Nanocarrier: New Viewpoint of Cancer Therapy

M. Naeemipour, S. Malah Livani and GH.R. Hashemitabar.
School of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran.
mohsen_dvm80@yahoo.com, s_malah_l@yahoo.com and hashemit@um.ac.ir

Abstract: *At the present time, drugs used for treatment of cancer, have side-effects, including degradation of cells and resistant drug. Nanotechnology can overcome these problems and provides basic changes in diagnosis and cancer therapy. Sub-micron systems (i.e. nanosystems) in pharmacy have surged; particularly nanocarriers are important tool for drug delivery. Targeted nano drug carriers provide more efficient drug distribution, intravascular or tumoral administration is discussed as well as the mechanism involved in tumor regression. Generally, nanotechnology as a novel science in biological discipline has a considerable potential in diagnosing cancers and caring them, as soon as possible, increases the hope of human life. In this paper, the different kind of nonocarriers and their role in cancer therapy is discussed elaborately.*

Keywords: Nanocarriers, Cancer, Drug delivery, Nanotechnology.

1 Introduction

Nanotechnology is a novel area of science that provides, with a new hope, the tools and technology to work at atomic, molecular and supramolecular levels leading to creation of devices and delivery systems with fundamentally new properties and functions. Nanocarriers offers a number of advantages making it an ideal drug delivery vehicle[1].

- Nanocarriers can better deliver drugs to tiny areas withinthe body[2].
- It represents engineering of particles, which are smaller than 100 nanometers.
- Sophisticated techniques and tools have enabled the better characterization and manipulation of material at nanoscale level to elucidate nanoscale phenomenon leading to generation of new era of nanostructure-mediated drug delivery.
- Nanocarriers overcome the resistance offered by the physiological barriers in the body because efficient delivery of drug to various parts of the body is directly affected by particle size.
- Nanocarriers aid in efficient drug delivery to improve aqueous of poorly soluble drugs that enhance bioavailability for timed release of drug molecules, and precise drug targeting[3,4].
- Targeted nano drug carriers reduce drug toxicity and provide more efficient drug distribution.
- Nanocarriers holds promise to deliver biotech drugs over various anatomic extremities of body such as blood brain barrier, branching pathways of the pulmonary system, and the tight epithelial junctions of the skin *etc*.
- Nanocarriers better penetrate tumors due to their leaky constitution, containing pores ranging from 100—1000 nm in diameter.

Nanotechnology will radically change the way we diagnose, treat and prevent cancer to help meet the goal of eliminating suffering and death from cancer. Nanotechnology can provide the technical power and tools that will enable those developing new diagnostics, therapeutics, and preventives to keep pace with today's explosion in knowledge. With nanomedicine, we might be able to stop cancer even before it develops[5].

2 Types of Nanocarriers

Nanocarriers are materials or devices of nanoscale (below 1 mm) made up of different biodegradable materials like natural or synthetic polymers, lipids

or phospholipids and even organometallic compounds. Nanocarriers being of submicron size have a very high surface to volume ratio, leading to increased dissolution rate.
Nanocarriers include a wide array of submicron system such as nanoparticles, nanocapsules, lipid complexes, polymeric micelles, and dendrimers.

2.1 Nanocrystals and Nanosuspensions

Nanocrystals are aggregates of around hundreds or thousands of molecules that combine in a crystalline form, composed of pure drug with only a thin coating comprised of surfactant or combination of surfactants. The production technique of nanocrystals is known as 'nanonisation'.
To produce nanosuspensions, the drug powder is dispersed in an aqueous surfactant solution by high speed stirring. The obtained macrosuspension is then homogenized to nanosize by wet milling, high-pressure homogenization, nanocrystallisation from supersaturated solution and spray drying[6,7]. The size of nanocrystals allows for safe and effective passage through capillaries. Potential of nanocrystals can be inferred by the FDA approval of Rapamune®, containing sirolimus which is an immunosuppressant drug to prevent graft rejection in children after liver transplantation and Emend®, which contains aprepitant, MK 869, is used in the treatment of emesis associated with the cancer chemotherapy.

