

An overview on recent new nano-anti-parasitological findings and application

Ramin Farhoudi *

Department of Laboratory Animal Science, Pasteur Institute of Iran, Tehran, Iran

(Received July 13, 2016, Revised October 07, 2016, Accepted November 24, 2016)

Abstract. Till now nanotechnology based anti-parasite pharmaceutical dosage forms development and application is being vastly developed worldwide. The field of nanotechnology involves an array of different areas of expertise with the application of innovative products in Medicine, Engineering, and to a less extent to Veterinary Medicine. In our conclusion, enriched experimental analysis is required, to announce the state of the art outputs to remove negative problems. Animals or human may benefit from nanotechnological products respectively, like vaccines, target recombinant peptides, or novel pharmaceutical alternatives. As a result, it would be desirable to give some energy for thought to drive nanomedical scientific introductions. To create more safe medium to animals and or humans. In this review all aspects of nanoparticles applications in parasitology will be carefully discussed depending on particle charge and size as well as kind of nanoparticles. Perspectives and prospective of nanoparticles in human parasitology will be predicted as well.

Keywords: human parasitology; nanoparticles; anti-parasite application

1. Introduction

Parasites as hazard microorganism regarding human health, which may live temporarily or permanently, on or during the human body. Too many diverse types of parasites were reported in literature which was elected as base for pharmacological human health worldwide. The competition for ascendancy that takes place between the host and therefore the parasite is noted as host-parasite relationship. Consequently, the host might have the favorable position and remains healthy or loses the competition, and a unwellness develops. Human parasites area unit either living thing (protozoa) or cellular (helminthes and arthropods). The parasites might live within the host (endoparasites) or on the host surface (ectoparasites). Endoparasites area unit classified into enteral, chamber or they'll inhabit body tissues inflicting serious health issues. Ectoparasites area unit arthropods that either cause diseases, or act as vectors transmittal alternative parasites. Human evolution and parasitic infections have run hand in hand and most parasitic diseases and ways of their transmission are discovered thousands of years gone. Environmental changes, human behavior and population movement have an excellent impact on transmission, distribution, prevalence, and incidence of parasitic diseases in an exceedingly community. Parasites will invade the frame in numerous ways; through oral route, skin, invertebrate vectors or sexual contact. Host

*Corresponding author, Ph.D., E-mail: raminfarhoudi110@yahoo.com; raminfarhoudi@yahoo.com

defense mechanisms contain resistance that mediates initial protection against infection and adaptational immunity that is simpler. Once parasites have evaded innate host defenses, adaptation in cellular and body substance immune responses area unit promoted against a good array of substance constituents. Nanotechnological sciences (Nanoparticle primarily based Science) virtually means that any technology performed on a nanoscale that has sensible applications to our everyday activities. This encompasses the assembly and usage of physical, chemical, or biological systems at scales starting from individual atoms or molecules to submicron dimensions, likewise because the integration of the ensuing na-nostructures into larger systems (Bhushan 2010).

More recently, the funding for applied science research was within the line of the many billion greenbacks, running at several money/year, principally within the USA, Germany, China and Japan. By 2013, the USA multi-agency National applied science Initiative, has dedicated nearly US\$1.8 billion to applied science, wherever US\$408 million was related to life sciences. the eu Union countries have a replacement money instrument known as Horizon 2020, that came to exchange the successful Seventh Framework Program initiative by the top of 2013. Running from 2014 to 2020, the planned EU\$80 billion analysis cash aims to harness innovation to drive new growth and jobs within the region (European Commission 2013). Since 2011, China's nanotech funding has already surpassed the USA centering the resources into drug delivery and medical diagnostic research (Arangoa *et al.* 2001, Oowaki *et al.* 2016).

Near findings, the Medical committee of the European Science Foundation outlined nanomedicine as "the science and technology of designation, treating, and preventing illness and traumatic injury, of relieving pain, and of conserving and up human health, exploitation molecular tools and molecular data of the human body". At an equivalent time, the United States' National Institutes of Health considers the nanomedicine as "an outgrowth of engineering, which indicates to extremely specific medical interventions at the molecular scale for solidifying illness or repairing broken tissues, like bone, muscle, or nerve".

In parallel, several practical applications on liposomes besd drug delivery emerged from the research work (Gregoriadis and Ryman 1972, Allison and Gregoriadis 1974) whereas albumin nanoparticles were provided for the first at the Johns Hopkins Medical Institution in Baltimore (Zolle *et al.* 1970). Concurrently, other nanoconstructs such as pharmaceutical nano-bio-polymer conjugates were first announced in the 1970s (Ringsdorf 1975) and proposed experimentally in the 1980s (Cossart 2004). Another pioneer was Patrick Couvreur, who described the production of biodegradable nanoparticles made of poly (methyl cyanoacrylate) and poly (ethyl cyanoacrylate) (Couvreur *et al.* 1979). At that time, other types of nanoparticles were also proposed as poly (acrylamide) (Ekman and Friesen 1976) or poly(lactic acid) nanoparticles based molecules (Gurny *et al.* 1981). The first review article about nanoparticles based molecules was explored by scientist named as Kreuter (1978), who also suggested polymeric nanoparticles for pharmaceutical performance that later was adopted by the Encyclopaedia of Pharmaceutical Technology (Kreuter, 1994) and the Encyclopaedia of Nanotechnology (Kreuter 1978) as well.

