BIOABSORBABLE POLYMERS IN CANCER THERAPY

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Abstract:Cancer is devastating disease, being responsible for 30% of all deaths worldwide. One of the main challenges in treating cancer concerns the fact that anti-cancer drugs are not highly specific for the cancer cells and the death of healthy cells in the course of chemotherapy treatment is inevitable. In this sense, the use of drug delivery systems (DDS) can be seen as a powerful tool to minimize or overcome this important issue.Encapsulation of therapeutic drugs inside nanoparticles has become the new norm in the field of drug delivery. Nanoparticles increase the therapeutic efficacy of the drugs by providing high loading efficiencies, shielding when in circulation, ability to target tumours, enhanced accumulations, and triggered release inside the tumours. This review intends to give an overview about the latest developments in the use of bioabsorbable polymeric nanoparticle as DDS in cancer therapy, with special focus on nanoparticles, micelles and implants.

Indexterms: Cancer therapy, Drug delivery system, Bioabsorbable polymers, Nanoparticles, Micelles, Implants.

Introduction

Cancer in its myriad forms affects millions of people worldwide and growing at an alarming rate to become the world's deadliest disease of all times. The disease was the cause of 7.6 million deaths worldwide and 12.7 million new cancer cases are reported per year. Cancer is a state of rapid, abnormal, uncontrolled and unwanted multiplication, disorganized distribution and anomalous growth of same types of cells, without normal differentiation. Surgery, Radiation therapy, chemotherapy are the three major treatments for cancer therapy. But inevitably, the lack of selectivity will damage healthy tissues causing adverse effects includes nausea & vomiting, hair loss, fatigue, increased chance of bleeding or infection and anemia [1-3].

On this context, the polymer in drug delivery system offers a breakthrough in cancer therapy. In general, a DDS allows the delivery of an active compound in a controlled way and allows the maintenance of the drug concentration in the body [4].The targeted polymer drug delivery systems can be formulated in the formal particles (micro particles, nanoparticles, micelles, liposomes) to be administered through the common routes (eg. oral, pulmonary) or can be used in the form of implants, both injectable (eg. gels, micro particles) and surgical (eg. sheets/films, foams, scaffold)[5].

There are both natural and synthetic bioabsorbable polymers used in cancer therapy. Their important characteristic is that they can undergo transformation in the biological environment. The use of natural bioabsorbable polymers in biomedical field is widely reported because it offers a greater biocompatibility and biodegradability than synthetic polymer. The synthetic polymers can be prepared in different concentration and composition according to the application. In the field of DDS, these manmade polymers are important because they are metabolized in the biological environment [6-8].

1. Bioabsorbable Polymers in drug delivery system

Advances in polymer science have resulted in the synthesis and design of polymers with unique properties. Polymers now have sophisticated and advanced properties can be engaged for the development

of novel drug delivery vehicles. The major peculiarity of bioabsorbable polymer is that it can undergo transformation in biological environment. It contains the appropriate functional groups needed for coupling or can incorporate with specific drugs. The bioabsorbable polymers used as drug delivery vehicles in cancer therapy are biocompatible, non- immunogenic and biodegradable materials, remain stable in circulation but readily release their chemo drug cargo intra tumorally or intracellularly [9]. Because of the potential to meet the requirements of an ideal drug delivery vehicle, synthetic, natural and genetically engineered polymers place an inevitable role in field of drug delivery.

1.1 Bioabsorbable Synthetic Polymers

Synthetic polymers are human made polymers, usually fabricated with organic solvents such as polyethlene glycol or n(2-Hydroxypropyl methacrylamide). According to the specific applications, they can be modified during preparation by varying concentration and composition. The bioabsorbable materials are commonly used in cancer therapy are the aliphatic polyester poly (lactic acid) (PLA), the copolymer poly (lactic – co- glycolitic acid) (PLGA), and poly (ε – capro lactone) (PCL) etc. [10].

Poly lactic acid is in the class of poly (2–hydroxy esters). They are formed by the poly condensation of lactic acid (LA) or by the ring opening polymerization (ROP) of lactide. L-PLA is used as dental, orthopedic and drug delivery devices D-PLA is used mainly for drug delivery. Both are of interest in the area of tissue engineering. Practically useful high molecular weight PLA can be synthesized by cationic ring opening polymerization of lactide using antimony, zinc, lead or tin as catalyst. They have good bio compatibility, bio degradable mainly by simple hydrolysis, a wide range of degradation rates, physical, mechanical and other properties can be achieved by PLA of various molecular weights, and they have good processibility [11].

