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A REVIEW ON ROLE OF NANOSTRUCTURES IN DRUG DELIVERY SYSTEM

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Abstract. The development of nanoparticles drug delivery system is widely expected to change the traditional pharmaceutical system through increased surface specific reactivity and bioavailability. There has been an important research interest in the area of drug delivery systems using nanoparticles. These particles have unique physicochemical properties such as ultra small and controllable size, large surface area to mass ratio and functionalizable structure. They have been used *in vivo* to protect the drug entity in the systemic circulation, control access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action. Various nanostructures have been used in the drug delivery research to increase therapeutic advantage. Present review discuss about the aspects of the characterization and applications of various nanostructures in drug delivery system.

1. INTRODUCTION

Nanotechnology is a rapid expanding field, encompassing the development of materials with 5–200 nanometers in size. It has a wide range of applications in the fields of engineering, medicine and life sciences. Advances in nanotechnology were utilized in medicine for therapeutic drug delivery and treatment for a variety of diseases and disorders. The drug is dissolved and entrapped into biodegradable nanoparticles which are specially designed to absorb drug and protecting it against chemical and enzymatic degradation [1]. The major goal in designing these nanostructures as delivery system is to release pharmacologically active molecules for site-specific action with accurate dose [2]. In current years, several biodegradable polymeric nanostructures have attracted the notice with their inherent capacity to target particular organ/tissue to deliver the drug. This versatility in targeting tissues, accessing deep molecular targets and controlling drug release has created a revolution in the field of pharmaceutical sciences. The present review details the recent developments of nanostructure drug delivery systems and their applications.

2. NANOSTRUCTURES AND DRUG DELIVERY

Nanoparticles for drug delivery can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of material depends on many factors such as the size of nanoparticles, inherent properties of the drug, surface characteristics such as charge and permeability, degree of biodegradability, etc. After selection, these nanoparticles were prepared most often by three methods; dispersion of preformed polymers, polymerization of monomers and ionic gelation of

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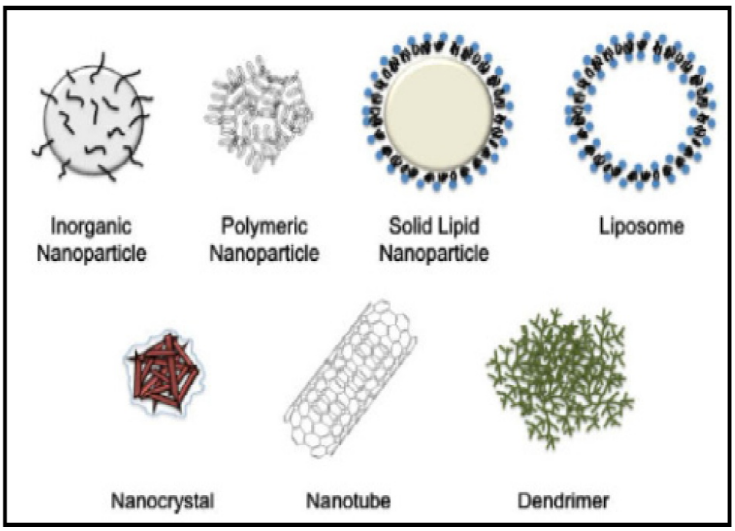

Fig. 1. Various types of nanoparticles used in biomedical research and drug delivery.

hydrophilic polymers. The other methods such as supercritical fluid technology and particle replication in non-wetting have also been in exploit. At the end of preparation; an ideal nanostructure system should have a high drug-loading capacity and reduce the quantity of matrix materials for administration. Particle size and size division are the most significant characteristics of nanoparticle systems [3]. They determine the *in vivo* distribution, biological fate, toxicity and the targeting ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Drug loading can be made by either incorporation or absorption/ adsorption method. The drug loading and entrapment efficiency are very much depend on the solid-state of the drug solubility in matrix material, polymer composition, the molecular weight and the drug polymer interaction (ref). Many advantages of nanoparticle-based drug delivery have been recognized, such as improved serum solubility, prolonged systemic circulation lifetime, sustained and controlled manner of drug delivery and concurrent delivery of multiple therapeutic agents to the same cells [4,5]. Several newly developed nanostructures illustrated in Fig. 1 such as nanoparticles, nanotubes, nanocrystals, dendrimers etc., give promising results with their own mechanism in drug delivery system.

