Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2015, 7 (7):213-220
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

A study on recent implication of nanotechnology in drug delivery systems

Mahendra Pratap Singh[1], Parjanya Kumar Shukla[1,2*], Amita Verma[2] and Ramesh Patel[1]

[1]*Krishnarpit Institute of Pharmacy, Allahabad*
[2]*Department of Pharmaceutical Sciences, Faculty of Health Science, Sam Higginbottom Institute of Agriculture, Technology & Sciences, Allahabad, India*

ABSTRACT

Efficient drug targeting to diseases by circumventing all the shortcomings of conventional drug delivery systems can be achieved by the significant approach of advances in nanotechnology. Nanotechnology will affect our lives tremendously over the next decade in very different fields, including medicine and pharmaceutical Sciences. Most of the available drugs now are lipophilic in nature and this stands as challenging aspect faced for scientists to formulate and deliver for better efficacy, so nanoparticles, nanosuspension, nanocapsules are used now days to deliver these drugs with greater bioavailability and also have been adopted to improve the solubility of poorly soluble drugs. The use of nanoparticles is an universal formulation approach to increase the therapeutic performance of drugs in any route of administration. This review article describes the preparation methods, physicochemical properties, applications, clinical advantages, and recants developments of nanoparticles and their potential in drug delivery systems.

Keywords: Nanoparticles; nanotechnology; Bioavailability enhancement; nanocrystals; drug delivery system

---

INTRODUCTION

Controlled drug delivery systems (DDS) have quite a lot of advantages compared to the conventional forms of drugs. A drug is transported to the place of action, hence, its influence on vital tissues and undesirable side effects can be minimized. Accumulation of therapeutic compounds in the target site increases and, consequently, the required doses of drugs are lower. This modern form of therapy is especially important when there is a discrepancy between the dose or the concentration of a drug and its therapeutic results or toxic effects. Cell-specific targeting can be accomplished by attaching drugs to specially designed carriers. Various nanostructures, including liposomes, polymers, dendrimers, silicon or carbon materials, and magnetic nanoparticles, have been tested as carriers in drug delivery systems.

Over Recent years advancement in nanoparticles drug delivery is widely expected to change the landscape of pharmaceutical industries for the foreseeable future. Nanotechnologies have become a significant priority worldwide. Several manufactured nanoparticles - particles with one dimension less than 100 nm are increasingly used in consumer products.The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site specific action of the drug at the therapeutically optimal rate and dose regimen [1]. Depending upon method of preparation nanoparticles, nanospehresor nanocapsule can be obtained. Drug nanocrystals of nanometer size range are with crystalline character. Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by

surfactants.They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size. Nanosuspension consist of drug nanocrystal in aqueous vehicle in presence of suitable surfactanct and/or polymer as stabalizer. The advantages of using nanoparticles as a drug delivery system include the following:

1. Easy manipulation of size and surface properties of particles which provides passive and active drug targeting after its administration.
2. Nanoparticles can achieve increase in drug therapeutic efficacy and reduction in side effects by controlling the release of rug and also by altering the drug distribution and its clearance.
3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents.
4. Nanoparticles plays an important role in preserving the drug activity by increasing the Drug loading and incorporation of drugs into the systems without any chemical reaction.
5. Nanoparticles easily carry targeting ligands with the surface of particles for increased Site-specificity of particular drug.
6. Nanoparicles also provides a wide range of choice of routes of administration like oral, nasal, parenteral,intra-ocular. The advantages of using nanosuspensions for different routes are shown in table no.1.
7. Nanonization can achieve Increased dissolution rate [2]

Table no.1 shows the benefits of nanoparticles

Route of Administration	Disadvantages of conventional formulation	Advantages of Nanoparticles
Oral	Slow onset of action/poor absorption	Fast onset of action/ good absorption
Ocular	Lacrimal-washoff low bioavailability	Higher bioavailability/ dose consistency
Intravenous	Poor dissolution/non specific action	Rapid dissolution/tissue targeting
Intramuscular	Low patient compliance due to pain	Reduced tissue irritation
Inhalation	Low bioavailability due to low solubility	Rapid dissolution/high bioavailabilitry/dose regulation