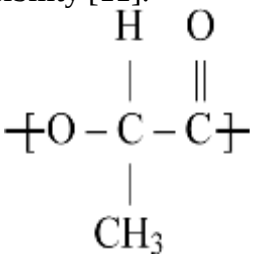

Fig.1.1a PLA-structure

As for drug release from microparticles or nanoparticles, it is generally controlled by both drug diffusion and polymer degradation. To ensure the efficacy of drug delivery, control over the particle size and particle size distribution is critical, since smaller particles and narrower size distributers facilitate the design of targeted drug delivery systems. These involve binding fragments specific to a tumor associated surface antigen with a ligand binding to its corresponding receptor on the tumor cell surface, which can be attached on the surface of the PLA based materials. Furthermore, polymers that display a physico-chemical response to changes in their environment are being intensively explained as potential drug and gene delivery systems [12].

PLGA is a FDA approved biodegradable and biocompatible copolymer of poly lactic acid (PLA) and poly glycolic acid.

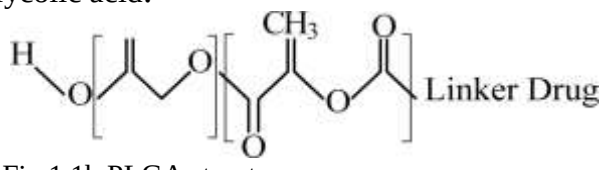

Fig.1.1b PLGA structure

This co-polymer has been conjugated to gemcitabine via amide bonding. Because of the biodegradability of PLGA, the conjugated gemcitabine released from the complex slowly and overtime. Stability and in vitro efficacy testing have shown that PLGA gemcitabine complex has advantages over free gemcitabine. PLGA can be processed into almost any shape and size, and can encapsulate molecules of virtually any size. It is soluble in wide range of common solvents including chlorinated solvents, tetra hydro

furan, acetone or ethyl acetate. The drug delivery specific vehicle, ie, PLGA, must be able to deliver its payload with appropriate duration, including material, geometry and location must incorporate mechanisms of degradation and clearance of the vehicle as well as active pharmaceutical ingredients (API). Biodistribution and pharmacokinetics of PLGA follows a non-linear and dose-dependent profile. Furthermore, previous studies suggest that both blood clearance and uptake by the mononuclear phagocyte system (MPs) may depend on dose and composition of PLGA carrier systems. Additionally whole – body autoradiography and quantitative distribution experiments indicate that some formulations of PLGA, such as nanoparticles, accumulate rapidly on liver, bone marrow, lymph nodes, spleen and peritoneal macrophages [13].

Another polymer used as drug delivery vehicle is the poly glutamic acid. Bae et al, developed a polymer nanogel which exhibits excellent bio compatibility and non-cytotoxicity made up of highly anionic polymer, poly (ν – glutamic acid) (ν – PGA) [13]. This can be naturally synthesized in microbial species, especially bacilli. For treating MCF 7 breast cancer, nanogel composed of thiolated ν -PGA conjugated with doxorubicin showed controlled drug release behavior. This suggests that thiolated ν -PGA nanogel may be a promosing along delivery vehicle in anticaner therapy. Furthermore, in the study of Yu et al, the PGA was added with another glutamic acid to each glutamic acid in the polymer backbone producing a poly (L-glutamyl-glutamine) (PGG) [14]. This modification offered an additional hydrophilicity on a PGG paclitaxel conjugate and also showed an improved paclitaxel loading efficiency in comparison to PGA paclitaxel conjugates.

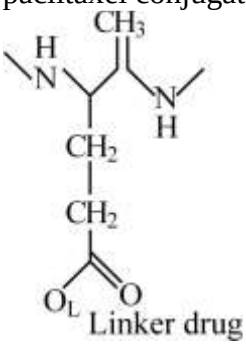

Fig.1.1c PGA-structure

Set et al,used poly (γ - glutamic acid) (γ - PGA) in a mouse melanoma tumor. It is used to deliver an immuno – stimulating agent, toll-like receptor – 7 (TLR – 7) agonist imiquimod and the chemotherapeutic agent paclitaxel. They are insoluble in water and are crystalline microstructures. They are dispersed into the PGA matrix and injected to the tumor site. This is an excellent example for the administration of insoluble chemotherapeutic agent and immuno-stimulating agent simultaneously into the body using a water soluble polymer [15].

