelE.Nanoparticles for drug delivery in cancer treatment.Urol Oncol.2008;26(1):57-64
[11] ChoK, Wang X Nie S,Chen ZG,Shin DM. therapeutic nanoparticle for drug delivery in cancer.Clin Cancer Res.2008;14(5):1301-1316
[12] Allen TM,Cullis PR(2004) Drug delivery system:entering the mailsteram Science 303:1818-1822
[13] Cai W,Chen X(2007) nanpoplatforms for targeted molecular imaging in living subjects. Small 3(11):1840-1854
[14] Gao X et al (2005) in vivo molecular and cellular imaging with quantam dots. Cirr opin Biotechnol 16(1):63-72
[15] Moghimi SM, Hunter AC, Murray JC(2005) Nanomedicine:current status and future prospects FASEB J 19(3):311-330
[16] Farokhzad OC,Langer R(2009) Impact of nanotechnology of drug delivery ACS Nano 3(1):16-20
[17] Liu R, Zheng HQ, Zhou Z, Dong JT.Chen C.KLF5 promotes breast cell survival partially through fibroblast growth factor-binding protein 1- pREk-meditated dual specificity MKP-1 protein phosphorylation and stabilization. Journal of biological chemistry. 2009 jun19;284 (25):16791-8
[18] Ladj R,Bitar A , Eissa MM, Fessi H, Muginer Y, Le Dantec R, Elasissari A. Polymer encapsulation of inorganic nanoparticles for biomedical application . international journal of pharmaceutics. 2013dec15;458(1):230-41
[19] Gu FX, Karnik R, Wang AZ,et al. targeted nanoparticle for cancer therapy.nano today.2007;2(3):14-21
[20] Byrne JD, Betancourt T,Brannonpeppas L.Active targeting scheme for nanoparticle system in cancer therapeutics. Adv Drug Delivery Rev.2008;60(15):1615-1626
[21] Alexis F, Pridgen E, Monlar LK,Farokhzad OC. Factor affecting the clearance and biodistribution of polymeric nanoparticle. Mol Pharm .2008;5(4):505-515
[22] SrinivasaGopalan S,Yarema KJ.Nanotechnologies for the life science : Dendrimers in cancer treatment and Diagnosis,volume7.New york:Wiley;2007
[23] Klajnert B, Bryszewska M. Dendrimers: properties and applications.Acta Biochim Pol.2001;09:199-208
[24] Xu H, Yan F, monsoon EE, Kopelman R. room temp. preparation and characterization pf polyethylene glycol-coated silica nanoparticle for biomedical application .J Biomed Mater Res A 2003;66:870-9Q
[25] Mohan raj VJ, Chen Y. Nanoparticle- A review, Tropical Journal of Pharmaceutical Research 5,2006,561-573
[26] Illum L, Davis S.S. The organ uptake of intravenously administrated collidal particle can be altered using a non-ionic surfactant (Poloxamer 338), FEBS Lett, 167,1984,79-82

[27] Gonzalo T, Lollo G, Garcia-Fuentes M, Torres D, Correa J, Riguera R, Fernandez-Megia,Calvo P, Aviles P, Guillen MJ, Alonso MJ. A new potential nano-onxological therapy based on polyamino acid nanocapsules. J control telease 2013;169(1-2):10-

[28] Mulder WJ, Strijkers GJ, Griffioen AW, van Bloois L, Molema G, Storm G, Koning GA, Nicolay K. A liposomal system for contrast-enhanced magnetic resonance imaging of molecular targets. Bioconjugate chemistry. 2004 Jul 21;15(4):799-806.

[29] Szebeni JL, Baranyi L, Savay S, Milosevits J, Bunger R, Laverman P, Metselaar JM, Storm G, Chanan-Khan A, Liebes L, Muggia FM. Role of complement activation in hypersensitivity reactions to doxil and hynic PEG liposomes: experimental and clinical studies. Journal of liposome research. 2002 Jan 1;12(1-2):165-72.