Techniques for nanosuspension preparation:

There are two main techniques which are used in nanoparticles preparation as shown in Fig no.1

1. Bottom up(controlled precipitation)
2. Top down(milling/homogenization)

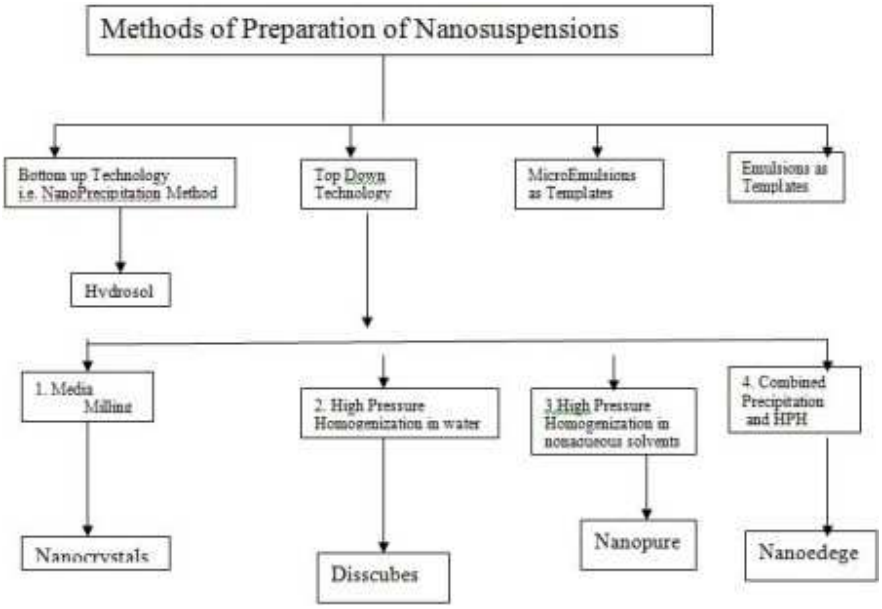

Fig no.1. Techniques of nanoparticles preparation (source: http://www.pharmainfo.net)

Applications of nanoparticles in drug delivery:

Parenteral administration:

Nanosuspensions have been found to increase the efficacy of parenterally administered drugs. The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions, complexation with cyclodextrin and recently liposomes. However, there are limitations on the use of these approaches because of the limitations on their solubilization capacity and parenteral acceptability. In this regard, liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost and difficulties in scale-up. Nanosuspensions would be able to solve the problems mentioned above [3].

Oral administration:

Nanosizing of drugs can lead to a dramatic increase in their oral absorption and subsequent bioavailability. Improved bioavailability can be explained by the adhesiveness of drug nanoparticles to the mucosa, the increased saturation solubility leading to an increased concentration gradient between gastrointestinal tract lumen and blood and the increased dissolution velocity of the drug. Aqueous nanosuspensions can be used directly in a liquid dosage form and a dry dosage form such as tablet or hard gelatin capsule with pellets. The aqueous nanosuspension can be used directly in the granulation process or as a wetting agent for preparing the extrusion mass pellets. A similar process has been reported for incorporating solid lipid nanoparticles into pellets [3].

Ophthalmic drug delivery:

Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high tonicity created by water soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus the intrinsic dissolution rate of the drug in lachrymal fluids governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids [3].

Bioavailability enhancement*:*

Nanoparticles and nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane.

Target drug delivery:

Nanoparticles can also be used for targeted delivery as their surface properties and *in vivo* behavior can easily be altered by changing either the stabilizer or the milieu. Their versatility, ease of scale up and commercial product enable the development of commercial viable nanosuspensions for targeted delivery. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems [3, 4].

Topical formulations:

Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin.

Many publications shows resent advantages and applications of nanoparticles in the drug delivery some of them are summarized here,

Hamidi *et al* studied Encapsulation of valproate-loaded nanogels inside human erythrocytes as a novel nanocell composite was the objective of the study to obtain a model novel drug delivery system with an intravenous sustained drug delivery characteristic. “Ionotropic gelation” was used for the fabrication of hydrogel nanoparticles [5].