PCL is a semi crystalline polymer with a low M.P range (59-64^{0}C), being suitable for the preparation of blends with other polymers or ceramic materials. PCL is synthesized by the ring opening polymerization of ε-caprolactone (ε-CL). This is mainly used in DDS that require long release profiles (eg. more than 1 year) because of its slow degradation. If the (ε-CL) is copolymerised with LA or GA, the product formed is degrades fastly. The products formed by the degradation of PCL are less acidic in nature in comparison with those products formed by PLA & PLGA [16].

Advanced studies in drug delivery shown that the synthetic polymer polyethylene glycol (PEG) and the natural polymer chitosan have been applied as conjugates in both invivo and invitro studies.

1.2 Bioabsorbable Natural Polymers

The easily available natural polymers has an advantage over synthetic polymers is that they are more biocompatible and biodegradable in comparison with synthetic polymers. The natural polymers have major three classes and they are polysaccharides, polypeptides and polynucleotides. Among them poly

saccharides and polypeptides are used in anti- cancer therapy. They are used as anti-tumor drug carriers,these polymers themselves possess antitumor characteristics. They are mostly used to deliver poorly soluble drugs to the tumor sites and it offeres less toxicity and less drug loss, by their targeted drug delivery [17].

Chitosan is a naturally occurring polymer used in drug delivery and it is composed of deacetylated β-(1-4) linked D glucosamine units and if acetylated N-acetyl-D-glucosamine units [18].Recently, Nogueria and colleagues produced chitosan-Methotrexate (MTX) conjugate which is an anticancer agent.The drug methotrexate is poorly soluble, and the drug in free- state adversely affects the body includes cell toxicity, inducing kidney failure, neurotoxicity and mucositis. Chitosan is biodegradable, bio compatible and they can effectively transport drugs across an epithelial surface. Relatively nontoxic chitosan oligomer derivative of 3-6 Da are widely used in drug delivery. Nam et al developed a grafted-chitosan polymeric micelles, carring two drugs. The chitosan derivative O-carboxy methyl chitosan (OCMch), is conjugated with α-tocopherol, forming α-toxopherol O-carboxy-methyl (TOC). Then it is conjugated with doxorubicin,which is an anticancer drug [19-21].

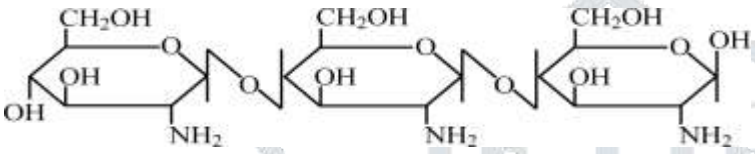

Fig.1.2aChitosan-structure

Dextran is a water-soluble polysaccharide composed by 1, 6 – linked D-glucopyranose units with branches extending mainly from the α-1, 3 – and occasionally from the α-1, 2 and α-1, 4 positions. Dextran is present in different molecular weights and molecular weight distributions. It is produced from sucrose through the action of dextran sucrose [22]. The degree of branching depending on the conditions and bacterial strain used in its production.It shows good biocompatibility non immunogenicity and non-antigenicity.Dextran based microspheres have been explored in vivo, in vitro and most recently, in clinical trials of breast, colon, hepatic and pancreatic tumors. They are mainly used to improve the solubility of insoluble anti-tumor drugs [23].Dextran based microspheres (MS) is used to carry mitomycin C (MMC) and doxorubicin; these are the promising, potent anticancer agents. This sequential application of two antitumor drugs resulted in a synergistically effective combination of cancer cell killing [30].

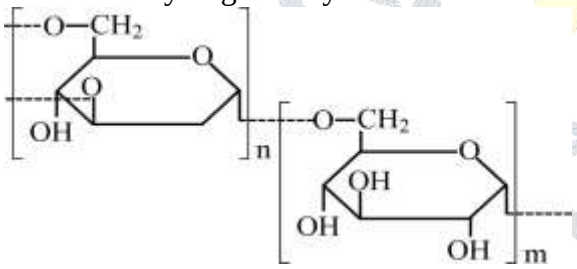

Fig.1.2b Dextran structure, composed of glucose molecules forming a complex branched glucan chain.

In the DDS albumin & gelatin place a major role. Albumin is present in human blood plasma and is abundant protein. The function of albumin are the following solubilization of long chain fatty acids, transport of metal ions (copper (II), nickel (II), calcium (II) and zinc (II)) in the blood stream. Clinical trials show that their immunogenicity, toxicity and biodegradability. Albumin is an ideal candidate for DDS. The tumor cells used the protein molecules for their nutrition. Thus, drug conjugated albumin can effectively induce apoptosis. An injectable formulation of PTX albumin nanoparticle known as Abruxane ® is widely used for the treatment of breast cancer [24].