[30] 17. Mc Devitt MR, Chattopadhyay D, Kappel BJ, Jaggi JS, Schiffman SR, Antczac et al. Tumor targeting with antibody-functunalized, radiolebelled carbon nanotubes. J Nucl Med 2007;48:1180-

[31] Minko T (2004)Drug targeting to the colon with lectins and nenoglyococonjugates Adv drug Deliv Rev 56:491-509

[32] Fang J, Sawa T, Maeda H(2003) Factor and mechanism of EPR effect and the enhanced antitumor effect of macromolecular drugs including smancs. Adv Exp Med Bio 519:29-49

[33] 6. Lipinski C. Poor aqueous solubility An industry wide problem in drug discovery. Am Pharm Rev. 2002;5(3):82-85

[34] 1 Shelanski HA, Shelanski MK. PVPiodine history, toxicity and therapeutic uses. 1956;25(6):727-734

[35] K. Knop, R. Hoogenboon, Fischer, U.S Schubert, "Poly(ethylene glycol) in drug delivery : pros and cons as well as potential alternatives,"Angewandte Chemie- international edition,vol. 49,no 36, pp. 6288-6308,2010

[36]M.D Bentely, J.M. Harris and A.Kozlowski, "Heterobifunctional Poly(ethylene glycol) derivatives and method for their preperation,"P.C.T. US99/23536,1999

[37] Hutanu D, Frishberg MD, Guo L, Darie CC. Recent applications of polyethylene glycols (PEGs) and PEG derivatives. Modern Chemistry & Applications. 2014 Aug 26.

[38] 2. HPMA copolomers:www.com.science direct83)

[39] 1. Easton CJ, Lincoln SF. Modified Cyclodextrins: Scaffold and Templates for Supramolecular chemistry. Imperial college london;1999

[40] 2 Loftsson T,Brewster ME. Pharmaceutical application of cyclodextrins:1. Drug solubilization and stabilization. J Pharm Sci 1996;85(10):1017-25.

[41] 7 Liu Guo Q. The driving forces in the inclusion complexations of cyclodextrins. J Incl Phenom Macrocycl Chem 2002;42:1-14

[42] Ansary RH, Awang MB, Rahman MM. Biodegradable poly (D, L-lactic-co-glycolic acid)-based micro/nanoparticles for sustained release of protein drugs-A review. Tropical Journal of Pharmaceutical Research. 2014;13(7):1179-90.

[43] Engineer C, Parikh J, Raval A. Review on hydrolytic degration behavior of bio degradable polymer from controlled drug delivery system. Trends biometer. Artif. Organ 2011;25:79-85

[44] Makadia HK,Siegal S.J Poly lacticcoglycolic acid (plga) as biodegradable controlled drug delivery carrier.Polymers baser2011;3:1377-1397

[45] Elgadir MA, Uddin MS, Ferdosh S, Adam A, Chowdhury AJ, Sarker MZ. Impact of chitosan composites and chitosan nanoparticle composites on various drug delivery systems: A review. journal of food and drug analysis. 2015 Dec 31;23(4):619-29.

[46] Lapienis G,Penczek S. Macromocules.1974;7:166-174

[47] Kaluzynski K, Libisowski J, Penczek S. Macromolecules.1976;9:365-367

[48] Pal SL, Jana U,Manna PK, Mohanta GP, Manavalan R. Nanoparticle : An overview of peperation and characterization (2000-2010