2. Some classifications

Till currently differing kinds of nanodevices and methods provided nanotechnologies appropriate for pharmaceutical delivery system were planned. In general, these devices might (i) to define a pharmaceutical dosage from degradation; (ii) to enhance drug absorption by facilitating diffusion through epithelial tissue; (iii) modify pharmacokinetic and drug tissue distribution profile;

and/or (iv) to boost animate thing penetration and distribution (Couvreur *et al.* 2006). Additionally, too many numbers of them have also additionally found helpful to boost the performance of imaging as molecular probes.

3. Nanocrystals based pharmaceuticals

Nanocrystals based pharmaceuticals, constructing of pure medicine products and a minimum of upper-surface active biomaterials needed for stabilization as well as square measure a carrier-free submicron mixture Nanocrystals based pharmaceuticals delivery with a mean particle size within the metric linear unit vary, generally ranging different between ten and a thousand nm (Müller 2001). Dispersion of Nanocrystals based pharmaceuticals in liquid media mostly water based results in the thus known as “nano-based-suspensions” (Möschwitzer 2013). The preparation of nanometer-sized Nanocrystals based pharmaceuticals is especially being fascinated for the formulation of nanomolecules with an awfully low liquid dispensability and good soluble parameters. It's calculable and noted that around four-hundredth of active recognized bio-nanomaterials during within the performed combinatorial screening programs square measure tough to formulate as a results of their lack of great hydrophilic solubility (Lipinski 2002). Once these molecules square measure developed victimisation typical approaches, the performance of the drug is frequently erratic and extremely variable, together with poor bioavailability, lack of fed/fasted equivalence and lack of best pharmaceutical dosing (Merisko-Liversidge *et al.* 2003, Merisko-Liversidge and Liversidge 2008).

4. Macromolecular nanoparticles

The term ‘polymer therapeutics’ encompasses at least three distinct classes of agents including polymer–drug conjugates, polymer–protein conjugates and supramolecular drug-delivery systems (i.e., polymer micelles, polyplexes and dendrimers).

5. A new kind: Dendrimeric structure

Dendrimers are higher monodisperse nano-molecules combining a number of unique parameters including (i) hyper branched and three-dimensional structural engineering; (ii) considering have no more significant polydispersity; and (iii) very good liability and functionality (Paleos *et al.* 2010). One of the first family of nano-dendrimers was recognized as the poly(amidoamine)s (PAMAM) (Klajnert and Bryszewska 2001, Svenson and Tomalia 2005). Another one so-called pamamos (polyamidoamine-orgasilicon derivatives), poly(propyleneimine) dendrimers, a diverse structural and Frechet-type dendrimers (Sakthivel and Florence 2003, Zhou *et al.* 2008). Dendrimers showed three distinguished engineering ingredients, such as (i) one core as base; (ii) subsequent interior or surface layers (generations depending on their repetitions), which conjugated on the mentioned core (Zhou *et al.* 2008). Considering all parameters of dendrimers such family o nanobiomaterials showed powerful bioavailability as well as biocompatibility in anti-parasite pharmaceutical assays (Yiyun and Tongwen 2005, D’Emanuele and Attwood 2005), by loading or conjugation of pharmaceuticals to their 3D structure interior or superior of molecules.

6. Nanopolymeric complexes

Complexes of chemically designed polymers with desoxyribonucleic acid square measure known as polyplexes worldwide. Most of such chemically screened polyplexes consisted ion nano-polymers and its chemical synthesis is elaborately regulated by routine ionic interactions with the negatively charged surface phosphate teams of naked desoxyribonucleic acid or diverse sequence biomaterial such as oligonucleotides which sometimes called lipoplexes in literature such chemically dsignated structures allow to a significant prevent desoxyribonucleic acid from First State-gradation (metabolize pathway) and makes easy its entry into the targeted cell (Tros de Ilarduya *et al.* 2010). Very diverse and different ion chemically designe nano-polymers were elaborately projected as sequence vehicles for interacellular gene delivery purposes in accom-paining diethylaminoethyl (DEAE)-dextran or poly(2-dimethylaminoethyl methacrylamide) and or poly-l-lysine, polyethylenimines (Sun *et al.* 2010).

Nano-lipid capsulated nano-biomaterials are highly considered as first line of research and clinical trials due to mimicing physiological lipoproteins (Huynh *et al.* 2009).

7. SLN nanomedical applications

SLN defined as solid lipid nanoparticulated materials were generated at the start of the Nineteen Nineties as another pharmaceutical effective vehicle for applications in emulsions, liposomes and chemical compound nanoparticles. Such nanomaterials were effectively used in pharmacological war against many diseases like viral and parasitological malignancies. Such nano-bioparticles made of solid lipids which were stable and solid at human body temperature and surfactants were vastly employed for their structural stabilizations (Pardeike *et al.* 2009, Müller and Lucks 1996).

8. Nanobiomaterial related immunological applications

The importance of vaccination within the management of infectious diseases and malignancies is unquestionable and of high global attraction and interest. Lastly within the past decades, different novel approaches in immunogen constructing have well shown to supply vital blessings over ancient ones as well as anti-parasites vaccine discovery. Such novel generation of nano-vaccines contains alternative outlined antigens, indicated to as “subunit vaccines” as well as nano-biomaterial. In such cases nanoparticulated nanobiopolymer was chemically conjugated to immunogen to produce nano-vaccine. In similar ways immunogenes linked chemically to hapten carrier protein. Difference between mentioned methodologies is the use of nanoparticle instead of carrier protein only other parts even synthesis is the same. Lower molecular weight related to nanoparticles (like PLGA, Dendrimers) makes such types of nano-vaccine very effective considering lower toxicological features comparing to general models (Storni *et al.* 2005).