Hyuk *et al* study a variety of bioactive molecules including anti-cancer drugs, enzymes, cytokines, and polysaccharides were entrapped within the interior or physically immobilized on the surface for controlled drug delivery. Surfaces of electrospun nanofibers were also chemically modified with immobilizing cell specific bioactive ligands to enhance cell adhesion, proliferation, and differentiation by mimicking morphology and biological functions of extracellular matrix. This review summarizes surface modification strategies of electrospun polymeric nanofibers for controlled drug delivery and tissue engineering [6].

Hanafy *et al* study the bioavailability of the poorly soluble fenofibrate following oral administration was investigated in rats. Four formulations were tested: a nanosuspension type DissoCube®, one solid lipid nanoparticle (SLN) preparation and two suspensions of micronized fenofibrate as reference formulations, one suspension in sirupus simplex and a second in a solution of hydroxyethy-cellulose in physiological saline [7].

Liu *et al* developed a post-conjugation strategy, which makes the ligand conjugation after the preparation of the drug-loaded nanoparticles of two copolymers blend. They synthesized the PLGA-PEG copolymer with PEG functioning as the linker molecule needed for herceptin conjugation. Docetaxel-loaded nanoparticles of the PLGA-PEG/PLGA copolymer blend were prepared by the nanoprecipitation method. Anti-HER2 antibody (heceptin), which targets the breast cancer cells of HER2 receptor overexpression, was conjugated on the drug-loaded PLGA-PEG/PLGA nanoparticles for sustained, controlled and targeted delivery of docetaxel [8].

Araujo *et al* give a study which was focus on microemulsions, polymeric nanoparticles, liposomes, solid lipid nanoparticles, and drug nanocrystals as formulations incorporating anti-inflammatory drugs for ophthalmic application [9].

Badawi *et al* developed two different chitosan (CS) nanocarriers namely nanoparticles and nanoemulsion to prolong Indomethacin (IM) precorneal residence time and to improve its ocular bioavailability the main limitations in its management of post-operative inflammation and intraocular irritation after cataract extraction. CS-nanoparticles were developed by modified ionic gelation of CS with tripolyphosphate while nanoemulsion was prepared by spontaneous emulsification technique [10].

Il'ina *et al* developed Nanoparticles based on galactomannan sulfates, alginic acid, a sulfated derivative of *N*-carboxymethylchitosan, and structures that simultaneously included galactomannan and chitosan sulfates were obtained for the first time. The formation conditions depended on the nature of the polysaccharides. The size and ζ-potential of the obtained nanostructures were determined. Their anticoagulant activity was studied in two tests: aIIa and aXa. It was shown that the activity of sulfated galactomannans and alginic acid in nanostructures increases when compared to the activity of these polysaccharides in solution [11].

Sahana *et al* investigated different solvents for optimizing nanoparticle preparation in terms of particle size, entrapment efficiency, and finally, release behavior using a model drug estradiol. Nanoparticles were prepared following emulsion–diffusion–evaporation method using didodecyldimethyl ammonium bromide (DMAB) or polyvinyl alcohol (PVA) as stabilizers. Ethyl acetate (EA), acetone (ACE), chloroform (CHL), and dichloromethane (DCM) were used as organic solvents either individually or in combinations [12].

Gupta *et al* develop and evaluate a new colloidal system, that is, poly(dl-lactide-*co*-glycolide) (PLGA) nanoparticles for sparfloxacin ophthalmic delivery, to improve precorneal residence time and ocular penetration. Nanoparticles were prepared by nanoprecipitation technique and characterized for various properties such as particle size, zeta potential, in vitro drug release, statistical model fitting, stability, and so forth. Microbiological assay was carried out against *Pseudomonas aeruginosa* using the cup-plate method [13].

Di *et al* study and reports a multifunctional biomaterial based on single-phased luminescent mesoporous lanthanide oxide nanoparticles that combine simultaneous drug delivery and cell imaging. A simple strategy based on solid-state-chemistry thermal decomposition process was employed to fabricate the spherical mesoporous Gd_2O_3:Eu nanoparticles with homogeneous size distribution [14].