2.2 Nanotubes and Nanowires

Nanotubes and nanowires are the self-assembling sheet of atoms arranged in the form of tubes and thread-like structures of nanoscale range. Nanostructures that have gained much attention are hollow, carbon-based cage like structures—nanotubes and fullerenes. Fullerenes are spherical structures, also known as bucky balls. Soluble derivatives of fullerenes such as C60—a soccer ball shaped arrangement of 60 carbon atoms per molecule shows promise as pharmaceutical agents. These synthetic nanocarriers offer a number of advantages in terms of increased internal volume and ease of functional modification of internal and external surfaces[8]. Nanotubes are of two types—single walled and double walled carbon tubes.Multiwalled carbon nanotubes are suitable delivery system for transformation specifically to bacterial cells (*E. coli*) and for nanoscale cell electroporation[9]. Pantarotto *et al.* demonstrated the potential of peptide functionalized carbon nanotubes in augmentation of virus specific neutralizing antibody response that could be further exploited in vaccine delivery.
Fullerenes are effective in tissue selective and intracellular targeting of mitochondria. Thus, these systems could be utilized further for targeting capabilities of biotech drugs such as genes, proteins and peptides.

2.3 Ceramic Nanoparticles

These are the nanoparticles made up of inorganic (ceramic) compounds such as silica, titania and alumina. Ceramic nanoparticles exist in size less than 50 nm, which helps them in evading reticuloendothelial system (RES) of body. These particles provide the complete protection to the entrapped molecules such as proteins, enzymes and drugs against the denaturizing effects of external pH and temperature as it involves no swelling and porosity changes with the change in pH. But these ceramic nanoparticles are non-biodegradable, slow dissolving and nonetheless must be somehow eliminated from the body.

2.4 Liposomes

Liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Liposomes are formed when thin lipid films or lipid cakes are hydrated and stacks of liquid crystalline ilayers become fluid and swell. It exhibits number of advantages in terms of amphiphilic character, biocompatibility, and ease of surface modification rendering it a suitable candidate delivery system for biotech drugs. Liposomes have been used successfully in the field of biology, biochemistry and medicine since its origin. These alter the pharmacokinetic profile of loaded drug to a great extent especially in case of proteins and peptides and can be easily modified by surface attachment of polyethylene glycol-units (PEG) making it as stealth liposomes and thus increase its circulation half-life[10].

2.5 Solid Lipid Nanoparticles (SLN)

SLN particles made from solid lipids are submicron colloidal carriers (50—1000 nm) dispersed either in water or in an aqueous surfactant solution. These consist of solid hydrophobic core having a monolayer of

phospholipid coating. Different delivery routes have been exploited such as parenteral, pulmonary and topical[11,12]. SLN are non-toxic when compared with polymeric nanoparticles.

2.6 Polymeric Nanoparticles

Nanoparticles are sub-nanosized colloidal structures composed of synthetic or semi-synthetic polymers that vary in size from 10—1000 nm. Depending upon the method of preparation, nanospheres, or nanocapsules can be obtained in which drug either is dissolved, entrapped, encapsulated or attached to the nanoparticle matrix. Polymeric materials exhibit several desirable properties including biocompatibility, biodegradability, surface modification, and ease of functionalization of polymers. Polymeric systems allow for a greater control of pharmacokinetic behaviour of the loaded drug, leading to more appropriate steady levels of drugs. These attributes make it a candidate system for effective entrapment or encapsulation of biotech drugs that are usually sensitive to the changes in the surroundings.
Recently FDA approved drug made up of albumin nanoparticles is Abraxane® containing paclitaxel for use in patients with metastatic breast cancer who have failed combination therapy.
Polymeric nanoparticles offer engineered specificity allowing them to deliver a higher concentration of pharmaceutical agent to a desired location. But, particulate drug carriers are subject to rapid removal from the circulation by the macrophages of MPS, the main obstacle in targeting various non-phagocytic cells of the body [13, 14].

2.7 Polymeric Micelles

These systems include amphiphilic block copolymers such as Pluronics (polyoxyethylene polyoxypropylene block copolymers that self-associate in aqueous solution to form micelles. These are characterized by size and surface properties. Polymeric micelles offer a number of advantages in terms of thermodynamic stability in physiological solution leading to their slow dissolution in vivo. Because of their core–shell structure, these serve as suitable carrier for water insoluble drugs, such drugs partition in the hydrophobic core of micelles and outer hydrophilic layer aids in dispersion in aqueous media making it an appropriate candidate for intravenous administration. Nanometric size range helps micelles to evade the RES, and aids passage through endothelial cells[15,16].
Immunomicelles is one such novel approach in which antibody conjugated polymeric micelles containing antitumor drug Taxol was prepared and results demonstrated effective delivery at tumour site.