Another fascinating example which indicated in literature was supported the application of tetanus antigen related (chemically conjugated) to sulfobutylated poly(vinylalcohol)-linked-PLGA nanoparticles, which has a very promising parameters like orally immunone system rasing response of upper specific immune globulin and immunoglobulin titers significantly more than management animal when once immunised by the intraperitoneal route (Jung *et al.* 2001). Another

reports suggested a very potent role for nanovaccines in HIV as well as parasitological applications as well (Le Buanec *et al.* 2001).

9. Conclusions

The application and announcement of a novel pharmaceutical delivery based antiviral or antiparasites favoring longer affected dose intervals (sustaining release dosage form in therapy or vaccinations) and additionally the significant rise in pharmaceuticals effectiveness against parasite's microorganism unit of measurement was elected as base variety of the most issues evaluated and assessed in nano-parasitology. Different types of targeting delivery against pathogens by nano-particulated systems (passive or non-passive) has been explored mistreatment liposomes, solid molecule nanoparticles and hydrophobic compound nanoparticles (Santos-Magalhães and Mosqueira 2010). Nanoparticles carriers have collectively improved the bioavailability and drug property, even in very subtle treatments like cerebral infection by *Plasmodium falciparum* infection (Waknine-Grinberg *et al.* 2013). Furthermore, a very usual difficulty and important problems in parasitology research equally as, to the Veterinary counterpart is regarding the progress and development of pharmaceutical resistance due to weak delivery of drugs to infected cells, as a result, parasites or viruses or microbe have enough times to develop a way to remove pharmaceutical effective dose at pharmaco-dynamically level at cellular and molecular interactions (Molento 2009). Nanoparticles may offer a potent tool to cut back the danger of resistance to ancient medication resulting from good cellular uptake and providing therapeutic pharmaceutical dosage forms at cellular level, avoiding variety of the resistance mechanisms, to enhance pharmaceutical bioavailability as well as potentiating the target of the potential cellular and molecular treatment. Some newer anti-parasitic medication will even be generated with the same mentioned technology similar to the case of titanium oxide nanoparticles was introduced as silver nanoparticles (Allahverdiyev *et al.* 2013), which has very unique cellular permeable size as well as drug loading liability. Comparing to Pegylated or polyplex nanoparticles suggested new fantastic arrays to make better significant changes in the biodistribution of a nominated anti-microorganism agent or pharmaceuticals respectively. Nanoparticles can facilitate huge amounts of medication and therefore provide effective treatments of ectoparasites, by lubricated the drug-parasite expose and subsequent interaction. The pharmacognosiological effectiveness of merchandise was also largely improved, similar to the recent reported treatment of antiparasitic silver nanoparticles concurrent therapy by application of such phytomedicines as *Cissus quadrangularis* against *Hippobosca aculata* and *Rhipicephalus (Boophilus) micro plus* (Santhoshkumar *et al.* 2012). Next literature example is regarding to explain one another nanoparticle drug delivery based on gold coated glass particles commonly depicted as nanoshells may facilitate pharmaceutical to target delivery to scale up the parasites therapeutically results and facilitating the infected cellular target by parasite and providing better drug delivery, physically destroying the developed infection. Nanotechnology, nanobiotechnology and nanomedicine will even permit the event of nanoparticle mediated adjuvants for veterinary parasite vaccines, significant boosting their present low liabilities. Vaccines developing and designing based on nanoparticle's applications (Nano-vaccines) as adjuvants have also shown extra potential to induce classical vaccine effects providing by nano-supermolecule and cellular response by at identical time activating the most natural phenomenon difficult class I and class II pathways or enhance the matter visibility and their amount, to satisfy the host system (Joe *et al.* 2016, Kumar *et al.* 2015,

Thakkar *et al.* 2016). Curcumin as a phyto-medical based agent has also shown a vast potential in antimalarial pharmaceutical therapy; but such agent has very low water solubility and as a result fewer bioavailability caused significant attenuate the in vivo effectualness. By the use of nanoparticles can overcome such difficulties and increase in biological availability and effectiveness as well (Oowaki *et al.* 2016).