3. GOLD NANOPARTICLES

In today's era of nanotechnology, gold nanoparticles were used for have some applications in drug delivery system. The loading of gold nanoparticles with drugs through covalent and non-covalent bonding (illustrated in Fig. 2) offers increased therapeutic efficacy. The combination of gold nanoparticles and laser irradiation to control the release of drugs give useful therapeutic benefits [6]. The gold nanoshell-antibody complex is broadly used in cancer treatment. The gold nanoparticles have also shown a selective transportation of drugs to cancer cell nucleus specially when incorporated with conjugated arginine-glycine- aspartic acid peptide (RGD) and PEG [7]. When getting the tumor cells, they can induce hyperthermia using non-invasive radiofrequency.

4. SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles are lipid based submicron colloidal carriers. Glyce behenate, glycerol palmitostearate, lecithin, triglycerides and tristearin glyceride are the widely used solid lipid nanoparticles

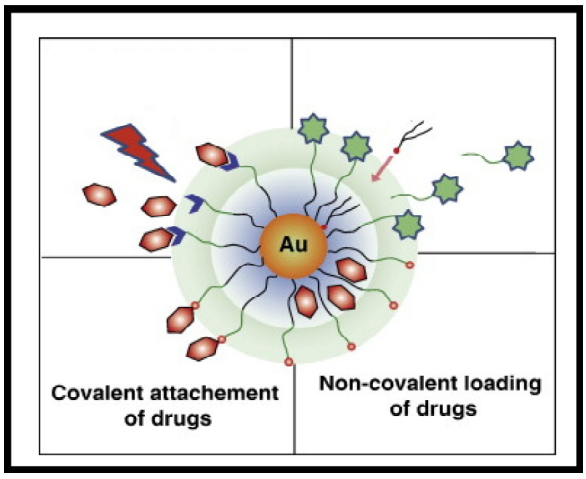

Fig. 2. Gold nanoparticles with drugs through covalent and non-covalent bonding.

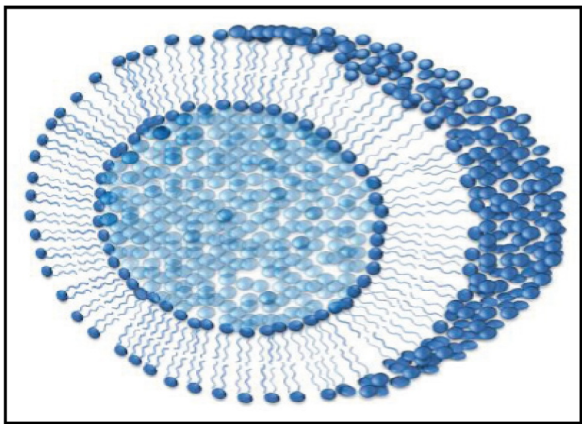

Fig. 3. Cross section view of a bilayered Liposome.

[8,9]. They need high amount of surfactants for stability. They can be used by different routes like oral, topical or pulmonary and stable for a long period. Proteins and antigens intended for therapeutic purposes may be incorporated or adsorbed onto these nanoparticles and further administered by parenteral routes or by alternative routes such as oral, nasal and pulmonary. Application in anti-cancer and antiviral therapy show good results [10,11]. Solid lipid nanoparticles can improve the ability of the drug to penetrate through the blood-brain barrier and is a promising drug targeting system for the treatment of central nervous system disorders. Because of entrapment of drug in solid lipid nanoparticles, permeability was enhanced 4-11 times than traditional delivery. Drugs like Indomethacin, Ketoprofen, Isoniazid and pyrazinamide has been reported to be targeted to the pulmonary system [12,13]. Administration of important peptides such as cyclosporine A, insulin, calcitonin and somatostatin have also currently under investigation. The limitations include the problems with loading efficiency due to the formation of a lipid crystal matrix and changes in physical state of the lipids [14,9,15].

5. POLYMERIC NANOPARTICLE

Biodegradable polymers are widely used for controlled drug release. These nanoparticles are structurally stable inorganic systems with porous characteristics. These particles can be easily engineered with the required size and porosity. Processes of drug loading into polymeric nanoparticles include entrapment, encapsulation and dissolution or dispersion. A wide spectrum of hydrophobic and hydrophilic drugs can be included into these nanoparticles for drug delivery, tissue engineering and different other biomedical applications. The surface of polymeric nanoparticles typically contains functional groups that can be chemically modified with targeting ligands [16,17]. Polymer–drug conjugates have made a important clinical impact through improving the pharmaceutical efficacy and dosing of a variety of already accepted drugs [18,19].These are also studied extensively for pulmonary delivery of antiasthmatic [20], antituberculosis [21], pulmonary hypertension [22], and anticancer drugs [23]. But, the biodegradability and toxicity of polymeric nanoparticles pulmonary formulation still require further close check to avoid accumulation of polymer carriers after repeated dosing. In order to further improve the drug loading capacity and incorporate the spatial and/or temporal control over drug delivery, many other biocompatible polymeric nanoparticle platforms have also been developed [24–26]. Recent research was exploring typical ceramic nanoparticles such as silica, titania, alumina etc., in drug delivery systems. The new strategies have also concentrating on the use of new biodegradable synthetic polymers and modified polymers from natural products such as chitosan and albumin.

