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Nanotechnology and Its Role in Drug Delivery Systems: A Review.

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ABSTRACT

Development in the field of drug delivery is a continuous and ongoing research in medicine and pharmaceutics. In recent years the use of nanoscience and technology in this field has accelerated immensely. Nanotechnology is a branch which involves creating materials, devices or systems on a nanometer scale. Nano materials, due to their enhanced surface area and encapsulation properties have proved to be better alternative components that can be used in drug delivery systems. This review gives a brief introduction on the most commonly and successfully researched nano drug delivery systems such as nano emulsions, liposomes, lipid nano carriers, polymeric nanoparticles, microvesicles etc.

Keywords: Nanotechnology, drug delivery, application, nanomedicine

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INTRODUCTION

Nanotechnology can be defined as the technology at the scale of one-billionth of a meter. It is the design, characterization, synthesis and application of materials, structures, devices and systems by controlling the shape and size at nanometer scale [1, 2]. It is an interdisciplinary field and has three main extensively overlapping areas which are nano electronics, nanomaterials and nanobiotechnology [3]. The prefix "nano" was first added to the word "technology" by Nario Taniguchi in 1974. He used the composite word to signify machining with tolerances of less than one micron [4]. Nanotechnology is most appropriately called nanoscience which refers to research at the scale of 100nm or less. One of the most important areas in nanotechnology is nanomedicine referring to highly specific medical intervention at the molecular scale for diagnosis, prevention and treatment of diseases. [5] Drug delivery nanosystems comprise a significant component of nanomedicine. Many of the current "nano" drug delivery systems are remnants of conventional drug delivery systems which are at the nanometer range [6]. With an increase in "nanotechnology" applications in the pharmaceutical and health care industries it has been estimated that 80% of the market will be related to nanotechnology by 2015 [7].

The challenge of pharmaceutical companies is to give the right therapy with minimal side effects at a reduced cost. Nanoparticles have the potential of improving the common drug delivery systems like oral, parenteral, ocular etc. and hence play a promising role in drug delivery systems. Some of the challenges of drug delivery systems include poor bioavailability, reduced therapeutic effectiveness, side effects and fluctuations in the drug plasma concentration. Nanotechnology in drug delivery systems is used to overcome these shortcomings [3]. Nanostructures deliver drugs that are highly water soluble. It can also bypass the liver hence preventing first pass metabolism. [4, 5] Due to their small size they are able to penetrate into tissues and are taken up by the cells, allowing efficient delivery of drugs to sites of action [10]. Through the manipulation of the characteristics of polymers, release of drug from nanostructures can be controlled to achieve the desired therapeutic concentration for the desired duration [11]. Hence nanotechnology has become an important field which when applied in drug delivery systems can expand drug markets.

Most of the current research focuses on using nanoparticles as drug delivery carriers in most chronic diseases like cancer, HIV and diabetes where treatment options are limited. Generally nanoparticles are in the form of polymers, ceramics, metals and biological materials with various forms. They might have spherical, branched or shell structures. Each structure offers unique characteristics that make it a suitable drug delivery system for a particular therapy [12]. In this review we concentrate on some important nanoparticles which are used as drug delivery systems.

Nanoemulsions

Emulsion by definition is the even distribution of one liquid in another. This property of mixing of two liquids has been used in delivery of materials in areas such as cosmetics and

drugs. Nanoemulsions are ultra-fine emulsions with droplet size below 1µm. They are transparent in nature due to the minute size and have good biophysical and sensorial properties. Nanoemulsions are biodegradable, biocompatible, and easy to produce and used as carriers for lipophilic drugs which are prone to hydrolysis [13]. They enhance gastrointestinal absorption and reduce inter- and intra-subject variability for various drugs. Due to their very large interfacial area, they exhibit excellent drug release profile [14]. However they have been found to be metastable and may be destabilized due to Ostwald ripening. To avoid these drawbacks a number of factors have to be considered during the synthesis process. These factors include selecting an appropriate composition, controlling the order of addition of components, applying the shear in a manner that will effectively rupture the droplets, and ensuring that the dispersed phase molecules are insoluble in the continuous phase so that Ostwald ripening does not occur rapidly [15]. Over recent years the solubility, stability and bioavailability of nanoemulsion formulation such as that of Ramipril has been studied [16]. Nanoemulsions have also been used to study immune response and for the prevention treatment of neurodegenerative diseases [17, 18].