2.8 Copolymerized Peptide Nanoparticles (CPP)

Another modification of a polymer-based system is copolymerized peptide nanoparticles. It is a novel approach utilized for delivery of therapeutic peptides as drug polymer conjugates in which the drug moiety is covalently bound to the carrier instead of being physically entrapped. In 1996,Hillery et al. reported in vitro stability of CPP of leutinizing hormone releasing hormone (LHRH), and results demonstrated the significant intestinal transport of associated hormone (LH) using Caco-2 cell lines. Ramnathan *et al.* further supported the efficiency of this conjugated system. Review in this context is also available. This system needs to be further explored for effective delivery of sensitive molecules such as peptides and proteins.

2.9 Dendrimers

Dendrimers are the macromolecular compounds that consist of a series of branches around an inner core whose size and shape can be altered as desired.
These represent a unique class of polymers that are fabricated from monomers using either convergent or divergent step growth polymerization. Drug molecules can be loaded either in the interior, or can be adsorbed or attached to the surface groups.
It offers enormous advantages such as nanometric size range, ease of modification by modifying their termini, ease of preparation, and availability of multiple copies of surface groups for biological reorganization processes.

3 Drug delivery

Anticancer drugs generally feature large volumes of distribution. As cancer fighting drugs are toxic to both tumor and normal cells, the efficacy of chemotherapy is often limited by important side-effects. Thus, to deliver therapeutic agents to tumor cells *in vivo*, one must overcome the following problems: (i) drug resistance at the tumor level due to physiological barriers (non

cellular based mechanisms), (ii) drug resistance at the cellular level (cellular mechaof and (iii) distribution, biotransformation and clearance of anticancer drugs in the body.

Several innovative methods of drug delivery are used in cancer. These include use of microparticles as carriers of anticancer agents. These may be injected into the arterial circulation and guided to the tumor by magnetic field for targeted drug delivery. Polyethylene glycol (PEG) technology has been used to overcome some of the barriers to anticancer drug delivery. Encapsulating anticancer drugs in liposomes enables targeted drug delivery to tumor tissues and prevents damage to the normal surrounding tissues.

Some nanoscale delivery devices, such as dendrimers (spherical, branched polymers), silica-coated micelles, ceramic nanoparticles, and crosslinked liposomes can be targeted to cancer cells. This increase selectivity of drugs towards cancer cells and will reduce the toxicity to normal tissue.4 These nanocarriers, which are both pH-sensitive and temperature-sensitive, are structurally stable in the normal physiological environment. However, in slightly acidic environments that are characteristic of tumor tissues and endosomes (a cell component), they deform and precipitate, thus releasing the enclosed drug molecules. This is done by attaching monoclonal antibodies or cellsurface receptor ligands that bind specifically to the cancer cells. Some cancer targeting molecules include high-affinity folate receptor, luteinizing hormone releasing hormone and integrin .

Some research on folate nanoparticles showed higher specificity for cancerous human cells.7 In addition, the folate nanoparticles improved the uptake of the encapsulated drugs that it carried. Surface modification of nanoparticles can also enhance the permeability of drugs to create high-permeability nanoparticle-based cancer therapeutics. Barriers to cancer drugs can be in the form of the cell's plasma membrane or epithelial or endothelial layers of cells. Research on the covalent attachment of peptidic membrane-translocation sequences (MTS), peptides with the ability to pass through membrane, to nanoparticles have shown increased permeability through membranes. With improved cell permeability, nanoparticles can become more therapeutically effective drug transport vehicles.

4 Conclusion

Utilization of nanotechnological approaches for the delivery of biotech drugs is rapidly becoming an important tool in the arsenal of drug delivery. This multidisciplinary approach offers a great deal of flexibility in terms of ease of modification and adaptation to meet the needs of pathological conditions.

Nanobiotechnology brings a new ray of hope for the delivery of biotech drugs that exhibit the problems of short half-life, poor bioavailability, strong side effects, efficient drug protection, cell internalization, controlled release, reversionof the MDR(Multidrug resistance), insolubility and instability in biological milieu. Moreover with the advent of novel nanoparticulate systems and their success in delivery of biotech drugs, it is poised to play a profound and dominant role in the field of molecular medicine and associated delivery of drugs in the future.