6. NANOTUBES

Nanotubes are self-assembling sheets of atoms in order in tubes. They can be classified into two common categories based on their structure: single-walled carbon nanotubes (SWCNTs) with a single cylindrical carbon wall and multiwall carbon nanotubes (MWCNTs) with multiple walls cylinders nested within other cylinders. They have unique electronic, thermal, and structural characteristics and suggest a promising approach for drug delivery for cancer therapy [27]. Carbon nanotubes are being highly researched in the field of efficient drug delivery and biosensing methods for disease treatment. These materials have shown potential in targeting specific cancer cells with a dosage lower than conventional drugs used [28]. Even though these are potentially promising candidates for pharmaceutical applications, the tolerance on human remains unidentified.

7. NANOCRYSTALS

Nanocrystals are aggregates of molecules that can be combined into a crystal form of drug surrounded via a thin coating of surfactant. These crystals are broadly used in materials research, chemical engineering, and in biological imaging [29-32], but comparatively less in nanomedicine for drug delivery. Nanocrystalline species are prepared using a hydrophobic compound coated with a thin hydro-

philic layer. The biological reaction of these nanocrystals strongly depends on the chemical nature of this hydrophilic coating. This hydrophilic layer also aids in the biological distribution and bioavailability of the crystalline drug material. These factors combine to enhance the efficiency of overall drug delivery [33,34]. In order to show their advantages *in vivo*, these drug nanocrystals require to be transferred into the right dosage form. Nanosuspensions can be directly used as oral suspensions to overcome the difficulties of swallowing tablets by pediatric or geriatric patients.

8. LIPOSOMES

Liposomes were first introduced for drug delivery as early as in the year 1965 [35].These is spherical lipid vesicles with a bilayered membrane structure consisting of amphiphilic lipid molecules illustrated in Fig. 3. These liposomes are the most frequently used antimicrobial drug delivery system [36,37]. Several procedures for the encapsulation of drugs into liposomes have been described [38]. Liposomes loaded with drugs can be done in a size range that makes them vulnerable to phagocytosis by macrophage. These liposomes can be digested within the macrophage's phagosome, thus releasing their drug contents. Opsonins and ligands that activate endocytosis in other cell types can also be incorporated into liposome membranes. One of the distinguishing features of liposomes is its lipid bilayer structure, which mimics cell membranes and can readily fuse with infectious microbes. By directly fusing with bacterial membranes, the drug can be released inside the directly bacteria [39].

9. DENDRIMERS

Dendrimers are well-structured globular macromolecules. They consist of three regions: a core, layers of branched repeat units emerging from the core, and functional end groups on the outer layer of repeat units. The highly-branched nature of dendrimers provides large surface area to size ratio and allows great reactivity with microorganisms *in vivo* [40,41]. Drug molecules can be included into dendrimers by either complexation or encapsulation. Both hydrophobic and hydrophilic agents can be loaded into dendrimers. Hydrophobic drugs can be loaded inside the cavity in the hydrophobic core, and hydrophilic drugs can be attached to the multivalent surfaces of dendrimers through covalent conjugation or electrostatic interaction. Thus, they can be used for oral, transdermal, ocular and intravenous deliveries [42,43]. Moreover, dendrimers have shown that they can easily cross cell barriers by both paracellular and transcellular pathways [44]. The most widely explored and used dendrimers are Poly-AmidoAmine dendrimers. Poly-AmidoAmine dendrimers can facilitate transport through epithelial barrier which show their potential as a carrier for oral delivery [45].

10. NANOFIBERS

Nanofibers for drug delivery applications are prepared by electrospinning process. As a fibrous scaffold, nanofibers are able to entrap drugs with a large loading capacity and high encapsulation efficiency because of their low weight and inherent large surface to volume ratio. They have been designed as promising carriers for delivering anticancer drugs, especially in postoperative local chemotherapy using surgical implantation of the scaffold. These allow the encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation. For instance, it was found that insulin-loaded nanoparticles have preserved insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following the oral administration.

