International Journal of Research in Advent Technology, Vol.4, No.3, March 2016
E-ISSN: 2321-9637
Available online at www.ijrat.org

Non-metallic Nanomaterials and their Potential Biomedical Application

Ashim Chanda[1], Dipyaman Mohanta[2]
Faculty[1] and Ph.D. Scholar[2]
Department of Chemistry, S. S. college, Hailakandi[1]
Department of Chemistry, NIT, Silchar[2]
Email: achanda64@gmail.com[1]

Abstract- Recent advances in nanotechnology have enabled the development of numerous nanomedicines and nanodevices for diagnostic and therapeutic purposes. Their unique size-dependent properties make these materials superior and indispensable in many areas of human activity. However, worries are expressed regarding the exact properties that make these nanomaterials attractive, and questions are raised regarding their potential toxicity, their long-term secondary effects or their biodegradability, particularly when thinking of their use in the (nano)medical field. These questions may be justified by switching to non-metallic nanomaterials instead of metallic ones as they are way superior to the metallic counterpart in terms of toxicology and health hazards. This brief review tries to summaries the potential pharmacological applications of some of the well-known non-metallic nanomaterials.

Keywords - Non-metallic Nanomaterials, Biomedicine, therapeutics, toxicology and health hazard.

1. INTRODUCTION

Nanotechnologies, defined as techniques aimed to conceive, characterize and produce material at the nanometer scale, represent a fully expanding domainof numerous applications both in material science and biomedicine (Lanone et al.,2006; Khanbabaie et al.,2012) [1-2].The use of nanotechnology in drug delivery and imaging in vivo is a rapidly expanding field. The technology could be a beneficial replacement of current practices of site remediation (Lü et al.,2009) [3]. Howeverpotential risks are poorly understood and it may lead unintended consequences.When conventional metallic nanomaterials exposed to inhalation, the specific sizes ofnon bio-compatible nanoscale particles could be deposited in the respiratory tract (Andrew et al., 2010; Sanchez et al.,2012 [4,5]. The tiny particles may facilitate uptake into cells and transcytosis across epithelial and endothelial cells into the blood and lymph circulation to reach potentially sensitive target sites such as bone marrow, lymph nodes, spleen, and heart](Andrew et al., 2010; Buzea et al 2007) [4,6]. Access to the central nervous system and ganglia via translocation along axons and dendrites of neurons could not be denied. There is also possibility of penetrating the skin and distribute via uptake into lymphatic channels. This activity includes a potential for inflammatory and pro-oxidant activity (Mahmoudi et al 2011; Karen et al 2014) [7,8].The non-metallic nanomaterials, on the other hand, are less hazardous and may be considered as good alternatives as long as proper knowledge of the toxic effects of metallic nanomaterialson health and corresponding remedies are established (Buzea et al 2007) [6].

2. CARBON NANOMATERIALS (CNM)

CNM exhibits a wide range of morphologies. The so called 'miracle molecules' fullerenes are made up of 60 or more carbon atoms with a polygonal structure. Carbon nano particles exhibit tubular, fibrous and bead like structures named as carbon Nanotubes (CNT), Carbon Nano fibres (CNF) and Carbon Nano beads(CNB) respectively have been used for their high electrical conductivity and excellent strength (Medina et al, 2007, 56)[9]. These materials are being studied for therapeutic applications. Fullerenes can be functionalized for delivery of drugs and biomolecules across cell membrane to the mitochondria (Xu et al, 2006)[10]. Carbon nanotubes (CNT) unique properties including low cytotoxicity and good biocompatibility attract their use as vector system in target delivery of drugs, proteins and genes (Xu et al, 2006)[10]. CNTs possess the feature of being able to enter a living cell without causing its death or without inflicting other damage. The diameter of CNTs is similar to the diameter of a molecule of DNA, hence can easily traverse through the cell. The use of CNTs in drug delivery systems by the attachment of different functional groups onto the external surface of the nanotubes makes it very ideal candidate. Carbon nano beads (CNB) has recently attracted attention to use as drug carrying vehicle as their smaller and desired sizes can be synthesized by controlling the reaction conditions (Sharon and Sharon, 2007)[11]

Carbon nanofibres(CNF) exist in various forms e.g., straight, coiled, spiral, branched, bamboo-like, octopus etc. it has been found that activation of CNF with KOH results into creating pores on CNF surfaces, thus increasing the available surface area for

functionalization or drug attachment; which is a necessary requirement for drug loading. CNF was successfully loaded with four different molecules aspirin, phenolphthalein, copper sulphate and an anticancer drug, doxorubicin hydrochloride (Parihar et al, 2006[12]; Sharon and Sharon, 2007)[11]. However, toxicity of carbon nanotubes is of concern. Carbon nanotubes may cause inflammatory and fibrotic reactions (Muller, et al, 2006)[13].