Gelatin is also a protein formed by the denaturation of animal collagen, by the breakdown of triple helix of collagen giving rise to water soluble strains. Targeted drug delivery in anticancer therapy is the major biomedical application of gelatin [25, 26].

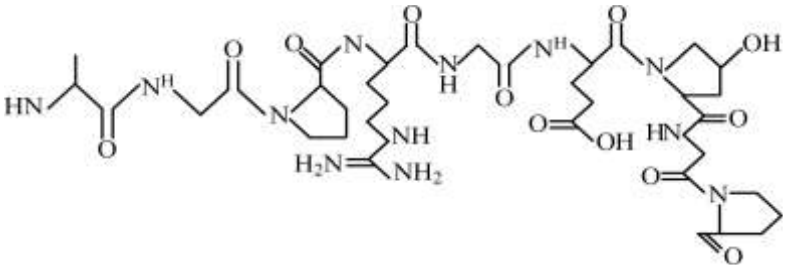

Fig.1.2cPullulan-structure

Pullulan is a natural polysaccharide composed of mallotriose units, structured as α-1-4; α-1-1-glucan and is biodegradable,nontoxic,non- mutagenic, and non- carcinogenic. Its low immunogenicity and satisfactory solubility in aqueous and several organic solvents have together led to a range of applications in cancer drug delivery [27].

Experimental studies held by Scomparin et al. used the pullulan derivatives with doxorubicin and doxorubicin and folic acid. The pullulan was activated by some chemical modifications as periodate oxidation and reductive conjugation with cysteaamide to get proper functionality. Their active targeting of tumor cells for anti- cancer drug delivery offered a new approach for in-vivo studies of conjugated pullulan [28].

The studies done by Ganeshkumar et al. reported that pullulan stabilized gold nanoparticles can be used in delivering the anticancer drug 5 – fluorouracil (5Fu) and folic acid. This drug was introduced in clinics in 1957 and is poorly soluble and a potent drug against cancer. Ganesh kumar and colleagues designed the pullulan conjugate in 2014 to increase the solubility, stability and specificity as well as to minimize the side effects of this potent drug. Thus 5-Fu @ PAuNPs-Fa bio conjugates opened a wide range of applications in cancer therapy including the active liver cancer targeting [29].

Zhan et al. constructed mutilated pullulan doxorubicin conjugated with a folate polymeric prodrug for active tumor-targeted delivery. FA-MP-DOX can be used in the treatment of ovarian cancer [30].

2. Nano Carrier

There are so many polymeric nano materials that can carry drugs to the target that are called nano carriers. This class includes miscelles, nano capsules, nanospheres, nanoshells, nano cages. They are classified according to the diameter and properties. These nanocarries are explored for a variety of applications, such as drug delivery, imaging, photo thermal ablation of tumors, radiation sensitizes detection of apoptosis, and sentinel lymph node mapping.

Polymers are most commonly explored materials for constructing nanoparticle-based drug carriers. One of the earliest reports of their use for cancer therapy dates to 1979 when adsorption of anti- cancer drugs to polyalkyl cyanoacrylate nanoparticles was described [31].Couvreur et al. revealed the release mechanism of the drugs from the polymer in calf serum, followed by tissue distribution and efficiency studies in a tumor model. This work laid the foundation and efficiency studies in a tumor model [32]. These nanoparticles were tested in clinical trials in the mid-1980s. Polymeric nanoparticles can be made from synthetic polymers, including poly (lactic acid) (PLA) and poly (lactic co-glycolic acid) or from natural polymers such as chitosan and collagen and may be used to encapsulate drugs without chemical modification [33-35]. The drugs can be released in a controlled manner through surface or bulk erosion, diffusion through the polymer matrix, swelling followed by diffusion, or in response to the local environment. Several multifunctional polymeric nanoparticles are now in various stages of pre-clinical and clinical development [36-38]. Cancers arising from the use of polymer based nanocarries include the inherent structural heterogeneity of polymers reflected, for example, in a high polydispersity index (the ratio of the weight-and-number-average molecular weight (Mw/Mn). There are however, a few examples of polymeric nanoparticles that show near homogenous size distribution [39].