[49] Lam KS et al (1991) A new type of synthetic peptide library for identifying ligand-binding activity. Nature 354:82-84
[50] Needels MC at al (1993) Generation and screening of an oligonucleotide-encoded synthetic peptide library. Proc Natil Acad Sci USA 90(22):10700-10704
[51] Arap W et al (2002) steps towards mapping the human vasculature by phage display. Nat Med 8(2):121-127
[52] Lam KS, Zhao ZG (1997)Targated therapy for lymphoma with peptides Hematol Oncol Clin North Am 11(5):1007-1019
[53] Danhier F at el (2009) Targeting of tumor endothelium by RGD grafted PLGA –nanoparticles loaded with Paclitaxel. J control release 140(2):166-173
[54] Korst AE, EEltink CM, Vermorken JB,Van der Vijgh WJ. Pharamacokinetics of amifostine and its metabolities in patients.european journal of cancer.1977 aug 1;33(9):1425-
[55] Chen CS, Lin JT, Gross KA, HE YA, Helpert JR, Waxmzn DJ. Activation of the anticancer prodrug cyclophosphamide and ifosfamide: indefication of cytochrome P450 2B enzymes and site –specific mutant with improved enzyme kinetics. Molecular pharmacology.2004may 1;65(5):1278-85
[56] Prabhu RH, Patravale VB, Joshi MD. Polymeric nanoparticle for targeted treatment in oncology: current insight. International journal of nanomedicine.2015;10:1001
[57] Bhhattacharaya S, Prajapati BG. International journal of Pharmaceutical research and bio-science
[58] Zee-Cheng RK, Cheng CC. Delivery of anticancer drug. Method of findings in experimental and clinical pharmacology. 1988dec;11(7-8):439-539
[59] Beduneau A, Saulnier P, Hindre F, Clavreul A, Benoit JP. Design of targeted lipid nanocapsules by conjugation of whole antibodies and antibody Fab fragments.Biomaterial. 2007;28:4978-4990
[60] Seymour, L.W. Passive tumor targeting of soluble macromolecules and drug conjuction. Crit. Rev. Ther. Drug Carrier Syst. 1992;9:135-187
[61] Petros RA, Desimone JM (2010) stratigies in the design of nanoparticles for therapeutic application. Nat Rev Drug Discover 9(8):615-627
[62] Nagayama S, Ogawara K-I, Fukuoka Y, Higaki T(2007) Time dependent changes in opsonin amount associated on nanoparticles alter their hepatic uptake characterstics Int J Pharm 342(1-2):215-221
[63] Fang C et al (2006) In vivo tumor targeting of tumor necrosis factor –[alpha]- loaded stealth nanoparticle: effect of mPEG molecular weight and particle size. Eur J Pharm Sci(1):27-36
[64] Alexix F,Pridgen E,Molnar LK, Farokhzad OC(2008) Factors affecting the clearance and biodistribution of polymeric nanoparticle. Mol Pharm 5(4):505-515
[65] Petros RA, DeSimone JM (2010) strategies in the design of nanoparticles for therapeuticApplication. Nat Rev Drug Discov 9(8):615-627
[66] Nagayama S, Ogawara K-I, Fukuoka Y, Higaki K, Kimura T (2007) Time-dependent Changes in opsonin amount associated on nanoparticles alter their hepatic uptake characteristics.Int J Pharm 342(1-2):215-221
[67] Fang C et al (2006) In vivo tumor targeting of tumor necrosis factor-[alpha]-loaded stealth nanoparticles:Effects of Mpeg molecular weight and particle size. Eur J Pharma sci 27(1):27-36
[68] Alexis F, Pridgn E, Molnar LK, Farokhzad OC (2008) Factors affecting the clearance andBiodistribution of polymeric nanoparticles.Mol Pharm 5(4):505-515
[69] Roser M, Fischer D, Kissel T (1998) Surface-modifi ed biodegradable albumin nano- and Microspheres. Effects of surface charge on in vitro phagocytosis and biodistribution in rate.Eur J Pharm Biopharm 46 (3):255-263
[70] Schwendener RA, Logocki PA, Rahman YE (1984) The effects of charge and size on theInteraction of unilamellar liposomes with macrophages. Biochim Biophys Acta (BBA) Biomembranes 772(1):93-101

[71] Salvador-Morales C, Zhang L, Langer R, Farokhzad OC (2009) Immunocompatibility propertiesOf lipid-polymer hybrid nanoparticles surface functional groups.Biomaterials 30(12):2231-2240

[72] Alexis F, Pridgen E, Molnar LK, Farokhzad OC(2008) Factors affecting the clearance and biodistribution of polymeric. Mol Pharm 5(4):505-515

[73] J. Panyam,V.Labhasetwar, Biodegradable namoparticles for drug and gene delivery to cell and tissue. Adv Drug Deliv Rev,2003,55,329-47.

[74] S.L. Flegler, J.W. Heckman Jr.and K.L. Klomparens, scanning and Ttansmission Electron Microscopy,W.H.Freeman and Company, New York(1993).

[75] J. J. Bozzola, and L.D. Russoll, Electron Microscopy, Jones and Bartlett Publishers Inc.,Boston (1992).

[76] Shanmugam S, Gabashvili A, Jacob DS, Gedanken A. Synthesis and characterization of Ti02@ C Core-Shell Composite Nanoparticles and Evaluation of Their Photocatalytic Activities. Chemistry of Materials.2006 May 2;18(9):2275-82