Das and Lin evaluate oral administration of poly (butylcyanoacrylate) nanoparticulate delivery systems (PBCA-NDSs), double-coated with Tween 80 and poly (ethylene) glycol (PEG) 20000 for brain delivery of hexapeptide dalargin, an anti-nociceptive peptide that does not cross blood–brain barrier (BBB) by itself [15].

Park *et al* prepared All-trans retinoic acid (ATRA)-incorporated nanoparticles of methoxy poly(ethylene glycol) (MPEG)-grafted chitosan were prepared through ion-complex formation between ATRA and chitosan. This nanoparticle has around 100 nm of diameter and favorable reconstitution properties. ATRA-incorporated nanoparticles has almost similar cytotoxicity against CT-26 tumor cells when compared to free ATRA [16].

Cui *et al* investigated the preparation of PLGA nanoparticles (PNP) and PLGA-Hp55 nanoparticles (PHNP) as potential drug carriers for oral insulin delivery. The nanoparticles were prepared by a modified emulsion solvent diffusion method in water, and their physicochemical characteristics, drug release in vitro and hypoglycemic effects in diabetic rats were evaluated [17].

Couvreur *et al* studied Polymethylcyanoacrylate nanoparticles, polyethylcyanoacrylate nanoparticles, and free ^{3}H-dactinomycin and ^{3}H-vinblastine were studied with emphasis on their distribution pattern in rat tissues after intravenous administration. The adsorption of cytostatic drugs to polyalkylcyanoacrylate nanoparticles can modify drug distribution in tissues. Particularly with vinblastine, modification of drug disposition is important. Data are given concerning the formation and stability of nanoparticle-drug complexes. Polyalkylcyanoacrylate nanoparticles seem to be an interesting drug carrier owing to their size, structure, degradability, and drug sorptive properties [18].

Sang Yoo *et al* formulated Biodegradable nanoparticles containing salmon calcitonin (sCT) using protein–fatty acid complexes, and their *in vitro* transport against a Caco-2 cell monolayer and the extent of *in vivo* oral uptake were assessed. Positively charged sCT was hydrophobically ion paired to form physical complexes with fatty acid, phospholipid, and surfactant. Among the complexes, sodium oleate was used to form sCT–oleate complexes, which were characterized and formulated into biodegradable poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles. Endocytosis of sCT nanoparticles by Caco-2 cells was studied by flow cytometry. Transcytosis of sCT across the Caco-2 monolayer was also quantitated by an ELISA method [19].

Rawat *et al* developed prolonged release binary lipid matrix-based solid lipid nanoparticles (SLN) of repaglinide (RG) for oral intestinal delivery and to improve the bioavailability of RG. SLN were designed by using glycerol monostearate and tristearin as lipid core materials and Pluronic-F68 as stabilizer [20].

Margulis-Goshen *et al* Studied the inhibitory effect of ammonium glycyrrhizinate (AG) on crystallization of celecoxib (CXB) nanoparticles in aqueous medium was studied. CXB nanoparticles in powder form were prepared by rapid evaporation of all solvents from a volatile oil-in-water microemulsion. A powder containing 13 wt % CXB was obtained by immediate conversion of microemulsion droplets into nanoparticles by spray drying [21].

Dalpiaz *et al* proposed a novel nonaqueous nanoprecipitation method to achieve the encapsulation of a small weight hydrophilic drug (N6-cyclopentyladenosine, CPA) in PLGA nanoparticles using a mixture of cottonseed oil and Tween-80 as nonsolvent phase. The nanoparticles were characterized in vitro as concerns size, morphology, drug loading, drug release, and drug stability in human blood. Human retinal pigment epithelium (HRPE) cells were employed to study intracellular accumulation of encapsulated or free CPA with and without unloaded particles, in the presence or absence of an equilibrative nucleoside transporter inhibitor [22].