3. POLYMERIC NANOPARTICLES

The polymeric nanoparticles are colloidal solid particles with a size range of 10 to 1000nm and they can be spherical, branched or shell structures (Yih and Al-Fandi, 2006)[14]. The first fabrication of nanoparticles was about 35 years ago as carriers for vaccines and cancer chemotherapeutics (Kingsley et al., 2006)[15]. They are developed from non-biodegradable and biodegradable polymers. Their small sizes enable them to penetrate capillaries and to be taken up by cells, thereby increasing the accumulation of drugs at target sites. Drugs are incorporated into nanoparticles by dissolution, entrapment, adsorption, attachment or by encapsulation, and the nanoparticles provide sustained release of the drugs for longer periods, e.g., days and weeks (Arias et al, 2008)[16]. Nanoparticles enhance immunization by prevention of degradation of the vaccine and increased uptake by immune cells (Singh et al, 2006)[17].

To target drugs to site of action, the drug can be conjugated to a tissue or cell specific ligand or coupled to macromolecules that reach the target organs. To target an anticancer agent to the liver, polymeric conjugate nanoparticles which comprised biotin and diamine-terminated poly (ethylene glycol) with a galactose moiety from lactobionic acid were prepared (Kim and Kim, 2003)[18]. Some other applications of nanoparticles include possible recognition of vascular endothelial dysfunction (Ikuta, 2007)[19]; oral delivery of insulin(Damge, 2008)[20]; brain drug targeting for neuron degenerative disorders such as Alzheimer's disease(Härtig, 2003)[21]; topical administration to enhance penetration and distribution in and across the skin barrier(Alvarez-Roman, 2004)[22]; and pH-sensitive nanoparticles to improve oral bioavailability of drugs.(Dai, 2004)[23].

4. LYPOSOMES

Liposomes have the composition of amphiphilic phospholipids and cholesterol that self associate into bilayers encapsulating an aqueous interior. These were first developed about 40 years ago (Kingsley, 2006)[15]. They are small artificial vesicles (50 - 100nm) developed from phospholipidssuch as phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine and phosphatidylserine, which have been used in biology, biochemistry, medicine, food and cosmetics (Kingsley, 2006[15]; Arias, 2008[16]).The characteristics of liposomes are determined by the choice of lipid, their composition, and method of preparation, size and surface charge (Yih and Al-Fandi, 2006)[14]. The potentiality of liposome as drug carrier was first proposed by Gregoriadis due to their ability to prevent degradation of drugs, reduce side effects and target drugs to site of action (Soppimath, 2001)[24]. These are encapsulating hydrophobic drugs in the lipid bilayer and hydrophilic drugs in the aqueous interior. The serious drawbacks of liposomes as drug carrier include low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability (Soppimath, 2001[24]; Lim, 2008[25]).

However, surface modification may confer stability and structure integrity against harsh bio-environment after oral or parenteral administration (Sihorkar and Vyas, 2001)[26]. Surface modification can be achieved by attaching polymers such as poly (methacrylic acid-co-stearyl methacrylate) and polyethylene glycol units to improve the circulation time of liposomes in the blood; and by conjugation to antibodies or ligands such as lectins for target specific drug delivery and stability(Lim, 2008[25]; Sihorkar and Vyas, 2001[26]; Bakowsky, 2008[27]). Applications of liposomes include transdermal drug delivery to enhance skin permeation of drugs with high molecular weight and poor water solubility (Qiu, 2008[28]); a carrier for delivery of drugs, such as gentamicin, in order to reduce toxicity (Jia, 2008[29]); possible drug delivery to the lungs by nebulisation (Zaru, 2007[30]); ocular drug delivery (Budai,2007[31]) and in the treatment of parasitic infections. However, solid lipid nanoparticles provide an effective alternative due to their stability, ease of scalability and commercialisability(Dat, 2007[32]). Other vesicular structures include transferosomes, ethosomes, niosomes and marinosomes which are used mainly for transdermal delivery (Moussaoui, 2002[33]; Barry, 2001a, b[34]). Transferosomes are developed by incorporation of surfactant molecules (edge activators) such as sodium chlorate into liposomes while ethosomes are liposomes that are high in ethanol (up to 45%). Niosomes are vesicles developed from non-ionic surfactants and marinosomes are liposomes produced from a natural marine lipid extract containing a high poly (unsaturated) fatty acid (PUFA) ratio.