In addition to the polymeric nanocarriers drug-eluting polymer implants also present a compelling parental route of administration for cancer chemotherapy. With potential for minimally invasive, image-guided placement and highly localized drug release, these delivery systems are playing an increasingly

important role in cancer management. This is particularly true as the use of labile proteins and other bioactive molecules is likely to increase in the upcoming years.

2.1 Nanoparticles

Over the past decades, the enhanced experimental studies in the field of polymer science and nanotechnology offered a breakthrough in the field of drug delivery systems. The combined studies of polymer science and nanotechnology have allowed synthesis and conjugation of functionalities which can respond to stimuli. This is an important advance in the field of cancer treatment because it allows not only a passive targeting strategy but also an active targeting strategy by using carrier monoclonal antibody conjugates and carrier-ligand conjugates which can be activated at desired moment or site [40].

Due to the fast cell differentiation, the tumor grows fast but the angiogenesis is slower and consequently non-matured or formative vasculature is characteristic of tumoral tissues. This is why the nanoparticles can easily enter into the leaky vasculatures of tumor cells and the healthy tissue prevents the penetration. Nanoparticles have advantage over conventional drug delivery system. Nanoparticles can pass through small blood capillaries and more drug availability at target site. The use of nanoparticles is beneficial because that can lead to a decrease in the amount of cytostatics and therefore decreases systemic toxicity. In the preparation of polymeric nanoparticles different methods are used, such as reverse salting nanoprecipitation, emulsification, solvent evaporation and diffusion method. Several factors are important in choosing an appropriate polymer for the preparation of polymeric nanoparticles, such as biocompatibility, safety and immunogenicity. The polymer must also be suitable for manufacturing techniques that generate nanoparticles, and ideal polymeric nanoparticles have adjustable morphological and bio degradable properties. Recent development in the anti-cancer drugs is as discussed in detail.

Paclitaxel loaded PLGA nanoparticle have markedly increased anticancer effect. Paclitaxel loaded PLGA nano particles are used in different cancers such as lung cancer, C6 glioma, HeLa cells and Retiobastoma cells. Vitamin E-TPGS emulsified PLGA nanoparticles shows improved bioavailability of pactitaxel in vitro and in vivo studies. An important application is that it can serve as a better therapy for brain cancer, while the conventional formulation of paclitaxel cannot cross blood brain barrier [41].

To delay tumor growth and survival of M729 tumor bearing mice, cisplatin loaded PLGA nanoparticles are used and the studies and experiment results shown that they can be used as an effective tool in cancer therapy. Cisplatin loaded nanoparticles can effectively use against prostate cancer, osteosarcoma and ovarian cancer [42].

Doxorubicin loaded PLGA nanoparticles are effectively used against lung cancer, breast cancer and uterine cancer. These nanoparticles shows synergistic effect when it is loaded with doxorubicin and paclitaxel. Curcumin and vicristine embedded PLGA nanoparticles are also used and shows they are ideal nanoparticles for the drug delivery, in comparison with conventional method. Xanthose loaded PLGA nanoparticles shows good physical stability at 4^0c for 3-4 months (Teixeiva et al.).PLGA conjugated with Rose bengal improved the half-life of that drug in the blood stream compared to free drug solution. According to the interaction of the drug Triptorelin and PLGA nanoparticle, its encapsulation efficiency varied from 4% to 83%. When the PLGA conjugated with Dexamethasone could complete drug release after 4^{th} incubation at $37.^0$ Highest drug loading was obtained using 10mg of dexamethasone and 100mg PLGA (75:25) in a mixture of acetone dichloromethane (1:1). All these experimental results establish the fact that PLGA nanoparticle is an ideal anticancer drug vehicle for the effective targeted drug delivery [43-45].

Rapid drug release from gelatin nanoparticles were observed when it is conjugated with paclitaxel. Concentration of doxorubicin in the brain, after systemic administration increased about 60 fold by incorporating doxorubicin into poly (butyl cyanoacrylate) (PBC) loaded with polysorbate 80 [46].

Alginate-Chitosan nanoparticles can be used in DDS, because of their biocompatibility, non-toxicity, gelation, biodegradability and membrane permeability. Alginate-Chitosan nanoparticles protect the drug from enzymatic degradation, deliver the drug to targeted organ and permit controlled release of the drug. Chitosan conjugated with Doxorubicin with dextran enhances the permeability and the retention effect of doxorubicin. Gaclopentetic acid was successfully incorporated into chitosan nanoparticles by a novel emulsion droplet colescence method. Chitosan nanoparticles had high affinity to tumor cells, resulting in greater accumulation in the cells. Carboplatin incorporated with alginate and chitosan showed high drug loading, fast release of the drug during the first 24 hour, followed by sustained release.