References

- Agrawal, S.K., Sanabria-DeLong, N., Coburn, J.M., Tew, G.N. and Bathia, S.R. (2006), "Novel drug release profiles from micellar solutions of PLAPEOPLA triblock copolymers", *J. Control. Release*, **112**(1), 64-71.
- Agüeros, M., Ruiz-Gaton, L., Vauthier, C., Bouchemal, K., Espuelas, S., Ponchel, G. and Irache, J.M. (2015), "Combined hydroxypropyl- β -cyclodextrin and poly(anhydride) nanoparticles improve the oral permeability of paclitaxel", *Eur. J. Pharm. Sci.*, **38**(4), 405-413.
- Agüeros, M., Zabaleta, V., Espuelas, S., Campanero, M.A. and Irache, J.M. (2010), "Increased oral bioavailability of paclitaxel by its encapsulation through complex formation with cyclodextrins in poly(anhydride) nanoparticles", *J. Control. Release*, **145**(1), 2-8.
- Alam, S., Pandai, J.J., Mukherjee, T.K. and Chauhan, V.S. (2016), "Short peptide based nanotubes capable of effective curcumin delivery for treating drug resistant malaria", *J. Nanobiotechnol.*, **14**, 26.
DOI: 10.1186/s12951-016-0179-8
- Allahverdiyev, A.M., Bagirova, M., Abamor, E.S., Ates, S.C., Koc, R.C., Miraloglu, M., Elcicek, S., Yaman, S. and Unal, G. (2013), "The use of platensimycin and platencin to fight antibiotic resistance", *Infect. Drug Resist.*, **6**, 99-114.
- Allemann, E., Gurnay, R. and Doelker, E. (1992), "Preparation of aqueous polymeric nanodispersions by a reversible salting-out process, influence of process parameters on particle size", *Int. J. Pharm.*, **87**(1-3), 247-253.
- Allison, A.C. and Gregoriadis, G. (1974), "Liposomes as immunological adjuvants", *Nature*, **252**, 252.
- Ambrosi, A., Yamamoto, H. and Kreuter, J. (2005), "Body distribution of polysorbate-80 and doxorubicin-loaded [¹⁴C]poly(butyl cyanoacrylate) nanoparticles after i.v. administration in rats", *J. Drug Target.*, **13**, 535-542.
- Arango, M.A., Campanero, M.A., Renedo, M.J., Ponchel, G. and Irache, J.M. (2001), "Gliadin nanoparticles as carriers for the oral administration of lipophilic drugs. Relationship between bioadhesion and pharmacokinetics", *Pharm. Res.*, **18**(11), 1521-1527.
- Berton, M., Turelli, P., Trono, D., Stein, C.A., Allemann, E. and Gurny, R. (2001), "Inhibition of HIV-1 in cell culture by oligonucleotide-loaded nanoparticles", *Pharm. Res.*, **18**(8), 1096-1101.
- Bhushan, B. (2010), "Nanomechanical characterization of skin and skin cream", *J. Microscopy*, **240**(2), 135-144.
- Bielinska, A.U., Kukowska-Latallo, J.F., Johnson, J., Tomalia, D.A. and Baker, J.R. (1996), "Regulation of in vitro gene expression using antisense oligonucleotides or antisense expression plasmids transfected using starburst PAMAM dendrimers", *Nucleic Acids Res.*, **24**(11), 2176-2182.
- Birrenbach, G. (1973), "Über Mizellpolymerisate, mögliche Einschlussverbindungen (Nanokapseln) und deren Eignung als Adjuvantien", Ph.D. Thesis, Dissertation; ETH Nr. 5071.
- Birrenbach, G. and Speiser, P.P. (1976), "Polymerized micelles and their use as adjuvants in immunology", *J. Pharm. Sci.*, **65**(12), 1763-1766.
- Bivas-Benita, M., Lin, M.Y., Bal, S.M., van Meijgaarden, K.E., Franken, K.L., Friggen, A.H., Junginger, H.E., Borchard, G., Klein, M.R. and Ottenhoff, T.H. (2009), "Pulmonary delivery of DNA encoding Mycobacterium tuberculosis latency antigen Rv1733c associated to PLGA-PEI nanoparticles enhances T cell responses in a DNA prime/protein boost vaccination regimen in mice", *Vaccine*, **27**(30), 4010-4017.
- Bivas-Benita, M., Laloup, M., Versteyhe, S., Dewit, J., De, B.J., Jongert, E. and Borchard, G. (2003), "Generation of Toxoplasma gondii GRA1 protein and DNA vaccine loaded chitosan particles: preparation,