5. DENDRIMERS

Dendrimers are nanostructures produced from macromolecules such as polyamidoamine (PAMAM), polypropyleneimine and polyaryl ether; and are highly

branched with an inner core. They are composed of three basic components:

a. A central core.
b. The interior dendritic structure (the branches).
c. The exterior surface (the end groups).

The particle size range is between 1 to 100nm although their sizes are mostly less than 10nm. They bear large numbers of reactive end group functionalities with shielded interior voids possessing low systemic toxicity. About 20 years ago, dendrimer studies centred on their synthesis, physical and chemical properties while exploration of their biological applications was initiated recently (Gilles and Frechet, 2005)[35]. The uniqueness of dendrimers is based on their series of branches, multivalency, well defined molecular weight and globular structure with controlled surface functionality, which enhances their potential as carriers for drug delivery(Gilles and Frechet, 2005[35]; Gupta et al, 2006[36]). The most important advantages enjoyed in using dendrimers in drug delivery are:

a. These can hold drug molecules in their structure and serve as a delivery vehicle.
b. These can enter easily and release drug on target.
c. These do not trigger immune system responses.

Their globular structures and the presence of internal cavities enable drugs to be encapsulated within the macromolecule interior. These have been reported to provide controlled release from the inner core (Gupta, 2006[36]). However, drugs are incorporated both in the interior as well as attached on the surface. Due to their versatility, both hydrophilic and hydrophobic drugs can be incorporated into dendrimers.

Controlled multivalency of dendrimers enables attachment of several drug molecules, targeting groups and solubilising groups onto the surfaces in a well defined manner (Gilles and Frechet, 2005[35]). These are employed due to their size (less than 10nm), ease of preparation, functionality and their ability to display multiple copies of surface groups for biological recognition process (Cloninger, 2002[37]). Water soluble dendrimers can bind and solubilise small molecules and can be used as coating agents to protect drugs and deliver to specific sites. Other applications of dendrimers include catalysis, gene and DNA delivery, biomimetics and as solution phase supports for combinatorial chemistry (Beezer et al, 2003[38]). Some of the drug delivery applications include therapeutic and diagnostic utilization for cancer treatment (Wolinsky and Grinstaff, 2008[39]); enhancement of drug solubility and permeability (dendrimer-drug conjugates) (Najlah, 2007[40]); and intracellular delivery (Najlah and Emanuele, 2006[41]).

6. SOLID LIPID NANOCARRIERS

These nanoparticles are made from solid lipids such as glycerylbehenate (Compritol), stearic triglyceride (tristearin), cetylpalmitate and glycerol tripalmitate (tripalmitin) with a size range of 50 and 1000 nm (Muller et al, 2000[42]; Wissing et al, 2004[43]. Solid lipid nano particles attract attention of research about 10 years ago due to their scalability potential. The lipids employed are well tolerated by the body; large scale production will be cost effective and simple by using high pressure homogenization. Some of the features include good tolerability, site-specific targeting, stability, controlled drug release and protection of liable drugs from degradation (Wissing et al, 2004[43]). However, these are known for insufficient drug loading, drug expulsion after polymorphic transition on storage and relative high water content of the dispersions (Wissing et al, 2004[43]). These nano particles has been studied and developed for parenteral, dermal, ocular, oral, pulmonary and rectal routes of administration (Wissing et al, 2004[43]; Pugli et al, 2008[44]; Cavalli et al, 2002[45]; Casadei et al 2006[46]; Liu et al, 2008[47], Jones et al, 1999[48]). To overcome the limitations, these were modified by introducing a certain amount of liquid lipids with improved drug loading and increased stability on storage thereby reducing drug expulsion (Wissing et al, 2004[43]; Cavalli et al, 2002[45]). These have been explored for dermal delivery in cosmetics and dermatological preparations (Wissing et al, 2004[43]; Cavalli et al, 2002[45]).