Liposomes

Liposomes are vesicular structures with an aqueous core surrounded by a hydrophobic lipid bilayer, created by the extrusion of phospholipids [19]. They may be single layered or multi layered, varying in size from 15nm to 100nm or more. They have been found to be useful in cosmetics, drug delivery and food industries. Liposomes are applied as drug carriers due to their ability to prevent degradation of drugs, reduce side effects and target drugs to site of action [20]. Liposomes work by attaching to the target cell or by its engulfment into the target cell, followed by the release of the drug encapsulated within to perform its function. For the attachment or engulfment to take place the modification of the surface properties of the liposome is essential. Surface modification is carried out based on the application of the liposome. They are used in transdermal drug delivery to potentiate skin permeation of drugs with high molecular weight and poor water solubility [21]. Liposomes have been used as carriers for gentamicin in order to reduce toxicity, as a means of delivery of drugs to the lungs by nebulization and in ocular delivery [22, 23]. Since liposomes are influenced by phagocytosis they may be eliminated by the cells of the reticuloendothelial system (RES). This affects the rate of drug release and stability of the vesicular structures and thus, is a major drawback of being used as vesicles for drug delivery [24].

Dendrimers

Dendrimers are unimolecular, monodispersed and micellar structures which are heavily branched**.** They are globular, in structure having a central symmetric core from which arise highly branched structures. Their size in the nano range varies depending on the method of synthesis, type of drug encapsulated and the application. The particle size range is between 1 to 100nm although their sizes are mostly less than 10nm. Drugs can be encapsulated within the core or attached to the surface. Dendrimers provide controlled release from the inner core and the encapsulation of both hydrophobic and hydrophilic drugs [25, 26]. Since they have multiple

attachment sites a number of different types of molecules such as drugs, solubilizing groups, etc. can be attached to the surface in a defined manner as required. In this way the surface can be modified according to the desired application.

Dendrimers have been extensively studied in the delivery of antitumor, antiviral, and antibacterial drugs, in intracellular drug delivery and gene delivery. They are also used in photodynamic therapy to detect tumors [27]. Variation in toxicity has been noted with the change in the functional groups attached. For example, it has been studied that primary amines are more toxic than secondary or tertiary amines [28]. The material of the core also affects the toxicity of the dendrimers. It is suggested that the aromatic interior of the dendrimer may cause hemolysis through hydrophobic membrane contact [29]. Dendrimer based carriers have been studied to investigate their ability to increase the permeability of the drug named paclitaxel and overcome the cellular barriers [30]. Studies have showed the ability of dendrimers to cross the pulmonary epithelium, for example beclometasone dipropionate (BDP) dendrimers have potential for pulmonary inhalation using air-jet and vibrating-mesh nebulizers [31, 32].

Ceramic Nanoparticles

Ceramic nanoparticles are inorganic compounds which are porous in nature. Because these particles can be easily engineered with the desired size and porosity, growing interest has recently emerged to utilize ceramic nanoparticles as drug vehicles [33]. These particles protect doped molecules (enzymes, drugs, etc.) against denaturation induced by external pH and temperature. Their ultra-low size (less than 50 nm) can help them evade the reticulo-endothelial system (RES) of the body [34]. Ceramic (inorganic) particles have been highlighted to provide increased mechanical strength, chemical stability, biocompatibility, and resistance to microbial attack as compared to their organic (polymeric) counterparts [35]. One of the most recent research carried out was on the study of lactose coated ceramic nanoparticles for oral drug delivery which showed an improved dissolution of drug in the form of ceramic nanoparticles [36]. Ceramic nanoparticles have been used in research involving cancer therapy such as targeting cancerous cells in liver as well as in the delivery of insulin by oral administration. They are also effective in delivering proteins and genes. However, these particles are not biodegradable and so there is a concern that they may accumulate in the body and cause harmful effects [37].

Microvesicles

Microvesicles are extracellular vesicles which are formed by the outward budding or fission of vesicles of the cell surface membrane. These are heterogeneous structures which vary in diameter from 50-1000 nm. In multi cellular organisms, intercellular communication is carried out by the transport of micro vesicles between cells, cytosolic proteins, RNA and lipids. [38] Studies have shown that these vesicles, due to excretion by antigen presenting cells play an important role in immune response and also find importance in their ability to carry genetic materials [39, 40].

Microvesicles play a major role in tumor invasion and metastases. They may be involved in transfer of oncogenic receptors, mRNAs and paracrine signals and also harness selective bioactive molecules. Thus they are capable of modulating the environment of tumor growth and survival, and altering immune response by fusion with immune cells [41]. Nanoparticulate carriers can also be functionalized safely cross the blood brain barrier to administer the required amount of drug. Studies have been carried showing an improved targeted neurotrophin delivery to localized areas of the central nervous system [42].

