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HERBONANOCEUTICALS AS A POTENTIAL STRATEGY IN DELIVERY OF ANTICANCEROUS COMPOUNDS

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ABSTRACT

Herbonanoceuticals are materials fabricated using herbs at nanoscale with the aim of changing physiological function of the body. Green nanotechnology is a novel concept brought about to synthesize nanoparticles from biologically active phytocompounds, utilizing full potential of natural resources in curing and treating diseases. These engineered products can enhance the delivery to the site of action, which overcomes the inefficient delivery of drugs due to difficulty in tumor penetration. The different nanoplatforms that are used to deliver these phytopharmaceuticals to the site include metallic nanocarriers, polymeric nanocarriers, ceramic nanocarriers, liposomes, etc. and can be achieved by means of either active or passive targeting. Nanotechnology opens the gate to wide applications in the field of research. Proper design of nanocarriers could enhance the tumor penetration, thereby the efficiency and effectiveness of the drug delivery system. Barriers that restrict the entry of tumor microenvironment should be considered while designing a nanocarrier, which generates the necessity of research in the influence of factors such as size, surface charge, biodegradability, etc. in enhanced tumor penetration.

KEYWORDS: Herbonanoceuticals, Green nanotechnology, anticancer therapy, EPR effect, biocompatibility.

INTRODUCTION

The application of nanotechnology in therapeutic field is evolving persistently. Its ability to fabricate minute particles ranging from 1 nm to 100 nm, marks a history in the cure and

prevention of numerous diseases especially cancer. In effect, it helps in the delivery of drugs into the tumors, which is considered to be the most important aspect of cancer therapy.[1] Doxil, manufactured by Orthobiotech[2] and Abraxane by Celgene corporation, USA are the two most popular nanomedicines in use.[3]

Current anticancer therapies have numerous drawbacks such as lack of tissue selectivity, dose-limiting toxicity, non-specific delivery of chemotherapeutic agents that potentially lead to the damage of the tissues treated and at the same time, it potentially harms healthy cells. Insufficient delivery of drugs leads to tumor relapse. With this regard, it has been found that nanomedicine-based therapeutics are the best approach to overcome these limitations of conventional methods.

Herbonanoceuticals, defined as engineered materials, fabricated at nanoscale using herbs for their synthesis designed for the physiological function of the body[4], are those prepared from plant extracts and phytoconstituents.[5] Plant-derived anticancerous compounds include anthracyclines[6], vinca alkaloids, podophyllotoxin, camptothecin, taxanes, berberine, etc.[7] Nanomaterials refer to products that involve the application of nanotechnology or nanotechnology products in nanoscale range and those that exhibit related dimension dependent properties or phenomena. By definition, provided by the National Nanotechnology Initiative, it is given as the development of research and technology at atomic, molecular or macromolecular levels within the scale of nanosize of approximately 1-100 nm in size. Such engineered products can deliver the drugs to specific sites by recognizing cancer-specific receptors. The main challenge that is observed with the drug delivery through nanoparticles is the inefficient delivery due to the difficulty in tumor penetration. However, numerous strategies have raised to overcome this obstacle.

'Green nanoparticle' brings the concept of synthesizing nanoparticles from biologically active phytocompounds[4], as the natural compounds are promising leads in the development of anticancer agents.[8] Nanomedicines are generally formulated to exhibit desired functions like prolonged release of the drug, protection of drug from enzymatic degradation and other instability issues, delivery of drug to cytoplasm, passive accumulation into tumor site, detainment of drug at the site for a desired period of time, protection from enzymatic degradation[9] etc. The various nanoplatforms used to deliver the drug are liposomes, polymeric nanoparticles, dendrimers, nanoconjugates, phage system, etc. Targeting can be achieved either through passive targeting or active targeting. So far the former method has

acquired more relevance compared to later, because active targeting systems are hard to accumulate in the specific sites due to its larger size attributed by the size of conjugated targeting ligands of formulation such as monoclonal antibodies. Also, such a system is easily eliminated due to non-specific protein adsorption or surface opsonization, resulting in the poor efficiency of these systems. Modifications of size, shape, physicochemical properties and development technique of the carrier system have a significant role in cancer biology on targeting tumor cells either by passive or active targeting.[10]

Telodendrimer, which is a linear dendritic copolymer, is a newly designed nanoplatform with improved *In-vivo* drug delivery characteristics. This has been formulated by choosing optimal building blocks through the virtual screening of a library of small molecules and optimizing the drug binding affinity of the carrier by inserting an optimal drug binding molecule.