7. POLYMERIC MICELLES

Micelles are formed when amphiphilic surfactant or polymeric molecules spontaneously associate in aqueous medium to form core-shell structures or vesicles. Polymeric micelles are formed from amphiphilic block copolymers (5-50nm), such as poly(ethylene oxide)-poly(β-benzyl-L-aspartate) and poly(N-isopropylacrylamide)- polystyrene, and are more stable than surfactant micelles in physiological solutions(Jones et al,1999[48]). They were first proposed as drug carriers about 25 years ago (Jones et al, 1999[48]).

The inner core of a micelle is hydrophobic which is surrounded by a shell of hydrophilic polymers such as poly (ethylene glycol) (Nishiyama and Kataoka, 2006[49]). Their hydrophobic core enables incorporation of poorly water soluble and amphiphilic drugs while their hydrophilic shell and size (<100nm) prolong their circulation time in the blood and increase accumulation in tumoural tissues (Jones et al, 1999[48]). Polymeric micelles are able to reach parts of the body that are poorly accessible to liposomes; accumulate more than free drugs in tumoural tissues

due to increased vascular permeability (Jones et al, 1999[48]). Thus, these can be employed to administer chemotherapeutics in a controlled and targeted manner with high concentration in the tumoural cells and reduced side effects.

However, the targeting ability of them is limited due to low drug loading (Yamamoto et al, 2007[50]; Seow et al, 2007[51]) and low drug incorporation stability (Yamamoto et al, 2007,[50]) which cause the loaded drug to be released before getting to the site of action. Consequently, manipulation of the production parameters and the design of the inner core can improve drug loading and drug incorporation stability (Yamamoto et al, 2007[50]; Seow et al, 2007[51]). Lipid moieties, such as cholesterol and fatty acyl carnitines, can also be employed to impart good stability to the polymeric micelles. This is based on increased hydrophobic interaction between the polymeric chains in the inner core due to presence of fatty acid acyls e.g. diacyllipid (Jones et al, 1999[48]). Polymeric micelles have been employed for targeted and intracellular delivery (Seow et al, 2007[51]), sustained release and parenteral delivery (Jones et al, 1999[48]).

8. NANO CAPSULES

Nanocapsules were developed about 30 years ago. These are spherical hollow structures in which the drug is confined in the cavity and is surrounded by a polymer membrane (Tiark et al, 2001[52]). The particle size ranges between 50 and 300nm are preferred for drug delivery and may be filled with oil which can dissolve lipophilic drugs. They have low density, high loading capacity and are taken up by the mononuclear phagocyte system, and accumulate at target organs such as liver and spleen (Jiang, 2006[53]). Nanocapsules can be employed as confined reaction vessels, protective shell for cells or enzymes, transfection vectors in gene therapy, dye dispersants, carriers in heterogenous catalysis, imaging and drug carriers (Meier, 2000[54]; Reinhold, 2007[55]). These are known to improve the oral bioavailability of protein and peptides which include insulin, elcatonin and salmon calcitonin (Tiark et al, 2001[52]; Prego et al, 2006[56]). Encapsulation of drugs such as ibuprofen (Jiang, 2006[53]) within nanocapsules protects liable drugs from degradation, reduces systemic toxicity, provide controlled release and mask unpleasant taste (Whelan, 2001[57]). The difficulty associated with these are due to their high stability and low permeability, drugs may not be loaded into the capsules after formulation and also the release of the drug at target site. To improve on their permeability, these are made responsive to physiological factors such as pH (Sauer and Meier, 2001[58]).

DNA nano capsule mimics the work mechanism of a virus. These nano capsules contain strands of viral DNA, which they smuggle into cells. Inside the cell, the capsule breaks down, the exposed DNA takes the control over the cell's machinery and triggers the production of compounds that would be expected in a virus attack, thus alerting and training the immune system to recognize them. This technology can also be used to direct living cells to produce 'ordered' compounds such as new proteins or toxins and thus possesses the potentiality to be used in bio warfare. (Fahmy et al, 2005[59]; Kim and Nie, 2005[60]; Biondi et al, 2008[61]).

9. NANOEMULSIONS

Nanoemulsions are emulsions with droplet size below 1μ but usually between 20 and 200nm (Solans et al, 2005[62]; Santos-Magalhaes et al, 2000[63]). Unlike microemulsions which are white in colour due to their light scattering ability, nanoemulsions whose nanosize is often smaller than visible wavelength, are transparent (Solans et al, 2005[62]; Chiesa et al, 2008[64]). Nanoemulsions are biodegradable, biocompatible, easy to produce and used as carriers for lipophilic drugs which are prone to hydrolysis. They are employed as a sustained release delivery system for depot formation via subcutaneous injection (Santos-Magalhaes et al, 2000[63]). 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 (Brusewitz et al, 2007[65]). Nanoemulsions have been studied and developed for parenteral, oral, ocular, pulmonary and dermal deliveries (Solans et al, 2005[62]).