- characterization, and preliminary in vivo studies”, *Int. J. Pharm.*, **266**(1-2), 17-27.
- Borges, O., Tavares, J., de Sousa, A., Borchard, G., Junginger, H.E. and Cordeiroda-Silva, A. (2007), “Evaluation of the immune response following a short oral vaccination schedule with hepatitis B antigen encapsulated into alginate-coated chitosan nanoparticles”, *Eur. J. Pharm. Sci.*, **32**(4-5), 278-290.
- Bottomley, K. (2006), “Nanotechnology for drug delivery: A validated technology?”, *Drug Deliv. Rep.* (Autumn/Winter), 20-21.
- Boudad, H., Legrand, P., Appel, M., Coconier, M.H. and Ponchel, G. (2001), “Formulation and cytotoxicity of combined cyclodextrin poly(alkylcyanoacrylate) nanoparticles on Caco-2 cells monolayers intended for oral administration of saquinavir”, *STP Pharm. Sci.*, **11**(5), 369-375.
- Bowman, K. and Leong, K.W. (2006), “Chitosan nanoparticles for oral drug and gene delivery”, *Int. J. Nanomed.*, **1**(2), 117-128.
- Cavalli, R., Gasco, M.R., Chetoni, P., Burgalassi, S. and Saettone, M.F. (2002), “Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin”, *Int. J. Pharm.*, **238**(1-2), 241-245.
- Chen, S.C., Jones, D.H., Fynan, E.F., Farrar, G.H., Clegg, J.C., Greenberg, H.E. and Herrmann, J.E. (1998), “Protective immunity induced by oral immunization with a rotavirus DNA vaccine encapsulated in microparticles”, *J. Virol.*, **72**(7), 5757-5761.
- Cheng, Y. and Xu, T. (2005), “Dendrimers as potential drug carriers. Part I. Solubilization of non-steroidal anti-inflammatory drugs in the presence of polyamidoamine dendrimers”, *Eur. J. Med. Chem.*, **40**(11), 1188-1192.
- Chiannikulchai, N., Ammoury, N., Caillou, B., Devissaguet, J.P. and Couvreur, P. (1990), “Hepatic tissue distribution of doxorubicin loaded nanoparticles after i.v. administration in reticulosarcoma M 5076 metastasis-bearing mice”, *Cancer Chemother. Pharmacol.*, **26**(2), 122-126.
- Conway, M.A., Madrigal-Estebas, L., McClean, S., Brayden, D.J. and Mills, K.H. (2001), “Protection against Bordetella pertussis infection following parenteral or oral immunization with antigens entrapped in biodegradable particles: Effect of formulation and route of immunization on induction of Th1 and Th2 cells”, *Vaccine*, **19**(15-16), 1940-1950.
- Cossart, P. (2004), “Bacterial invasion: A new strategy to dominate cytoskeleton plasticity”, *Dev. Cell*, **6**(3), 314-315.
- Couvreur, P., Kante, B., Roland, M., Guiot, P., Baudin, P. and Speiser, P. (1979), “Polycyanoacrylate nanocapsules as potential lysosomotropic carriers – preparation, morphological and sorptive properties”, *J. Pharm. Pharmacol.*, **31**(1), 331-332.
- Couvreur, P. and Puisieux, F. (1993), “Nano- and micro-particles for the delivery of polypeptides and proteins”, *Adv. Drug Deliv. Rev.*, **10**(2-3), 141-162.
- Couvreur, P., Barratt, G., Fattal, E., Legrand, P. and Vauthier, C. (2002), “Nanocapsule technology: A review”, *Crit. Rev. Ther. Drug Carrier Syst.*, **19**(2), 99-134.
- Couvreur, P., Gref, R., Andrieux, K. and Malvy, C. (2006), “Nanotechnologies for drug delivery: Application to cancer and autoimmune diseases”, *Prog. Solid State Chem.*, **34**(2-4), 231-235.
- Couvreur, P. and Vauthier, C. (2006), “Nanotechnology: Intelligent design to treat complex disease”, *Pharm. Res.*, **23**(7), 1417-1450.
- Cronkhite, R.I. and Michael, J.G. (2004), “Sub-compartmentalization of the gastrointestinal (GI) immune system determined with microbeads that differ in release properties”, *Vaccine*, **22**(17-18), 2106-2115.
- Croy, S.R. and Kwon, G.S. (2006), “Preparation of small-sized particles from vicilin (vegetal protein from *Pisum sativum* L.) by coacervation”, *Eur. J. Pharm. Biopharm.*, **42**(1), 36-41.
- D’Emanuele, A. and Attwood, D. (2005), “Dendrimer-drug interactions”, *Adv. Drug Deliv. Rev.*, **57**(15), 2147-2162.
- Ekman, P. and Friesen, W.V. (1976), *Pictures of Facial Affect*, Consulting Psychologists, Palo Alto, CA, USA.
- Ezpeleta, I., Irache, J.M., Stainmesse, S., Chabenat, C., Gueguen, J., Popineau, Y. and Orecchioni, A.M. (1996b), “Gliadin nanoparticles for the controlled release of all-trans retinoic acid”, *Int. J. Pharm.*, **131**(2), 191-200.
- Fattal, E., Youssef, M., Couvreur, P. and Andreumont, A. (1989), “Treatment of experimental salmonellosis