Lipid Nanocarriers

Lipid nanocarriers, as the name suggests are nanoparticles with a lipid matrix. The different lipid based carriers include solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and lipid drug conjugate (LDC). These contain lipids, drugs and surfactants which act as stabilizers. The first generation of solid lipid nanoparticles (SLN) was developed at the beginning of the nineties as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles. The main features of SLN with regard to parenteral application are the excellent physical stability, protection of incorporated labile drugs from degradation, controlled drug release (fast or sustained) depending on the incorporation model, good tolerability and site specific targeting [43]. However, SLN have disadvantages such as high water content, drug expulsion after polymorphic transition on storage and insufficient loading capacity limited by the solubility of drug in lipid melt.

Nanostructured lipid carriers which are also solid at room temperature are produced by the blend of a solid lipid with a liquid lipid. They were introduced to overcome the limitations of SLN. They show an increase in the payload and prevent drug expulsion. NLC have been used mainly for topical delivery and hence find application in cosmetics and dermatology [43].

Lipophilic drugs are usually incorporated in SLN but due to partitioning effects during production, only highly potent hydrophilic drugs effective in low concentrations are incorporated in SLN. LDC allows the incorporation of hydrophilic as well as lipophilic drugs and has a drug loading capacity of up to 33 % [43].

Lipid Nanocarriers with Internal Liquid Structures

The types of lipid nanoparticles with internal liquid crystalline structures include cubosomes, spongosomes, multicellular liposomes, nanostructured emulsions and hexosomes [44]. Cubosomes are liquid crystalline particles consisting of a honeycombed structure separating two internal aqueous channels. They are made up of surfactants, the most common being monoglyceride glycerol monoolein [45]. They have a small pore size of 5-10 nm which helps in controlled release such as that of solubilized substances [46]. Cubosomes sterically stabilized by an amphiphilic poly ethylene glycol (PEG) derivative have been studied for their ability to entrap protein molecules [47]. Research shows that proteocubosomes might become promising carriers of proteins as well as nanobioreactors comprising interface-confined environment [48].

Hexosomes can be used as an alternative drug delivery system. Biologically active molecules can be accommodated within the aqueous domains or can be directly coupled to the lipid hydrophobic moieties and thus they can be used to improve solubility of poorly water soluble drugs and to transport therapeutic peptides and proteins [49]. They can be applied in the trans mucosal delivery of hormones, transdermal delivery of peptides, delivery of anti cancer agents and as parenteral or oral sustained drug delivery systems [50]. Studies on multi-compartment liquid crystalline lipid NPs, incorporating omega-3 polyunsaturated fatty acids, have proved to be effective in promoting neurite growth and inhibition of neuronal cell apoptosis [51].

Polymeric Nanoparticles

Polymeric nanoparticles are solid, colloidal particles which may have varying shapes such as spherical, branched or shell structures. They vary in size from 10nm to 100nm. Their main advantage is their size which enables them to penetrate capillaries [12]. Drugs can be introduced into them by encapsulation, attachment and entrapment enabling a sustained drug release system. The extent of uptake by cells depends on the type of polymer used. Polymeric nanoparticles have been used for vaccines and cancer chemotherapeutics for more than 45 years. Some other applications of these nanoparticles include possible recognition of vascular endothelial dysfunction; oral delivery of insulin, brain drug targeting for neurodegenerative disorders such as Alzheimer's disease, topical administration to enhance penetration and distribution in and across the skin barrier, and application as pH-sensitive nanoparticles to improve oral bioavailability of drugs such as cyclosporine A [33]. However, the main concern of polymeric nanoparticles is the possible cytotoxic effect which may prove to be a major drawback.

Transferosomes

Transferosomes are a modified form of liposomes. They are more elastic than liposomes which make them a good vessel for transdermal drug delivery by deforming and passing through even narrow constrictions. The flexibility can be altered by altering the composition and mixing suitable surface active agents [52]. Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility [53]. They are able to entrap a variety of drugs of varying molecular weights. They prevent the degradation of drugs and can be used for controlled drug delivery over a long period of time. They have been used as carriers for other proteins, peptides and even certain interferons. Transferosomes also have their drawbacks like high cost, predisposition to oxidative degradation, chemical instability and concern regarding the purity of the phospholipids used [53].