2.1.1. Preparative technique for polymeric nanoparticles (PNP)

a) Emulsification solvent evaporation method

This method is frequently used for nanoparticles preparation. In first step, drug and polymer needs to dissolve is a water-immiscible volatile solvent, such as chloroform, thereafter it is emulsified in stabilizer containing aqueous solution. Emulsification is carried-out in a high-energy shearing source such as ultrasonic device or homogenizer. The volatile organic phase is evaporated in vaccum or reduced pressure, which results into the formation of fine nano-particles. The nano-particles are collected by high speed ultracentrifuge and washed with distilled water and lyophilized for the better storage. This method is useful for lipophilic drugs. However, for hydrophilic drugs, double emulsion technique is used. In this method, aqueous drug is mixed with organic polymer with vigorous stirring [47].

b) Dialysis

Dialysis offers a simple and effective method for the preparation of small, narrow-distributed polymer nanoparticle. Polymer is dissolved in an organic solvent and placed inside a dialysis tube with proper molecular weight cut off. Dialysis is performed against a non –solvent, miscible with former miscible. The displacement of the solvent inside the membrane is followed by progressive aggregation of polymer due to a loss of solubility and formation of homogeneous suspensions of nanoparticles. The mechanism of polymer nanoparticle formation by dialysis method is not fully understood at present. It is thought that it may be based on a mechanism similar to that of nano precipitation proposed by Fessi et al. A number of polymer and copolymer nanoparticles were obtained by this technique. Poly (benzyl-l-glutamate)-b-poly (ethlene oxide), poly (lactide)-b-poly (ethylene oxide) nanoparticles were prepared using DMF as the solvent. The solvent used in the preparation of the polymer solution affects the morphology and particle size distribution of the nanoparticles. Chronopoulou et al. reported a novel osmosis based method, for the preparation of various natural and synthetic PNP. It is based on the use of a physical barrier, specially dialysis – membrane or common semi permeable membranes that allow the passive transport of solvents to slow down the mixing of the polymer solution with a non- solvent; the dialysis membrane contains the solution of the polymer[48].

c) Nanoprecipitation

Nanoprecipitation is also called solvent displacement method. It involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium, in the presence or absence of a surfactant. The polymer generally PLA, is dissolved in a water-miscible solvent of intermediate polarity, leading to the precipitation of nanospheres. This phase is injected into a stirred aqueous solution, containing a stabilizer as a surfactant. Polymer deposition on the interface between the water and the organic solvent, caused by fast diffusion of the solvent, leads to the instantaneous formation of a colloidal suspension. To facilitate the formation of colloidal polymer particles during the first step of the procedure, phase separation is performed with a totally miscible solvent that is also a non-solvent of the polymer. The solvent displacement technique allows the preparation of nano capsules, when a small volume of nano- toxic oil is incorporated in the organic phase. Considering the oil-based central cavities of the nano-particles, high loading efficiencies are generally reported for lipophilic drugs, when nano capsules are prepared [49].

d) Emulsification reverse salting-out method

This emulsification technique is carried out by addition of polymer and drug into water miscible solvent, such as acetone. Thereafter, above preparation has been vigorous mixed with aqueous solution containing salting-out agents, such as calcium chloride, magnesium chloride and colloidal stabilizer, like polyvinyl pyrolidine. This oil in water emulsion is diluted in pure water, which causes diffusion of acetone in the aqueous phase and subsequently formation of nanoparticles. At the same time, dilution leads to sudden decrease in the salt concentration from continuous phase of emulsion and pushes the polymer solvent out of emulsion droplets. The excess of the solvent and salting out agents are removed by cross flow filtration [49].

e) Emulsification solvent diffusion method

In this method, partially water soluble solvent is used for emulsification. Polymer is added with vigorous stirring in the stabilizer containing aqueous solution. Which is resulted into formation of oil-in-water emulsion, it is then diluted by using pure water. This dilution is resulted into dispersion of droplets by diffusion from the droplets and precipitation of polymers [50].