Unlike microemulsions, nanoemulsions are metastable and can be destabilized by Ostwald ripening whereby the small droplets dissolve and their mass is taken up by the large droplets and depletion induced flocculation due to addition of thickening polymers. When this happens, the nanoemulsion becomes opaque and creaming will occur (Sonneville-Aubrun, 2004[66]). However, addition of a small amount of a second oil with low solubility into the aqueous phase and addition of a second surfactant may reduce Ostwald ripening (Solans et al, 2005[62]). Also, a number of factors that should be controlled during production such as 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 (Chiesa et al, 2008[64]).

10. CONCLUSION

Nanomaterials are indeed the most exciting and revolutionary biomedicine in the

pharmacological arena. In spite of some serious health concern, their potentiality to be a good biomedicine can never be denied. However, non-metallic nanomaterials having unique properties like bio-compatibility, non-cytotoxicity, bio-degradability ect.,can overcome these limitations and prove themselves a better alternative biomedicine until a concrete solution to the toxicity of conventional metallic nanomaterials is established.

Acknowledgments

The author is thankful to Mr. abhijit Nath and Dr. Sudip choudhury for useful support and discussion.

REFERENCES

[1] Lanone, Sophie.; Boczkowski, Jorge. (2006) .Biomedical Applications and Potential Health Risks of Nanomaterials: Molecular Mechanisms. Current Molecular Medicine,**13**, pp. 651-663

[2] Reza, Khanbabaie.; Mohsen, Jahanshahi. (2012). Revolutionary Impact of Nanodrug Delivery on Neuroscience. Current nanopharmacology,**10**(4), pp. 370–392.

[3] Jian-Ming, Lu.; Xinwen, Wang,; Christian, Marin-Muller.; Hao,Wang.; Peter, H Lin.; Qizhi, Yao.; Changyi, Chen. (2009). Current advances in research and clinical applications of PLGA-based. Nanotechnology,**9**(4), pp. 325–341.

[4] Andrew, D.Maynard.; David, B. Warheit.; Martin, A. Philbert. (2010). The New Toxicology of Sophisticated Materials: Nanotoxicology and Beyond, Toxicol sci., **120**, pp. 109-129.

[5] Vanesa, C. Sanchez.; Ashish, Jachak.; Robert, H. Hurt.; Agnes, B. Kane. (2012). Biological Interactions of Graphene-Family Nanomaterials – An Interdisciplinary Review.Chem Res Toxicol,**25**(1): pp. 15–34.

[6] Cristina, Buzea.; Ivan, I. Pacheco Blandino.; Kevin, Robbie.(2007). Nanomaterials and nanoparticles.Biointerphases,**4**: pp. 17 – 25.

[7] Morteza, Mahmoudi.; Kayhan, Azadmanesh.; Mohammad, A. Shokrgozar.; W, Shane Journeay.; Sophie, Lauren.(2011):Effect of Nanoparticles on the Cell Life Cycle.Chemicall review,**111** (5), pp. 3407–3432.

[8] Karen, Peynshaert.; Bella, B. Manshian.; Freya, Joris.; Kevin, Braeckmans.; Stefaan, C. De Smedt.; Jo, Demeester.; Stefaan, J. Soenen. (2014): Chemical reviews,**114** (15), pp. 7581–7609.

[9] Medina, C.; Santos-Martinez, MJ.; Radomski, A.; Corrigan, OI.; Radomski, MW. (2007): Nanoparticles: Pharmacological and toxicological significance. Br. J. Pharmacol,**150**, pp. 552-558.

[10] Xu, ZP.; Zeng, QH.; Lu, GQ.; Yu, AB. (2006): Inorganic nanoparticles as carriers for efficient cellular delivery. Chem. Eng. Sc,**61**, pp. 1027-1040.

[11] Sharon and Sharon. (2007): Nano forms of Carbon, 1st Ed., Monad Nanotech Pvt. Ltd,India.

[12] Parihar, S.; Sharon, M.; Sharon, M. (2006): Carbon nanomaterial shows drug delivery promise: Part 1—Selection of carbon nanomaterial and drug loading. Synthesis and reactivity in inorganic. Metal- organic and nano metal chemistry,**36**(1), pp. 107-113.