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Table 1: Advantages and Disadvantages of different types of Nano Drug Delivery systems

Drug Delivery System	Advantages	Disadvantages
Nanoemulsions	Nontoxic, nonirritant, do not damage cells, can penetrate through rough skin, thermodynamically & kinetically stable.	Instability possible due to pH, temperature or Oswald ripening effect, requires large quantity of surfactants
Liposomes	Targeted delivery, toxicity and side effects reduced, biocompatible, biodegradable, drugs protected from degradation	Encapsulation & storage efficiency low, leakage of drugs in some environments, influenced by phagocytosis
Dendrimers	Multivalency, highly branched, accommodate large number of molecules, well defined molecular weight	Controlled release difficult to control from the core and in physiological media.
Ceramic Nanoparticles	Biocompatible, easily engineered according to size and porosity.	Not biodegradable, may accumulate in the body causing harmful effects,
Lipid Nanocarriers	Physical stability, protection of drugs from degradation, controlled and site specific drug delivery.	Prevent drug expulsion, increase in payload
Polymeric Nanoparticles	Controlled release, increase drug stability, per oral route of administration possible for drug delivery	Possible cytotoxic effect
Transferosomes	Can carry wide range of drugs, high entrapment efficiency, better penetration into vesicles, drugs protected from degradation, easy to scale up	Chemically unstable, formulations expensive

Other Drug Delivery Systems

Nanocapsules are hollow structures having a polymer membrane which encapsulates the drug in the cavity. Metallic nanoparticles, as the name suggests are made up of metals such as iron oxide, gold, silver and nickel. They are used for targeted drug delivery wherein their surface can be modified by changing the functional groups according to the application. Carbon nanomaterials include carbon nanotubes and fullerenes. They have been studied for various therapeutic applications; however, the toxicity of carbon nanotubes is a concern.

Polymeric micelles are composed of amphiphilic block copolymers. They have a hydrophobic inner core surrounded by a shell of hydrophilic polymers. They are able to reach targets that are not accessible by liposomes, but have a limited targeting ability due to the low drug loading and low drug incorporation stability.

Ethosomes are similar to liposomes but have high alcohol content. The ethanol from ethosomes' composition plays the same role as the surfactant from the transferosomes, namely disorganizing the lipid bilayer and thus conferring a ten times higher deformability to the particles [54, 55].

CONCLUSION

Some of the common challenges for most drug delivery systems are poor bioavailability, intestinal absorption, sustained and targeted delivery to the site of action, therapeutic effectiveness, adverse effects and fluctuation in the drug plasma concentration. Nanotechnology as a drug delivery system is a step forward to overcome all these challenges. A better understanding and application of nanotechnology in drug delivery systems can play a significant role in improving the efficacy of treatment, patient compliance and make the treatment cost affective for the patients.

REFERENCES

[1] Stylios GK, Giannoudis PV, Wan T. Injury 2005; 36:S6-S13.
[2] The Royal Society and the royal academy of Engineering. Nanoscience and Nanotechnologies. The Royal Society and the Royal Academy of Engineering Report, July 2004. (Accessed February 25, 2014, at http:/www.nanotec.org.uk/finalReport.htm).
[3] Nelson AO, Patrick OO, Ndidi CN. Trop J Pharm Res 2009; 8(3):265-274.
[4] Taniguchi N. Proc Int Conf Prod Eng, Part II, Jao. Soc. Precision Engineering ,Tokyo,(1974)
[5] NIH Roadmap Initiatives. http://nihroadmap.nih.gov/initiatives.asp
[6] Kinam P. J Controll Rel 2007; 120(1-2):1-3.
[7] The nanotechnology opportunity report 2008. www.cientifica.com.
[8] Italia JL, Bhatt DK, Bhardwaj V, Tikoo K, Ravi K. J Control Rel 2007; 119(2):197-206.
[9] Sahoo SK, Labhasetwar V. Drug Disc Today 2003; 8(24):1112-1120.
[10] Panyam J, Labhasetwar V. Adv Drug Del Rev 2003; 55(3):329-347.
[11] Peppas NA. Adv Drug Del Rev 2004; 56:1529-1531.
[12] Brigger I, Dubernet C, Couvreur. Adv Drug Del Rev2004;54:631-651.
[13] Santos-Magalhaes NS, Pontes A, Pereira VMW, Caetano MNP. Int J Pharm 2000; 208(1-2):71-80.
[14] Brusewitz C, Schendler A, Funke A, Wagner T, Lipp R. Int J Pharm 2007; 329:1173-181.
[15] Chiesa M, Garg J, Kang YT, Cheng G. Colloids Surf A: Physicochem and Eng Aspects 2008; 67-72.
[16] Shafiq S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK, & Ali M. European J Pharm Biopharm 2007; 66(2), 227-243.
[17] Myc A, et al. Vaccine 2013; 31(7), 1072-1079.
[18] Gabizon R, et al. Neurol 2014; 82(10 Supplement), P5-236.
[19] Anju S, Senthil K, Mahadevan N. Int J Recent Adv Pharm res 2012; 2(2):54-61.
[20] Soppimath KS, Aminbhavi TM, Kulkarni AR, Rudzinski WE. J Control Rel 2001; 70(1-2)1-20.
[21] Qiu Y, Gao Y, Hu K, Li F. J Control Rel 2008; 129: 144-150.