11. QUANTUM DOTS

Quantum dots are inorganic fluorescent semiconductor nanoparticels composed of 10–50 atoms with 2-10 nm diameters [46-50]. The achievement of using these quantum dots in biological imaging, sensing and detection has encouraged scientists to further improve this technology in other application of medicine. One of the most significant emerging applications is drug delivery. Quantum dots have a potential for better treatment of cancer by targeted drug delivery systems.Apart from targeting of anticancer drugs, Quantum dots are also useful to deliver other biomolecules such as siRNA [51]. Due to concerns about long-term *in vivo* toxicity and degradation, quantum dots are currently limited to cell and small animal uses.

12. CONCLUSION

Nanomedicine is the application of nanostructures in an innovative way to develop new approaches and therapies. Products of nanotechnology are expected to revolutionize modern medicine, as evidenced by recent scientific advances and global initiatives. The field of drug delivery is one of the direct beneficiary fields of these advancements. The most important advantage here is the side-effects can be lowered significantly by depositing the active agent in the

morbid region only with accurate dose. The nanoscale platforms to deliver drugs have made important progress in formulation preparations and achieved more precise treatments. But still more understanding of the different mechanisms of biological interactions, and particle engineering, are required. Although drug delivery through nanostructure systems is mainly investigated in preclinical animal models, too few studies are carried out. This will turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system. More number of clinical trials on epidemiological view is requested to get more precise information.

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REFERENCES

[1] D. Peer, J.M. Karp, S. Hong, O.C. Farokhzad, R. Margalit and R. Langer // *Nat. Nanotechnol*. **2** (2007) 751.
[2] N. Jain, R. Jain, N. Thakur, B.P. Gupta, D.K. Jain, J. Banveeri and S. Jain // *Asian J. Pharm. Clin*. *Res.* **3**, Issue 3 (2010) 177.
[3] J. Panyam and V. Labhasetwar // *Adv Drug Deliv Rev*. **55** (2003) 329.
[4] L. Zhang, F.X. Gu, J.M. Chan, A.Z. Wang, R.S. Langer and O.C. Farokhzad // *Clin. Pharmacol. Ther*. **83(5)** (2008) 761.
[5] M.E. Davis, Z.G. Chen and D.M. Shin // *Nature* **7** (2008) 771.
[6] S. Sonke and D.A. Tomalia // *Advanced Drug Delivery Reviews* **57** (2005) 2106.
[7] P.C. Chen, S.C. Mwakwari and A.K. Oyelere // *Nanotechnology*, *Science and Applications* **1** (2008) 45.
[8] S. Wang, M. Tan, Z. Zhong, M. Chen and Y. Wang // *Journal of Nanomaterials* **2011** (2011) 8.
[9] G. Fricker, T. Kromp, A. Wendel, A. Blume and J. Zirkel // *Pharmaceutical Research*. **8** (2010) 1469.
[10] R.S. Mulik, J. Mönkkönen, R.O. Juvonen, K.R. Mahadik and A.R. Paradkar // *Int J Pharm*. **398** (2010) 190.
[11] H. Heiati, R. Tawashi, R.R. Shivers and N.C. Phillips // *Int J Pharm*. **146** (1997) 123.
[12] H. Schreier, R.J. Gonzalez-Rothi and A.A. Stecenko // *J Control Release* **24** (1993) 209.
[13] C. Beaulac, S. Sachetelli and J. Lagace // *J Drug Target*. **7** (1999) 33.
[14] H.C. Korting and M. Schafer-Korting // *Handbook of Experimental Pharmacology* **197** (2010) 435.
[15] G.A. Castro, R.L. Orefice, J.M. Vilela, M.S. Andrade and L.A. Ferreira // *Journal of Microencapsulation* **5** (2007) 395.
[16] Z. Ahmad, R. Pandey, S. Sharma and G.K. Khuller // *Ind. J. Chest Dis. Allied. Sci*. **48** (2006) 171.
[17] R. Pandey and G.K. Khuller // *J. Antimicrob. Chemotherapy* **57** (2006)1146.
[18] M.E. Davis, Z. Chen and D.M. Shin // *Nat Rev Drug Discov.* **7** (2008) 771.
[19] F. Greco and M.J. Vicent // *Adv Drug Deliv Rev*. **61** (2009) 1203.
[20] J.H. Seong, K.M. Lee, S.T. Kim, S.E. Jin and C.K. Kim // *J Gene Med*. **8** (2006) 314.
[21] R. Pandey, A. Sharma, A. Zahoor, S. Sharma, G.K. Khuller and B. Prasad // *J Antimicrob Chemother*. **52** (2003) 981.
[22] S. Kimura, K. Egashira and L. Chen // *Hypertension* **53** (2009) 877.
[23] S. Azarmi, X. Tao and H. Chen // *Int J Pharm.* **319** (2006) 155.
[24] Y. Bae // *Bioconjug Chem*. **16** (2004) 122.
[25] J.M. Chan, P.M. Valencia, L. Zhang, R. Langer and O.C. Farokhzad // *Methods Mol Biol* **624** (2010) 163.
[26] M.E. Napier and J.M. DeSimone // *Polym Rev* **47** (2007) 321.
[27] C.P. Firme and P.R. Bandaru // *Nanomedicine* **6** (2006) 245.
[28] C. Srinivasan // *Current Science* **94** (2008) 300.
[29] W.C. Chan and S. Nie // *Science* **281** (1998) 2016.
[30] B.O. Dabboussi, J. Rodriguez-Viejo, F.V. Mikulec, J.R. Hein, H. Mattoussi, R. Ober, K.F. Jensen and M.G. Bawendi // *J. Phys. Chem*. **101** (1997) 9463.
[31] B. Dubertret, P. Skourides, D.J. Norris, V. Noireaux, A.H. Brivanlou and A. Libchaber // *Science*. **298** (2002) 1759.
[32] X. Gao, Y. Cui, R.M. Levenson, L.W.K. Chung and S. Nie // *Nat. Biotechnol*. **22** (2004) 969.
[33] S.J. Rosenthal, I. Tomlinson, E.M. Adkins, S. Schroeter, S. Adams, L. Swafford, J. McBride, Y. Wang, L.J. DeFlice and R.D.