[13] Muller, J.; Huaux, F.; Lison, D. (2006): Respiratory toxicity of carbon nanotubes: how worried should we be Carbon, **44**(6),pp. 1048-1056.

[14] Yih, TC.; Al-Fandi, M. (2006). Engineered nanoparticles as precise drug delivery systems. J. Cellular Biochemistry, **97**,pp. 1184-1190.

[15] Kingsley, JD.; Dou, H.; Morehead, J.; Rabinow, B.; Gendelman, HE.; Destache, CJ. (2006). Nanotechnology: a focus on nanoparticles as drug delivery system. J. NeuroimmunePharmacol, **1**(3), pp. 340-350.

[16] Arias, JL., Ruiz, MA.; Lopez-viota, M.; Delgado, AV.(2008). Poly (alkylcyanoacrylate) colloidal particles as vehicles for antitumour drug delivery: a comparative study. Colloids and Surfaces B: Biointerfaces, **62**, pp. 64-70.

[17] Singh, J.; Pandit, S.; Bramwell, VW.; Alpar, OH. (2006). Diphtheria toxoid loaded-(β-caprolactone) nanoparticles as mucosal vaccine delivery systems. Methods, **38**, pp. 96-106.

[18] Kim, IS.; Kim, SH.; (2003). Development of polymeric nanoparticulate drug delivery systems: evaluation of nanoparticles based on biotinylated poly (ethylene glycol) with sugar moiety. Int. J. Pharm.,**257**,pp. 195-203.

[19] Ikuta, K.; Mori, T.; Yamamoto, T.; Niidome, T.; Shimokawa, H.; Katayama, Y. (2007). Development of polymeric drug delivery system for recognizing vascular endothelial dysfunction. Bioorganic and Medicinal Chemistry, **16**, pp. 2811-2818

[20] Damge, C.; Maincent, P.; Ubrich, N. (2008). Oral delivery of insulin associated to polymeric nanoparticles in diabetic rats. J. Controlled Release, **117**,pp. 163-170.

[21] Hartig, W.; Paulke, B-R.; Varga, C.; Seege,r J.; Harkany, T.; Kacza, J. (2003). Electron microscopic analysis of nanoparticles delivering thioflavin-T after intrahippocampal injection in mouse: implications for targeting B-amyloid in Alzheimer's disease. Neuroscience Lett., **338**(2), pp. 174-176.

[22] Alvarez-Roman, R.,Naik, A.; Kalia,YN.; Guy, RH.; Fessi, H. (2004). Skin penetration and distribution of polymeric nanoparticles. J. Controlled Release, **99**, pp. 53-62.

[23] Dai, J.; Nagai, T.; Wang, X.; Zhang, T.; Meng, M.; Zhang, Q. (2004). pH-sensitive nanoparticles for improving the oral bioavailability of cyclosporine A. Int. J. Pharm.,**280**, pp. 229-240

[24] Soppimath, KS.; Aminabhavi, TM.; Kulkarni, AR.; Rudzinski, WE. (2001). Biodegradable polymeric nanoparticles as drug delivery devices. J. Controlled Release, **70**(1-2), pp. 1-20.

[25] Lim, HJ.; Cho, EC.; Shim, J.; Kim, D-H.; An, EJ.; Kim, J. (2008). Polymer-associated liposomes as a novel delivery system for cyclodextrin-bound drugs. J. Colloid and Interface Science, **320**, pp. 460-468.

[26] Sihorkar, V.; Vyas, SP. (2001). Potential of polysaccharide anchored liposomes in drugs delivery, targeting and immunization. J. Pharm Pharmaceut Sci.,**4**(2), pp. 138-158.

[27] Bakowsky, H.; Richter, T.; Kneuer, C.; Hoekstra, D.; Rothe, U.; Bendas, G.; Ehrhardt, C.; Bakowsky, U. (2008). Adhesion characteristics and stability assessment of lectin-modified liposomes for site-specific drug delivery. BiochimicaetBiophysicaActa,**1778**, pp. 242-249.

[28] Qiu, Y.; Gao, Y.; Hu, K.; Li, F. (2008). Enhancement of skin permeation of docetaxel: a novel approach combining microneedle and elastic liposomes. J. Controlled Release, **129**: pp. 144-150.