- in mice with ampicillin-bound nanoparticles”, *Antimicrob. Agents Chemother.*, **33**(9), 1540-1543.
- Fattal, E. and Vauthier, C. (2002), “Nanoparticles as drug delivery systems”, In: *Encyclopedia of Pharmaceutical Technology*, (J. Swarbrick, J.C. Boylan Eds.), Marcel Dekker, New York, NY, USA, pp. 1864-1882.
- Fernandez, L., Gonzalez, M., Cerecetto, H., Santo, M. and Silber, J.J. (2006), “Solubilization and release properties of dendrimers. Evaluation as prospective drug delivery systems”, *Supramol. Chem.*, **18**(8), 633-643.
- Fessi, H., Puisieux, F., Devissaguet, J.P., Ammoury, N. and Benita, S. (1989), “Nanocapsule formation by interfacial deposition following solvent displacement”, *Int. J. Pharm.*, **55**(1), R1-R4.
- Florence, A.T., Hillery, A.M., Hussain, N. and Jani, P.U. (1995), “Nanoparticles as carriers for oral peptide absorption: studies on particle uptake and fate”, *J. Control. Release*, **36**(1-2), 39-46.
- Florindo, H.F., Pandit, S., Lacerda, L., Gonçalves, L.M.D., Alpar, H.O. and Almeida, A.J. (2009), “The enhancement of the immune response against *S. equi* antigens through the intranasal administration of poly-epsilon-caprolactone-based nanoparticles”, *Biomaterials*, **30**(5), 879-891.
- Föger, F., Noonpakdee, W., Loretz, B., Joojuntr, S., Salvenmoser, W., Thaler, M. and Bernkop-Schnürch, A. (2006), “Inhibition of malarial topoisomerase II in Plasmodium falciparum by antisense nanoparticles”, *Int. J. Pharm.*, **319**(1-2), 139-146.
- Fouarge, M., Dewulf, M., Couvreur, P., Rolland, M. and Vranckx, H. (1989), “Development of dehydroemetine nanoparticles for the treatment of visceral leishmaniasis”, *J. Microencapsul.*, **6**(1), 29-34.
- Fréchet, J.M.J. (1994), “Functional polymers and dendrimers: Reactivity, molecular architecture, and interfacial energy”, *Science*, **263**(5154), 1710-1715.
- Fresta, M., Fontana, G., Bucolo, C., Cavallo, G., Giammona, G. and Puglisi, G. (2001), “Ocular tolerability and in vivo bioavailability of poly(ethylene glycol) (PEG)-coated polyethyl-2-cyanoacrylate nanosphere-encapsulated acyclovir”, *J. Pharm. Sci.*, **90**(3), 288-297.
- Gbadamosi, J.K., Hunter, A.C. and Moghimi, S.M. (2002), “PEGylation of microspheres generates a heterogeneous population of particles with differential surface characteristics and biological performance”, *FEBS Lett.*, **532**(3), 338-344.
- Gomez, S., Gamazo, C., San Roman, B., Vauthier, C., Ferrer, M. and Irache, J.M. (2006), “Development of a novel vaccine delivery system based on Gantrez nanoparticles”, *J. Nanosci. Nanotechnol.*, **6**(9-10), 3283-3289.
- Gomez, S., Gamazo, C., San Roman, B., Ferrer, M., Sanz, M.L., Espuelas, S. and Irache, J.M. (2008), “Allergen immunotherapy with nanoparticles containing lypopolysaccharide from *Brucella ovis*”, *Eur. J. Pharm. Biopharm.*, **70**(3), 711-717.
- Gomez, S., Gamazo, C., San Roman, B., Grau, A., Espuelas, S., Ferrer, M., Sanz, M.L. and Irache, J.M. (2009), “A novel nanoparticulate adjuvant for immunotherapy with *Lolium perenne*”, *J. Immunol. Methods*, **348**(1-2), 1-8.
- Gradishar, W.J., Tjulandin, S., Davidson, N., Shaw, H., Desai, N., Bhar, P., Hawkins, M. and O’Shaughnessy, J. (2005), “Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer”, *J. Clin. Oncol.*, **23**(31), 7794-7803.
- Greco, F. and Vicent, M.J. (2009), “Combination therapy: Opportunities and challenges for polymer–drug conjugates as anticancer nanomedicines”, *Adv. Drug Deliv. Rev.*, **61**(13), 1203-1213.
- Green, M.R., Manikhas, G.M., Orlov, S., Afanasyev, B., Makhson, A.M., Bhar, P. and Hawkins, M.J. (2006), “Abraxane, a novel cremophor-free, albuminbound particle form of paclitaxel for the treatment of advanced nonsmall-cell lung cancer”, *Ann. Oncol.*, **17**(8), 1263-1268.
- Gref, R., Minamitake, Y., Peracchia, M.T., Trubetskoy, V., Torchilin, V. and Langer, R. (1994), “Biodegradable long-circulating polymeric nanospheres”, *Science*, **263**(5153), 1600-1603.
- Gregoriadis, G. and Ryman, B.E. (1972), “Lysosomal localization of β -fructofuranosidase-containing liposomes injected into rats. Some implications in the treatment of genetic disorders”, *Biomech. J.*, **129**(1), 123-133.
- Gurny, R., Peppas, N.A., Harrington, D.D. and Banker, G.S. (1981), “Development of biodegradable and