Drug specific designing of a formulation is important in effective anticancer therapy. Molecular docking or simulation techniques can be used to screen building blocks for the design of a specific nanocarrier to target a particular site of action nowadays.[11]

TARGETING MECHANISMS OF NANOPARTICLES

Passive targeting

It is the extensively employed mechanism in clinical use[3], by which the nanocarriers are transported through leaky tumor capillary fenestrations into tumor interstitium and cells by passive diffusion. This improves the circulation time and thereby selective accumulation of drug by enhanced permeation and retention (EPR) effect, thereby the drug retention period in tumors is found to be more than days to weeks.[12] EPR effect is more attributed to the tumor vasculature abnormalities such as the irregular architecture, poor lymphatic drainage and upregulation of factors that increase paracellular permeability. The cut off size for extravasation from tumor vasculature varies from 200nm to 1.2 μm.[13] EPR effect is mediated by the presence of bradykinin, nitric oxide, collagenase, etc.[5]

The characteristics that should be considered for the effective passive targeting of the nanocarrier include the size of the carrier which should be between 10 and100 nm, and at the same time, they should bypass the reticulo-endothelial system that attributes to destroy any foreign material through opsonization.

This mechanism is mostly attributed to the degree of tumor vascularization and angiogenesis, which limits the accumulation of drug at site. Also the high interstitial fluid pressure of solid tumors inhibits the successful uptake and uniform distribution of drugs.[14] Passively targeting nanomedicines in clinical use include Doxil, a pegylated liposomal Doxorubicin and Daunoxome, a non-pegylated liposomal Daunorubicin.[3] Most passive targeted nanocarriers are stealth systems, those nanocarriers coated with polyethylene glycol, that have the ability to escape capture by mononuclear phagocyte system.[2]

Active targeting

Here we use targeting ligands such as antibodies and peptides[3], which can be attached to drugs or drug delivery systems for binding to receptors expressed at target sites or by targeting biomarkers specific to a tumor[2], which improves the selectivity to tumor cells.[15] Ligand is chosen to bind to a particular receptor overexpressed by tumor cells and not expressed by normal cells.[14] These targeting ligands could improve cellular internalization through endocytosis prone surface receptors such as folate, galactosamine, transferrin, etc.[3] In this strategy, two cellular targets being recognized are targeting of cancer cells and tumor endothelium.

Transferrin conjugated nanoparticles can deliver chemotherapeutic agents with an improved cellular uptake and enhanced cytotoxicity. Hyaluronic acid, a linear glycosaminoglycan can bind specifically to CD44 receptor which is overexpressed on various cancer cells.[15] Hyaluronic acid-grafted PLGA copolymer nanoparticle exhibits higher cellular uptake as compared with that of non-targeted nanoparticles.[16] Antibodies that have been used as targeting ligands are anti-CD47, anti-CD20 monoclonal antibodies, EGFR monoclonal antibody, etc. EGFR antibody-conjugated PLGA nanoparticles have shown enhanced apoptotic effect in cancer cells.[15]

Wide discoveries are occurring in the field of developing active targeted systems, however these are physicochemically unstable and hard to accumulate in targeted tissues.[3]

NANOCARRIERS FOR HERBAL DRUG DELIVERY

Metallic nanocarriers

Passive or active targeting agents of size ranging between 15 and 60 nm are made of superparamagnetic agents.[17] Metal nanocarriers used in cancer therapy includes those fabricated out of Iron, Gold, Titanium dioxide, Zinc Oxide, Cerium Oxide, Silicon, Copper,

Silver etc. Aceituno V et al. investigated the cytotoxic and oxidative effects of *Panax ginseng* silver nanoparticles, and are found to induce cell apoptosis. Silver nanoparticles can induce toxicity by bringing about ROS (reactive oxygen species) production[4] the interaction with and disruption of the mitochondrial function that suppress ATP synthesis subsequently lead to DNA damage. Also it exhibits an improved anticancer activity in the acidic tumor environment, as there is an increased release of silver ions at acidic pH. Scientific community focused on the green synthesis of metal nanoparticles due to its high efficacy and bio-friendly nature.[18]

Polymeric nanocarriers

These are colloidal system with a particle size ranges between 10 and 1000 nm. Improved absorption, biodegradability and bioavailability are the main features of these particles.[17] Behaviour of these carriers are determined by the morphology and composition of both core and periphery. Dendritic polymer, polyamidoamine (PAMAM) dendrimers having monodispersity and modified surface groups recognized as a suitable carrier for berberine, has potential anticancer effects on MCF-7 and MDA-MD-468 breast cancer cells. Chitosan nanoparticles can incorporate negatively charged RNA and DNA through electrostatic interactions and are used to treat solid tumors.[7] Curcumin-PLGA nanoparticles show a ten-fold increase in water solubility and three-fold increase in anticancer activity of human breast cancer compared to free Curcumin.[6]

Ceramic nanocarriers

Limitation with this nanocarrier is that they are non-biodegradable, and as a result, they accumulate and produce adverse events.[17] These are usually made up of inorganic porous biocompatible materials, such as silica, titanium and alumina[19], and are of size range less than 100 nm.[18] Mesoporous silica nanoparticles exhibit more biocompatibility as compared to other silica amorphous materials, and have the ability to functionalize the exterior surface of nanoparticle.[20]