[29] Jia, Y.; Joly, H.; Omri, H. (2008). Liposomes as a carrier for gentamicin delivery: development and evaluation of the physicochemical properties. Int. J. Pharm.,**359**,pp. 254-263.

[30] Zaru, M.; Mourtas, S.; Klepetsanis, P.; Fadda, AM.; Antimisiaris, SG. (2007). Liposomes for drug delivery to the lungs by nebulisation. Eur. J. Pharm. Biopharm., **67**,pp. 655-666.

[31] Budai, L.; Hajdu, M.; Budai, M.; Grof, P.; Beni, S.; Noszal, B.; Klebovich, I.; Antal, I. (2007). Gels and liposomes in optimized ocular drug delivery: studies on ciprofloxacin formulations. Int. J. Pharm,**343**,pp. 34-40.

[32] Dat, AA.; Joshi,MD.; Patravale, VB. (2007). Parasitic diseases: liposomes and polymeric nanoparticles versus lipid nanoparticles. Adv. Drug Deliv. Rev., **59,**pp,505-521.

[33] Moussaoui, N.; Cansell, M.; Denizot, A. (2002).Marinosomes, marine lipid-based liposomes: physical characterization and potential application in cosmetics. Int. J. Pharm.,**242** (1-2),pp. 361-385.

[34] a) Barry, BW. (2001). Novel mechanisms and devices to enable successful transdermal drug delivery. Eur. J. Pharm. Sci., **14**(2),pp. 101-114.

b) Barry, BW. (2001). Is transdermal drug delivery research still important today? Drug Discov. Today, **6**(19),pp. 967-971

[35] Gilles, ER.; Frechet,JMJ. (2005). Dendrimers and dendritic polymers in drug delivery. Drug Discov. Today, **10**(1),pp. 35-43.

[36] Gupta, U.; Agashe, HB.; Asthana, A.; Jain, NK. (2006). A review of in vitro-in vivo investigations on dendrimers: the novel nanoscopicdrug carriers. Nanomedicine:NBM,**2,** pp. 66-73.

[37] Cloninger, MJ. (2002). Biological application of dendrimers. Current Opinion in Chemical Biology, **6**(6),pp. 742-748.

[38] Beezer, AE.; King, ASH.; Martin, IK.; Mitchel, JC.; Twyman, LJ.; Wain, CF. (2003). Dendrimers as potential drug carriers; encapsulation of acidic hydrophobes within water soluble PAMAM derivatives. Tetrahedron, **59**(22),pp. 3873-3880.

[39] Wolinsky, JB.; Grinstaff, MW. (2008). Therapeutic and diagnostic applications of dendrimers for cancer treatment. Adv. Drug Deliv. Rev., **60**,pp. 1037-1055.

[40] Najlah, M.; Freeman, S.; Attwood, D.; D'Emanuele, A. (2007). In vitro evaluation of dendrimerprodrug for oral drug delivery. Int. J. Pharm., **336**, pp. 183-190.

[41] Najlah, M.; D'Emanuele, A. (2006). Crossing cellular barriers using dendrimer nanotechnologies. Curr. Opin. Pharmacology, **6**, pp. 522-527.

[42] Muller, RH.; Mader, K.; Gohla, S. (2000). Solid lipid nanoparticles (SLN) for controlled drug delivery- a review of the state of the art. Eur. J. Pharm. Biopharm., **50**(1),pp. 161-177.

[43] Wissing, SA.; Kayser, O.; Muller, RH. (2004). Solid Lipid nanoparticles for parenteral drug delivery. Adv. Drug Deliv. Rev., **56**(9),pp. 1257-1272.

[44] Puglia, C.; Blasi, P.; Rizza, I.; Schoubben, A.; Bonina, F.; Rossi, C.; Ricc, M. (2008). Lipid nanoparticles for prolonged topical delivery: an in vitro and in vivo investigation. Int. J. Pharm., **357**, pp295-304.

[45] Cavalli, R..; Gasco, MR.; Chetoni, P.; Burgalassi, S.; Saettone, MF. (2002). Solid Lipid nanoparticles (SLN) as ocular delivery system for tobramycin. Int. J. Pharm., **238**,pp. 241-245.

[46] Casadei, MA.; Cerreto, F.; Cesa, S.; Giannuzzo, M.; Feeney, M.; Marianecci, C.; Paolicelli, P. (2006). Solid lipid nanoparticles incorporated in dextran hydrogels: a new drug delivery system for oral formulations. Int. J. Pharm., **325**,pp. 140-146.