- injectable lattices for controlled release of potent drugs”, *Drug Dev. Ind. Pharm.*, **7**(1), 1-25.
- Huynh, N.T., Passirani, C., Saulnier, P. and Benoit, J.P. (2009), “Lipid nanocapsules: A new platform for nanomedicine”, *Int. J. Pharm.*, **379**(2), 201-209.
- Joe, Y.H., Park, D.H. and Hwang, J. (2016), “Evaluation of Ag nanoparticle coated air filter against aerosolized virus: Anti-viral efficiency with dust loading”, *J. Hazard Mater.*, **301**, 547-553.
- Jung, G., Brandl, M., Eisner, W., Fraunberger, P., Reifemberger, G., Schlegel, U., Wiestler, O.D., Reulen, H.J. and Wilmanns, W. (2001), “Local immunotherapy of glioma patients with a combination of 2 bispecific antibody fragments and resting autologous lymphocytes: Evidence for in situ t-cell activation and therapeutic efficacy”, *Int. J. Cancer*, **91**(2), 225-230.
- Klajnert, B. and Bryszewska, M. (2001), “Dendrimers: Properties and applications”, *Acta Biochemica Polonica*, **48**(1), 199-208.
- Kreuter, J. (1978), Book Chapter: New Generation Vaccines; Volume 261 of the series NATO ASI Series, Nanoparticles as Potent Adjuvants for Vaccines, pp. 73-81.
- Kumari, A., Yadav, S.K. and Yadav, S.C. (2010), “Biodegradable polymeric nanoparticles based drug delivery systems”, *Colloid Surf. B: Biointerf.*, **75**(1), 1-18.
- Kwon, G.S. (2003), “Polymeric micelles for delivery of poorly water-soluble compounds”, *Crit. Rev. Ther. Drug Carrier Syst.*, **20**(5), 357-403.
- Kumar, R., Ray, P.C., Datta, D., Bansal, G.P., Angov, E. and Kumar, N. (2015), “Nanovaccines for malaria using Plasmodium falciparum antigen Pfs25 attached gold nanoparticles”, *Vaccine*, **33**(39), 5064-5071. DOI: 10.1016/j.vaccine.2015.08.025
- Labhasetwar, V., Song, C., Humphrey, W., Shebuski, R. and Levy, R.J. (1998), “Arterial uptake of biodegradable nanoparticles: Effect of surface modifications”, *J. Pharm. Sci.*, **87**(10), 1229-1234.
- Lasic, D.D. (1998), “Novel applications of liposomes”, *Trends Biotechnol.*, **16**(7), 307-321.
- Le Buanec, H., Vetu, C., Lachgar, A., Benoit, M.A., Gillard, J., Paturance, S., Aucouturier, J., Gane, V., Zagury, D. and Bizzini, B. (2001), “Induction in mice of anti-Tat mucosal immunity by the intranasal and oral routes”, *Biomed. Pharmacother.*, **55**(6), 316-320.
- Le Buanec, H., Vetu, C., Lachgar, A., Benoit, M.A., Gillard, J., Paturance, S., Aucoututier, J., Gane, V., Zaguri, D., Miyake, A., Akagi, T., Enose, Y., Ueno, M., Kawamura, M., Horiuchi, R., Hiraishi, R., Adachi, M., Srizawa, T., Narayan, O., Akshi, M., Baba, M. and Hayami, M. (2004), “Induction of HIV-specific antibody response and protection against vaginal SHIV transmission by intranasal immunization with inactivated SHIV-capturing nanospheres in macaques”, *J. Med. Virol.*, **73**(3), 368-377.
- Merisko-Liversidge, E.M. and Liversidge, G.G. (2008), “Drug nanoparticles: Formulating poorly water-soluble compounds”, *Toxicol. Pathol.*, **36**(1), 43-48.
- Merisko-Liversidge, E., Liversidge, G.G. and Cooper, E.R. (2003), “Nanosizing: A formulation approach for poorly-water-soluble compounds”, *Eur. J. Pharm. Sci.*, **18**(2), 113-120.
- Moghimi, S.M. and Hunter, A.C. (2000), “Poloxamers and poloxamines in nanoparticle engineering and experimental medicine”, *Trends Biotechnol.*, **18**(10), 412-420.
- Moghimi, S.M., Hunter, A.C. and Murray, J.C. (2001), “Long-circulating and target-specific nanoparticles: Theory to practice”, *Pharmacol. Rev.*, **53**(2), 283-318.
- Moghimi, S.M. and Szebeni, J. (2003), “Stealth liposomes and long circulating nanoparticles: critical issues in pharmacokinetics, opsonization and protein-binding properties”, *Prog. Lipid Res.*, **42**(6), 463-478.
- Molento, M.B. (2009), “Parasite control in the age of drug resistance and changing agricultural practices”, *Vet Parasitol*, **163**(3), 229-334.
- Möschwitzer, J.P. (2013), “Drug nanocrystals in the commercial pharmaceutical development process”, *Int. J. Pharmaceutics*, **453**(1), 142-156.
- Mozarafi, M.R. (2005), “Liposomes: An overview of manufacturing techniques”, *Cell. Mol. Biol. Lett.*, **10**, 711-719.
- Müller, T. (2001), “Identification of plant-associated enterococci”, *J. Appl. Microbiol.*, **91**(2), 268-278
- Müller, R.H., Radtke, M. and Wissing, S.A. (2002), “Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations”, *Adv. Drug Deliv. Rev.*, **54**, S131-S155.
- Munn, L.L. (2003), “Aberrant vascular architecture in tumours and its importance in drug-based therapies”,