Blakely // *J. Am. Chem. Soc.* **124** (2002) 4586.
[34] F. Osaki, T. Kanamori, S. Sando, T. Sera and Y. Aoyama // *J. Am. Chem. Soc*. **126** (2004) 6520.
[35] A.D. Bangham, M.M. Standish and J.C. Watkins // *Journal of Molecular Biology*. **13** (1965) 238.
[36] I. Schumacher and R. Margalit // *J. Pham. Sci.* **86** (1997) 635.
[37] A. Omri, Z.E. Suntres and P.N. Shek // *Biochem. Pharmacol*. **64** (2002) 1407.
[38] Q.F. Defrise, In: *Liposome technology*, vol. 2, 1st ed., ed. by G. Gregoriadis (Boca Raton, CRC Press, 1984).
[39] L. Zhang, D. Pornpattananangkul, C.M.J. Hu and C.M. Huang // *Curr. Med. Chem*. **17** (2010) 585.
[40] L. Balogh, D.R. Swanson, D.A. Tomalia, G.L. Hagnauer and A.T. McManus // *Nano.Lett*. **1** (2001) 18.
[41] B. Devarakonda, R.A. Hill RA, Liebenberg W, Brits M and de Villiers MM// *Int. J. pharm*. **304(1-2)** (2005)193-209.
[42] A.K. Patri, A. Myc, J. Beals, T.P. Thomas and N.H. Bander // *Bioconjugate Chemistry* **6** (2004) 1174.
[43] K. Sugisaki, T. Usui, N. Nishiyama, W.D. Jang and Y. Yanagi // *Investigative Ophthalmology & Vis-ual Science* **3** (2008) 894.
[44] A.R. Menjoge, R.M. Kannan and D.A. Tomalia // *Drug Discovery Today*. **5-6** (2010) 171.
[45] K.M. Kitchens, R.B. Kolhatkar, P.W. Swaan and N.D. Eddington // *Pharm Res*. **23** (2006) 2818.
[46] B. Liu, M. Yang and R. Li // *European Journal of Pharmaceutics and Biopharmaceutic*s **69** (2008) 527.
[47] K.M. Huh, H.S. Min, S.C. Lee, H.J. Lee, S. Kim and K. Park // *Journal of Controlled Release* **126** (2008) 122.
[48] Y.T. Ko, A. Kale, W.C. Hartner, B. Papahadjopoulos-Sternberg and V.P. Torchilin // *Journal of Controlled Release* **133** (2008) 132.
[49] S. Purushotham, P.E. Chang, H. Rumpel, I.H. Kee, R.T. Ng, P.K. Chow, C.K. Tan and R.V. Ramanujan // *Nanotechnology* **29** (2006) 305101.
[50] M. Rawat, D. Singh, S. Saraf and S.W. Saraf // *Biol. Pharm. Bull.* **29** (2006) 1790.
[51] G. Xu, K.-T. Yong, I. Roy, S.D. Mahajan, H. Ding and S.A. Schwartz // *Bioconjugate Chem*. **19** (2008) 1179.