Nanoparticles could do so by an indirect mechanism consisting in targeting the tissue adjacent to the tumor, which in turn can act as a drug reservoir in the fight against the neighboring neoplastic cells.

As far as encapsulation of antitumor drugs within nanoparticles is concerned, it is suspected that developments will concentrate on emerging molecules acting at the cancerous cell level (taxol, for instance), as well as on drugs acting at the vascular level like angiostatin [19], and tumor necrosis factors [20]. In this later case, there are less biological barriers to overcome, as there is no need for extravasation in the tumoral interstitium, for cell internalization as well as for scaping from the lysosome compartment. Finally, novel approaches of associating drugs to the nanoparticles should also emerge (prodrugs formulated in nanoparticles, for example) [21].

References

[1]. RAWAT M., SINGH D. and SARAF S., *India.* Received; accepted May 17, 2006. In press.

[2]. Roco M. C., Williams R. S., Alivisatos P. (eds.),, *Chap. 8, Kluwer Academic Publishers, Boston*, 2000.

[3]. Dubin C. H., Mech. Enz, "Nanotechnol".126 (Suppl.), pp. 10—12, 2004.

[4]. Yamamoto H., Kuno Y., Sugimoto S., Takeuchi H., Kawashima Y., *J.Contr. Rel.*, Vol. 102, pp. 373—381, 2005.

[5] I. Brigger, C. Dubernet, P. Couvreur, "Advanced Drug Delivery Reviews. Vol.54, pp.631–651, 2002.

[6]. Sarkari M., Brown J., Chen X., Swinnea S., Williams Robert O.,Johnston Keith P., *Int. J. Pharm.*, Vol . pp. 243, 17—31, 2002.

[7]. Chow L. C., Sun S., Hockey B., J. Res. Natl. Inst. Stand. Technol., Vol. pp. 543—551, 2004.
[8]. Goldstein A. S. M., Amory J. K., Martin S. M., Vemon C., Matrumotom A., Yagerm P., *Bioorg. Med. Chem.*, Vol. 9, pp. 2819—2825 2001.
[9]. Rojas C. J., Troszczynska J., Firkowska I., Morsczeck C., Giersig M.,*Lab. Chip.*, Vol. 5, pp. 536—539, 2005.
[10] Lasic D. D., Vallner J. J., Working P. K., *Curr. Opin. Mol. Ther*, Vol. 1, pp.177—185 1999.
[11]. Muller R. H., Dinglet A., *Eurocosmetics*, Vol. 7, pp. 19—26, 1998.
[12]. Jenning V., Gysler A., Korting M. S., Gohla S. H., *Eur. J. Pharm.Biopharm.*, Vol. 49, pp.211—218, 2000.
[13]. Peppas L. B., *Int. J. Pharm.*, Vol. 116, pp.1—9, 1995.
[14]. Soppimath K. S., Aminabhavi T. M., Kulkarni A. R., Anandrao R.,Rudzinski W., *Eur. J. Control. Rel.*, Vol. 70, pp. 1—20, 2001.
[15]. Torchilin V. P., *J. Control. Rel.*, Vol.73, pp.137—172, 2001.
[16]. Rosler A., Vandermeulen G. W. M., Klok H. A., *Adv. Drug. Deliv.Rev.*, Vol. 53, pp.95—108. 2001.
[17]. Padilla D. J., Omayra L., Ihre H. R., Gagne L., Frechet J. M. J., Szoka
J., Francis C., *Bioconj. Chem.*, Vol.13, pp.453—461,2002.
[18]. Orive G., Hernandez R. M., Gascon A. R., Pedraz J. L., *Cancer Therapy*, Vol. 3, pp.131—138, 2005.
[19] M. Kirsh, J. Strasser, R. Allende, L. Bello, J. Zhang, P. McL. Black, Cancer Res. Vol.58, pp.4654–4659. 1998.
[20] Y.-P. Li, Y.-Y. Pei, Z.-H. Zhou, X.-Y. Zhang, Z.-H. Gu, JDing, J.-J. Zhou, X.-J. Gao,. J. Control. Release. Vol.71, pp. 287–296. 2001.
[21] H.S. Yoo, K.H. Lee, J.E. Oh, T.G. Park, J. Control. Release Vol. 68, pp.419–431, 2000.