- Drug Discov. Today*, **8**(9), 396-403.
- Murillo, M., Gamazo, C., Irache, J.M. and Goñi, M.M. (2002), "Polyester microparticles as a vaccine delivery system for brucellosis: Influence of the polymer on release, phagocytosis and toxicity", *J. Drug Target.*, **10**(3), 211-219.
- Nagpal, K., Singh, S.K. and Mishra, D.N. (2016), "Chitosan nanoparticles: A promising system in novel drug delivery", *Chem. Pharm. Bull. (Tokyo)*, **58**(11), 1423-1430.
- Nahar, M. and Jain, N.K. (2009), "Preparation, characterization and evaluation of targeting potential of amphotericin B-loaded engineered PLGA nanoparticles", *Pharm. Res.*, **26**, 2588-2598.
- Nayak, B., Panda, A.K., Ray, P. and Ray, A.R. (2009), "Formulation, characterization and evaluation of rotavirus encapsulated PLA and PLGA particles for oral vaccination", *J. Microencapsul.*, **26**(2), 154-165.
- Nechaeva, E.A., Varaksin, N., Ryabicheva, T., Smolina, M., Kolokoltsova, T., Vilesov, A., Aksenova, N., Stankevich, R. and Isidorov, R. (2001), "Approaches to development of microencapsulated form of the live measles vaccine", *Ann. N. Y. Acad. Sci.*, **944**, 180-186.
- Nechaeva, E. (2002), "Development of oral microencapsulated forms for delivering viral vaccines", *Exp. Rev. Vaccines*, **1**(3), 385-397.
- Niwa, T., Takeuchi, H., Hino, T., Kunou, N. and Kawashima, Y. (1993), "Preparations of biodegradable nanospheres of water-soluble and insoluble drugs with dl-lactide/glycolide copolymer by a novel spontaneous emulsification solvent diffusion method, and the drug release behaviour", *J. Controlled Release*, **25**(1-2), 89-98.
- Noguchi, Y., Wu, J., Duncan, R., Strohmalm, J., Ulbrich, K., Akaike, T. and Maeda, H. (1998), "Early phase tumor accumulation of macromolecules: a great difference in clearance rate between tumor and normal tissues", *Jpn. J. Cancer Res.*, **89**(3), 307-314.
- Noyes, A.A. and Whitney, W.R. (1897), "The rate of solution of solid substances in their own solutions", *J. Am. Chem. Soc.*, **19**(12), 930-934.
- Lipinski, C.A. (2002), "Single-mode compound retrieval for QSAR, QSPR data sets, and batch mode exact structure searching", *J. Pharm. Sci.*, **91**(12), 2470-2472.
- Ojer, P., Salman, H., Da Costa Martins, R., Calvo, J., Lopez de Cerain, A., Gamazo, C., Lavandera, J.L. and Irache, J.M. (2010), "Spray-drying of poly(anhydride) nanoparticles for drug/antigen delivery", *J. Drug Deliv. Sci. Technol.*, **20**(5), 353-359.
- Oowaki, H., Matsuda, S., Sakai, N., Ohta, T., Iwata, H., Sadato, A., Taki, W., Hashimoto, N. and Ikada, Y. (2000), "Non-adhesive cyanoacrylate as an embolic material for endovascular neurosurgery", *Drug Deliv. Transl. Res.*, **21**(10), 1039-1046. URL: <http://link.springer.com/article/10.1007%2Fs13346-016-0290-2>
- Paleos, C.M., Sideratou, Z., Kontoyianni, C. and Drossopoulou, G.I. (2010), "Synthesis of a folate functionalized PEGylated poly(propylene imine) dendrimer as prospective targeted drug delivery system", *Bioorg. Med. Chem. Lett.*, **20**(22), 6513-6517.
- Ringsdorf, H. (1975), "Structure and properties of pharmacologically active polymers", *J. Polym. Sci., C Polym. Symp.*, **51**(1), 135-153.
- Sakthivel, T. and Florence, A.T. (2003), "Adsorption of amphipathic dendrons on polystyrene nanoparticles", *Int. J. Pharm.*, **254**(1), 23-26.
- Santhoshkumar, T., Rahuman, A.A., Bagavan, A., Marimuthu, S., Jayaseelan, C., Kirthi, A.V., Kamaraj, C., Rajakumar, G., Zahir, A.A., Elango, G., Velayutham, K., Iyappan, M., Siva, C., Karthik, L. and Rao, K.V. (2012), "Evaluation of stem aqueous extract and synthesized silver nanoparticles using *Cissus quadrangularis* against *Hippobosca maculata* and *Rhipicephalus (Boophilus) microplus*", *Exp. Parasitol.*, **132**(2), 156-165.
- Santos-Magalhães, N.S. and Morsqueira, V.C. (2010), "Nanotechnology applied to the treatment of malaria", *Adv. Drug Deliv. Rev.*, **62**(4-5), 560-575.
- Storni, T., Kündig, T.M., Senti, G. and Johansen, P. (2005), "Immunity in response to particulate antigen-delivery systems", *Adv. Drug Deliv. Rev.*, **57**(3), 333-355.
- Sun, L., Zhang, S., Sun, X. and He, X. (2010), "Effect of the geometry of the anodized titania nanotube array on the performance of dye-sensitized solar cells", *J. Nanosci. Nanotechnol.*, **10**(7), 4551-4561.
- Svenson, S. and Tomalia, D.A. (2005), "Dendrimers in biomedical applications--reflections on the field",

- Adv. Drug Deliv. Rev.*, **57**(15), 2106-2129.
- Thakkar, A., Chenreddy, S., Thio, A., Khamas, W., Wang, J. and Prabhu, S. (2016), "Preclinical systemic toxicity evaluation of chitosan-solid lipid nanoparticle-encapsulated aspirin and curcumin in combination with free sulforaphane in BALB/c mice", *Int. J. Nanomedicine*, **11**, 3265-3276.
- Tros de Ilarduya, C., Sun, Y. and Düzgüneş, N. (2010), "Gene delivery by lipoplexes and polyplexes", *Eur. J. Pharm. Sci.*, **40**(3), 159-170.
- Waknine-Grinberg, J.H., Even-Chen, S., Avichzer, J., Turjeman, K., Bentura-Marciano, A., Haynes, R.K., Weiss, L., Allon, N., Ovadia, H., Golenser, J. and Barenholz, Y. (2013), "Glucocorticosteroids in nano-sterically stabilized liposomes are efficacious for elimination of the acute symptoms of experimental cerebral malaria", *PLoS One*, **8**(8), e72722.
- Zhou, X., Li, Q., Yin, Y., Chen, Y. and Lin, J. (2008), "Identification of medicinal *Ganoderma* species based on PCR with specific primers and PCR-RFLP", *Planta Med.*, **74**(2), 197-200.
- Zolle, I., Hossain, F., Rhodes, B.A. and Wagner, H.N., Jr. (1970), "Human serum albumin millimicrospheres for studies of the reticuloendothelial system", *J. Nucl. Med.*, **11**, 379-380.