[22] Jia Y, Joly H, Omri H. Int J Pharm 2008; 359:254-263.
[23] Zaru M, Mourtas S, Klepetsanis P, Fadda AM, Antimisiaris SG. European J Pharm Bio pharm 2007; 76:655-666.
[24] Dhandapani NV, et al. Int J Res Pharm Sci 2013; 4(2), 187-193.
[25] Svenson S, Tomalia DA. Adv Drug Del Rev 2005; 57:2106-2129.
[26] Nelson AO, Patrick OO, Ndidi CN. Trop J Pharm Res 2009; 8(3):275-287.
[27] Boas U, Heegaard PMH. Chem Soc Rev 2004; 33:43-63.
[28] Fischer D, Li Y, Ahlemeyer J, Krieglstein J, Kissel T. Biomaterials 2004; 24: 1121-1131.
[29] N Malik, Wiwattananpatapee R, Klopsche K, Lorenz H, Frey JW, Weener EW et al. J Control Rel 2000; 65:133-148.
[30] Teow HM., Zhou Z, Najlah M, Yusof SR, Abbott NJ, & D'Emanuele A. Int J Pharm 2013; 441(1), 701-711.
[31] Bharatwaj B, Dimovski R, Conti DS, & da Rocha SR. The AAPS J 2014; 1-17.
[32] Nasr M, Najlah M, D'Emanuele A, & Elhissi, A. Int J Pharm 2014; 461(1), 242-250.
[33] Yih TC, Al-fandi M. J cell Biochem 2006; 97:1184-1190.
[34] Jain TK. J Am Chem Soc 1998; 120:11092-11095.
[35] Rosenholm JM, Sahlgren C, & Lindén M. Nanoscale 2010; 2(10), 1870-1883.
[36] Vengala P, Dintakurthi S, & Subrahmanyam CVS. J Pharm Res 2013; 7(6), 540-545.
[37] Medina C, Santos MJ, Radomski A, Corrigan OL, Radomski MW. British J Pharmacol 2007; 150:442-558.
[38] Raposo G, & Stoorvogel W. The J Cell Biol 2013; 200(4), 373-383.
[39] Bobrie A, Colombo M, Raposo G, & Théry C. Traffic 2011; 12(12), 1659-1668.
[40] Chaput N, & Théry C. immunopathol 2011;33(5):419-440.
[41] Muralidharan-Chari V, Clancy JW, Sedgwick A, & D'Souza-Schorey C. J Cell Sci 2010; 123(10), 1603-1611.
[42] Angelova A, Angelov B, Drechsler M, & Lesieur S. Drug Disc Today 2013; 18(23), 1263-1271.
[43] Wissing SA, Kayser O, Muller RH. Adv Drug Del Rev 2004; 56:1257-1272.
[44] Angelova A, Angelov B, Drechsler M, Garamus VM, Lesieur S. Int J Pharm 2013;454:625–632.
[45] Garg G, & Saraf S. Biol Pharm Bull 2007; 30(2), 350-353.
[46] Thadanki M, Srivalli P, & Prabha K. Int J Res Pharm Chem 2011; 1, 535-41.
[47] Angelov B, et al. The J Phy Chem B 2012; 116(26), 7676-7686.
[48] Angelova A, et al. J Drug Del Sci Technol 2005, 15, 108-112.
[49] Hirlekar R, Jain S, Patel M, Garse H, & Kadam V. Curr Drug Del 2012; 7(1), 28-35.
[50] Revathi S, & Dhanaraju M. Int J Pharm Pharm Sci 2014; 6.
[51] Géral C, Angelova A, Lesieur S. Pharmaceutics (Basel, CH), 2013;5:127-167.
[52] Kulkarni PR, Yadav JD, Vaidya KA, Gandhi PP. IJPSR 2011; 2(4):735-741.
[53] Pandey S, Goyani M, Devmurari V, Fakir J. Der Pharmacia Lettre 2009; 1(2):143-150.
[54] Godin B, Touitou E. Crit Rev Ther Drug Carrier Systems 2003; 20(63):102-123.
[55] Jain S, Umamaheshwari RB, Bhadra D, Jain NK. Indian J Pharm Sci 2004; 66(1):72-81.