2.2 Micelles

Micelles are nano sized self-assembling co-polymers comprising of a hydrophilic and hydrophobic part and is known as amphiphilic in nature. These can carry water soluble as well as water insoluble drugs [51]. These are formed, when the concentration of amphiphilic co-polymer attains the critical micelle concentration (CMC). By the dehydration of the hydrophobic part of the co-polymer, micelles are formed spontaneously. Their properties include size in nano-range, stability in plasma, longevity in vivo and pathological characteristics of tumor allow, PMs to be targeted to the tumor site by a passive mechanism called the enhanced permeability and retention effect. Other characteristic of PMs like separate functionality at the outer shell is useful for targeting the anticancer drug to tumor by active mechanisms [52].

Most poly vivo block copolymer products are inherently amphiphilic as they contain both hydrophobic polyester blocks (PLA, PLGA or PCL) and hydrophilic poly (ethylene glycol) block (PEG) [53, 54].

When the drug is administered orally, it must survive transit through the gastrointestinal tract. The absorption of drug is mainly in small intestine due to the presence of salivary amylase and gastric protease (pepsin). Many pathways are there, for the absorption of nutrients. The orally administered drugs are absorbed through the cell (trans- cellular pathway) or between adjacent cell (para- cellular pathway). Two major pathways exist by which the encapsulated drug is released from the micellar core block. These pathways are micellar dissociation followed by drug cleavage from the unimer and drug cleavage within the micelle followed by diffusion out of the delivery system.

Micelles are stimuli-responsive and they carry a targeting ligand at the surface. Thus, they can able to target a specific tumor. For encapsulating Doxorubicin Kim et al. used micelles composed of poly (ethylene oxide)-b-poly (3-hydroxy butyrate)–b-poly (ethylene oxide) (PEO-PHB-PEO) tri-block polymer. PHB at the center is having high hydrophobicity and this makes the micelle more stable with the encapsulated drug. This can effectively act as a drug carrier in tumor sites and used in the treatment of human cervical cancer [55-57].

Star shaped PCL extended with a terminal block of poly (ethylene phosphate) (PEEP) yield PCL-PEEP star-shaped co-polymer. They forms micelles in aqueous solutions and used to encapsulate Dox. Micelle loaded the drug and interesting fact is that, the drug resistant cells also uptake the drug, if it is embedded in micelle.

Micelles with similar PEG-PLA copolymer compositions have demonstrated that significant increase in in-vivo half-lives of drugs (eg. paclitaxel) to 11 hour in cancer patients. Using PEG-b-poly (acryloyl carbonate)-b-poly caprolactone (PEG-b-PAC-b-RCL) triblock copolymer, Yang et al. recently prepared interface cross linked micelles. During, the experiment, resulted that they can effectively transfer paclitaxel in mice. Bicalutamide loaded crosslinked micelles made up of core crosslinkable copolymer methoxy poly (ethylene glycol)-b-poly(carbonate-co-lactide-co-5-methyl-5-allyloxy carbonyl-1, 3-dioxane-2-one) and core corona interfaces linkable copolymer methoxy poly (ethylene glycol)-b poly (acryloyl carbonate-co-lactide) are used to treat prostate cancer [58].

An example of a polymeric micelle under clinical evaluation is NK 911, which is a block copolymer of PEG and poly (aspartic acid). NK 911, which consists of a bound doxorubicin fraction (~45%) and a free drug, was evaluated for metastatic pancreatic cancer treatment. Another carrier is NK 105, a micelle containing paclitaxel, was evaluated for pancreatic, colonic and gastric tumor treatment [59, 60].

3. Polymeric implants for cancer therapy

Polymer implants have a major role in localized drug delivery. The drug loaded polymer implant can deliver drugs to the tumor sites over longer periods of time. Treatments that have been studied extensively

include intra tumoral- infusions, injections, and implantable devices that deliver chemotherapeutic drugs or other therapeutic agents [61, 62]. Infusion of chemotherapeutic drug has been extensively studied in the area of brain tumors. The field is known as convention – enhanced delivery (CED). In this method, a micro catheter is inserted into a tumor and the therapeutic agent is slowly administered to the surrounding tissue using positive pressure infusion. Major advantages of CED to brain tumors including bypassing the blood-brain barrier and delivering drugs further from the infusion site due to convection. They are important tool for the delivery of bacterial toxins and therapeutic antibodies.

Intra tumoral injections of therapeutic solutions are used in the treatment of lung, pancreas and liver. Intra tumoraly injected drugs may distribute irregularly and be cleared quickly. Several investigators have introduced injectable drug depots to prolong the extent of drug release. Examples include PLGA, alginate and albumin micro spheres as well as injectable gels which solidify upon intratumoral injection. These have the advantage of easy administration and prolonged tumor drug exposure [63,64].