Tiyaboonchai *et al* developed a new aqueous nanoparticle system using complex coacervation employing the oppositely charged polymers polyethylenimine (PEI) and dextran sulfate (DS), with zinc sulfate as a stabilizing agent. Amphotericin B (AmB) was loaded into the nanoparticles as a model drug [23].

Damge *et al* prepared Nanoparticles with a blend of a biodegradable polyester (poly(ε-caprolactone)) and a polycationic nonbiodegradable acrylic polymer (Eudragit® RS) have been used as a drug carrier for oral administration of a short-acting insulin analogue, aspart-insulin. Insulin-loaded nanoparticles, about 700 nm in diameter, encapsulated 97.5% of insulin and were able to release about 70% of their content *in vitro* in a neutral medium over 24 h [24].

Choi *et al* prepared adriamycin (ADR)-encapsulated core–shell type nanoparticles of a poly(DL-lactide-co-glycolide) (PLGA) grafted-dextran (DexLG) copolymer and evaluated its antitumor activity in vitro and in vivo [25].

Mainardes et al developed PLA and PLA/PEG blend nanoparticles containing zidovudine and their uptake by polymorphonuclear leucocytes were studied in vitro. The influence of polymer type on particle size, Zeta potential and particle uptake by polymorphonuclear leucocytes was investigated. The cells were isolated from rat peritoneal exudate and their activation by nanoparticles was measured by luminol-dependent chemiluminescence and microscopical analysis [26].

Sun *et al* designed and characterized curcumin loaded polybutylcyanoacrylate nanoparticles (PBCN) coated with polysorbate 80, and to evaluate the effect of PBCN as a delivery system on carrying curcumin across BBB [27].

Kommareddy *et al* modified thiolated gelatin nanoparticles with poly(ethylene glycol) (PEG) chains and examine their long circulating and tumor-targeting properties *in vivo* in an orthotopic a human breast adenocarcinoma xenograft model. The resulting nanoparticulate systems with long circulation properties could be used to target encapsulated drugs and genes to tumors passively by utilizing the enhanced permeability and retention effect of the tumor vasculature [28].

Giri *et al* develop hepatitis B surface antigen (HBsAg) surface-adsorbed cationic poly (d,l-lactic-co-glycolic acid) PLGA nanoparticles for interferon alpha (IFNα) delivery targeted to hepatocytes. Cationic PLGA nanoparticles loaded with IFNα were prepared using the double emulsification technique. Delipidated HBsAg was passively adsorbed on the surface of nanoparticles by using the simple dipping and drying method [29].

Li *et al* prepared the poly(lactide-co-glycolide)-coated magnetic nanoparticles (PLGA MNPs) as carriers of doxorubicin (PLGA-DOX MNPs) through water-in-oil-in-water (W/O/W) emulsification method. The characteristics of PLGA-DOX MNPs were measured by using transmission electron microscopy (TEM) and vibrating-sampling magnetometry (VSM). It was found that the synthesized nanoparticles were spherical in shape with an average size of 100±20nm, low aggregation and good magnetic responsivity. Meanwhile, the drug content and encapsulation efficiency of nanoparticles can be achieved by varying the feed weight ratios of PLGA and DOX particles [30].

Calvo *et al* study the ability of bioadhesive cyclodextrin-poly(anhydride) nanoparticles as carriers for the oral delivery of atovaquone (ATO). In order to increase the loading capacity of ATO by poly (anhydride) nanoparticles, the following oligosaccharides were assayed: 2-hydroxypropyl-β-cyclodextrin (HPCD), 2,6-di-O-methyl-β-cyclodextrin (DCMD), randomly methylated-β-cyclodextrin (RMCD) and sulfobuthyl ether-β-cyclodextrin (SBECD). Nanoparticles were obtained by desolvation after the incubation between the poly(anhydride) with the ATO-cyclodextrin complexes. %. The encapsulation of atovaquone in cyclodextrins-poly(anhydride) nanoparticles seems to be an interesting strategy to improve the oral bioavailability of this lipophilic drug [31].