Liposomes

These are bilayered nanovesicles, resembles biomembrane and enhance the safety and efficacy of drugs[17]. Ochi MM et al. (2016) studied the *In vitro* co-delivery of silibinin and glycyrrhizic acid in pegylated nanoliposomal formulation. These nano-phyto-liposomes are found to be a significant revolution that improves the bioavailability, solubility and synergize the therapeutic effect of flavonoids.[21] Liposomal formulations have diverse applications like

it can enhance the stability, therapeutic efficacy and modify the surface area and integrity.[22] These are usually prepared by reverse evaporation technique, film-ultrasound method, thin film hydration method, ethanol injection method, etc.[23]

CHALLENGES FOR DRUG DELIVERY TO SOLID TUMOR

Nanoparticles after uptaken by tumor cells, get adsorbed by serum proteins called opsonins and result in the clearance of the carriers by reticuloendothelial system, gradually reduce the circulation time and thereby tumor accumulation. Targeting efficiency of the nanocarrier is affected by immunogenicity, release kinetics of the encapsulated drug, route of administration, coating formed by opsonins, etc.[23]

Substantial rise in interstitial fluid pressure causes obstruction in the transport of nanocarriers from circulation system by means of EPR effect, which prevents its penetration to the tumor vasculature.

Extracellular matrix of tumor microenvironment that provides structural support to the tissue is made up of polysaccharides, collagen, elastin, proteoglycan and fibrous proteins.[24] High level collagen results in enhanced stiffness of ECM, which imparts decreased nanoparticle interstitial diffusion rate.[1]

The major concerns with herbal drugs are low aqueous solubility, instability and poor oral bioavailability. Modifications of these drugs can cure much of these inherent problems. These are susceptible to extensive metabolism in the intestinal environment. Nano-sized carriers can deliver the drugs at the site of action and exhibit potent anticancer efficacy.[25]

FACTORS TO BE CONSIDERED IN THE DESIGN OF NANOCARRIERS

Size

Particle size reduction decreases the diffusional hindrance and improves its penetration into the interstitial matrix.[26] Body distribution and elimination are affected by the particle size[27]. Targeting efficiency of size variant nanoparticles are determined in terms of tumor-to-background ratio (TBR), which is a measure of specificity of radiopharmaceutical uptake within the target organ.[4] Diameter near 100 nm exhibits enhanced systemic circulation and tumor accumulation, but smaller particles of size less than 250 nm diffuse for a long time within the tumor.[26] Nanoparticles offer large surface area, which makes it feasible for the attachment with cell and provides the shortest path for drug diffusion into target cell.[28]

Sukmawati et al. (2018) conducted a study on effect of tween 80 on nanoparticle preparation of modified chitosan for targeted delivery of combination doxorubicin and curcumin analogue, and arrived at the conclusion that size of nanoparticle can be reduced by addition of higher concentration of tween 80. It has been shown that incorporation of 0.5% v/v surfactant forms much smaller size particles as compared to that of formed with 0.1% v/v. Tween 80 which acts as a stabilizing agent at the formation step, later reduces the particle size by preventing the crystal growth.[28] The properties of nanoparticles are greatly affected by the manufacturing method adopted for the formulation. Particles of desired size can be produced by controlling the process parameters.[29]

Size switching nanocarriers, triggered by enzymes, tumor pH, light, etc. are under development. These are designed to have large sizes during circulation and switch to small particles once accumulated for better penetration and tumor distribution.[24]

Surface charge

Solubility, cytotoxicity and biodistribution can be affected by the surface charge property of the carrier system.[30] It is indicated by the zeta potential of particles which reflects its electrical potential[9], and this inturn influences pharmacokinetics and intratumoral transport of nanoparticles.[36] Charge of the particles must be anionic or neutral for efficient evasion of renal elimination.[31] Neutral particles are preferential in terms of circulation time. The difference in uptake preference by phagocytic cells for both charged nanoparticles may influence its selectivity and efficacy to exert its action.

Xiao et. al.(2011) in their in vivo bio distribution studies showed that tumor uptake is high with nanoparticles having negative surface charge.[32] The current trend is on developing charge switchable nanoparticles which can alter surface charge with respect to their environment of action, thus created a positive impact on efficacy.[33]

Biodegradability

Biodegradability affects drug delivery efficacy and toxicity of nanocarriers. This character is imparted from the polymers by which it is fabricated. They could improve pharmacokinetics and pharmacodynamics profiles of the drug, also the internalization and intracellular drug delivery. Synthetic biodegradable polymers in use are poly(lactones), poly(amino acids), poly(phosphazines), polycarbonates, etc. Natural biodegradable polymers used in formulation include cellulose, starch, alginic acid, chitosan, collagen, gelatin[25], Pullulan[9], etc. Such

nanoparticles which are fabricated out of biodegradable polymers can act as a local drug depot and help in continuous delivery of encapsulated therapeutic compounds at tumors.[30]

CONCLUSION

Green nanotechnology furnishes novel strategies for anticancer therapy. Proper design of nanoparticles results in effective delivery systems with efficient drug loading capacity and sustained release of the drug. Formulating into nanoparticles overcomes difficulties of conventional chemotherapy. Phytofabrication of nanomedicine forge ahead from conventional medicine to personalized medicine.

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