There are three categories for polymer implants for drug delivery. They are intra tumoral implants (placed directly into the tumor), adjuvant implants (implant is placed in the tumor after another treatment) and pallative implants that are implanted intramuscularly used to avoid the repeated injections [65]. Implantable devices containing either radioactive elements or chemotherapeutic drugs are used in the treatment of prostate and brain cancers. The only clinically approved chemotherapeutic implant for cancer treatment is the Gladiel wafer, carmustine (BCNU) eluting implant fabricated from a polyanhydride copolymer, 1, 3-bis-(p-carboxy phenoxy), propane/poly (sebacic acid) (pCPP:SA). These implants are useful for the treatment of glioblastoma multi forme, an aggressive brain cancer. After placement, the implants release their drug load, over a period of approximately 5 day and the drug has been shown to penetrate several millimeters into the brain parenchyma. A recent long-term study showed that, the Gladiel implant placement after surgery increased patient survival to 13.8 months versus 11.6 months from control and maintained this survival advantage for at least 3 years after initial treatment. To evaluate further effectiveness of Gladiel in the initial therapy of malignant gliomas, Valtonex et al conducted a clinical trial in Europe. The evaluation of several years, he established that polymer technology is a safe, effective treatment for patients presenting with malignant gliomas [66].

A hydrophilic derivative of cyclo phosphamide (cytexan), 4-hydroperoxy-cyclophosphamide (4-MC), spontaneously converts to the active metabolite of cyclophosphamide, 4-hydroxy-cyclophosphamide and does not effectively cross the blood-brain barrier. This makes it in apt candidate for cancer therapy. Preclinical studies show that 4-MC incorporated into an FAD-SA poly anhydride polymer matrix significantly prolongs survival in rates challenged with intracranial F98 gliomas. When compared to control rates receiving empty polymers, the median survival was extended from 14 days to 77 days.

The bio degradable polymer millirods have been fabricated from poly (D, L–lactide–co-glycolide) (PLGA) to deliver chemotherapeutic agent and thus, maximizing tumor destruction and reducing the risk of tumor recurrence. Millirods can be prepared by two different techniques, i) hot melt extrusion (NME) and injection Molding (IM), and loaded with disulfiram (DSF). Once, the rod reaches the pancreas it unfolds and conforms to the shape of the tumor; with medication secreted only from the side of the film in contact with the growth [67-69].

When cancer spreads to the bones, the spine is the most common skeletal location for it to appear. While removing the spinal tumors, have to remove significant amounts of bone and even entire intervertebral discs, leaving significant gap. To fill the gaps injectable implants are used, when it enter into the body it can expand and fill the gaps which is more strong and flexible.

Conclusion and Future outlook

Cancer therapy has seen extraordinary growth in the past two decades due to the advent of variety of strategies to design and functionalize nanocarriers, and a huge selection of therapeutics including drugs, nucleic acids, antibodies etc. The importance of bioabsorbable polymers in the field of cancer therapy is undeniable, taking into account the high number of publications related to the use of these materials as DDS for anti-cancer drugs. Moreover, there are already in the market formulations for chemotherapy treatments making use of bioabsorbable polymers, and many others are currently under clinical trials.Compared to free drugs, nanocarrier-encapsulated drugs preferentially accumulate in the tumour sites through the enhanced

permeability and retension effects, thereby improving therapeutic outcomes and reducing side-effects. Targeting of nanocarrier can further improve the efficiency and specificity of drug delivery.

When targeting cell surface markers presents a significant challenge, as in the case for solid tumours, targeting tumour vasculature or the extracellular matrix surrounding the tumour microenvironment may be necessary. In the case of circulating cancer cells, as in leukemia and lymphoma, a therapy that targets surface antigens with high affinity and includes a carrier with a long circulating half-life may be the most efficacious. Similar to combination drug strategies that may be personalized to optimize treatment regimens, oncologists in the near future may be presented with the ability to choose specific nanocarrier/targeting molecule combinations which could lead to improved therapeutic outcomes and reduced costs. Although the current investigations on targeted, multifunctional and stimuli responsive polymeric nanoparticles are encouraging, there is a pressing need for careful evaluation in terms of physicochemical properties in vivo, pharmacokinetics, bio-distribution, and biodegradability. These challenges can be successfully addressed with increased cooperation between polymer scientists, pharmaceutical, chemical and biomedical engineers, and medical scientists.

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