[47] Liu, J.; Gong, T.; Fu, H.; Wang, C.; Wang, X.; Chien, Q.; Zhang, Q.; He, Q.; Zhang, Z. (2008). Solid lipid nanoparticles for pulmonary delivery of insulin. Int. J. Pharm., **356**, pp. 333-344.

[48] Jones, MC.; Leroux, JC. (1999). Polymeric micelles-a new generation of colloidal drug carriers. Eur. J. Pharm. Biopharm., **48**(2), pp. 101-111.

[49] Nishiyama, N.; Kataoka, K. (2006). Current state achievements and future prospects of polymeric micelles as nanocarriers for drug and gene delivery. Pharmacology and Therapeutics, **112**, pp. 630-648.

[50] Yamamoto, T.; Yokoyam, M.; Opanasopit, P.; Hayama. A.; Kawano, K.; Maitani, Y. (2007). What are determining factors for stable drug incorporation into polymeric micelle carriers? Consideration on physical and chemical characters of the micelle inner core. J. Controlled Release, **123**,pp. 11-18.

[51] Seow, WY.; Xue, JM.; Yang, YY. (2007). Targeted and intracellular delivery of paclitaxel using multifunctional polymeric micelles. Biomaterials, **28**(9),pp. 1730-1740.

[52] Tiark, F.; Landfester, K.; Antonietti, M. (2001). Preparation of polymeric nanocapsules by miniemuslion polymerization. Langmuir,**17,** pp. 908-918.

[53] Jiang, B.; Hu, L.; Gao, C.; Shen, J. (2006).Crosslinked polysaccharide nanocapsules: preparation and drug release properties. ActaBiomaterialia, **2**, pp. 9-18.

[54] Meier, W. (2000). Polymer nanocapsules. Chem. Soc. Rev., **29**, pp. 295-303.

[55] Reinhold, C. (2007). Smart tailoring of nanocapsules. NanoToday, **2**(2),pp. 13.

[56] Prego, C.; Torres, D.; Fernandez-Megia, E.; Novoa- Carballal, R.; Quinoa, E.; Alonso, MJ. (2006). Chitosan - Peg nanocapsules as new carriers for oral peptide delivery: effect of chitosan pegylation degree. J. Controlled Release, **111**, pp. 299-308.

[57] Whelan, J. (2001). Nanocapsules for controlled delivery. Drug Discov. Today, **6**(23),pp. 1183- 1184.

[58] Sauer, M.; Meier, W. (2001). Responsive nanocapsules. Chem. Commun, pp. 55-56.

[59] Tarek, M. Fahmy.; Peter, M. Fong.; Amit,Goyal.; W, Mark Saltzman. (2005). Materialstoday:Targeted for drug delivery.**8**, pp. 18-26

[60] Kim, GJ.; Nie, S. (2005). Targeted cancer nanotherapy, Materials today, **8**, pp. 28-33.

[61] Biondi, M.; Ungaro, F.; Quagila, F.; Netti,PA. (2008). Controlled drug delivery in tissue engineering, Adv. Drug Deliv. Rev., **60**, pp. 229-242.

[62] Solans, C.; Izquierdo, P.; Nolla, J.; Azemar, N.; Garcia- Celma, MJ. (2005). Nano-emulsion. Curr. Opin. Colloid Interface Sci, **10**, pp. 102-110.

[63] Santos-Magalhaes, NS.; Pontes, A.; Pereira, VMW.; Caetano, MNP. (2000). Colloidal carriers for benzathin penicillin G: nanoemulsions and nanocapsules. Int. J. Pharm., **208** (1-2), pp. 71-80.

[64] Chiesa, M.; Garg, J.; Kang, YT.; Chen, G. (2008). Thermal conductivity and viscosity of water-in-oil nanoemulsions. Colloids Surf. A: Physicochem. Eng. Aspects, **326**, pp. 67-72.

[65] Brusewitz, C.; Schendler, A.; Funke, A.; Wagner, T.; Lipp,R. (2007). Novel poloxamer-based nanoemulsions to enhance the intestinal absorption of active compounds. Int. J. Pharm., **329**, pp. 1173-1181.

[66] Sonneville-Aubrun, O.; Simonnet, JT.; L'Alloret, F. (2004). Nanoemulsions: a new vehicle for skin care products. Adv. Colloid and interface Sci., **108**-109, pp. 145-149.