Cavalli et al investigated the drug incorporation capacity using tamoxifen, a lipophilic anticancer drug with poly(amidoamine)-cholesterol nanoparticles. The incorporation of the tamoxifen did not affect the shape and sizes of nanoparticles showing a drug loading of 40%. Tamoxifen-loadednanoparticles exhibited a higher dose-dependent cytotoxicity than free tamoxifen, while blank nanoparticles did not show any cytotoxic effect at the same concentrations [32].

Shen *et al* prepared Poly(methyl methacrylate)-based bone cements, functionalized with mesoporous silica nanoparticles (MSN) to enable a highly efficient and sustained release of antibiotics to reduce the risk of post-operative joint infection. To overcome the limited drug release of 5% for only 1 day with the current commercial-grade bone cements, a 8 wt% MSN-formulated bone cement is able to increase the drug release efficiency by 14-fold and sustain the release for up to 80 days [33].

Pourshahab *et al* prepared spray dried inhalable powders containing isoniazid-loaded chitosan/tripolyphosphate (TPP) nanoparticles for sustained delivery of the drug to the lung.Nanoparticles were prepared by ionic gelation method. In-vitro drug release study indicated that the rate of drug release from nanoparticles was decreased by increasing the amount of chitosan. Entrapment of isoniazid into chitosan/TPP nanoparticles decreased minimum inhibitory concentrations (MIC) of the drug against mycobacterium avium intracellulare.Nanoparticles were spray dried using excipients such as lactose, mannitol and maltodextrin alone or with leucine [34].

Pillay *et al* study the design, biometric simulation and optimization of an intracranial nano-enabled scaffold device (NESD) for the site-specific delivery of dopamine (DA) as a strategy to minimize the peripheral side-effects of conventional forms of Parkinson's disease therapy. The NESD was modulated through biometric simulation and computational prototyping to produce a binary crosslinked alginate scaffold embedding stable DA-loaded cellulose acetate phthalate (CAP) nanoparticles optimized in accordance with Box–Behnken statistical designs [35].

Adeli *et al* synthesized and characterized Polyrotaxanes consisting of cyclodextrin rings, polyethylene glycol axes and quantum dot (QD) stoppers. The potential applications of the molecular self-assemblies as drug-delivery systems was investigated by conjugation of doxorubicin (DOX) to their functional groups and then release the drug inside the cancer cells in mouse tissue connective fibroblast adhesive cell line L929 [36].

On the basis of recent literature review we can say that the importance of nanotechnology in therapeutics and the role played by it in combating some of the chronic diseases, such as cancer. Some of the important areas in drug delivery where nanotechnology can build a difference are:

1. Deigning Delivery of repaired genes or the replacement of incorrect genes is fields in which nanoscale objects could be introduced successfully.
2. Systems for improvement of the solubility and bioavailability of hydrophobic drugs.
3. Systems for eliminating or minimizing toxicity.
4. Designing delivery vehicles that can improve the circulatory presence of drugs.
5. Delivery systems for targeting drugs to specific cells or tissues.
6. Development in increasing specificity.
7. Systems for improving vaccine adjuvant and delivery.
8. Helping hand in specific applications, e.g. ocular, cancer therapy, neurology, orthopaedics.
9. Developing delivery systems for slow release.

FUTURE PROSPECTIVE

Nanotechnology is relatively new, and although the full scope of contributions of these technological advances in the field of human health care remains unexplored, recent advances suggest that nanotechnology will have a profound impact on disease prevention, diagnosis, and treatment. It is extensively projected that nanotechnology will persist to advance and develop in over the next couple of years in many areas of life and science, and the achievements of nanotechnology will be applied in medical sciences, including diagnostics, drug delivery systems, and patient treatment. Future of Pharmaceutical industry in the field of drug delivery represents a strategic tool for expanding drug markets, because new delivery technologies could repackage classical drugs, offering a competitive edge after the expiry of patents and avoiding competition from generics.

CONCLUSION

Nanotechnology implanted delivery system would consent to faster drug absorption, controlled dosage release into the human body and would have other unique properties of minimizing side-effects by eliminating requirement of co-solvent as used in conventional dosage form. Nanoparticles would dramatically reduce drug dosage, such that, there is improvement in the absorption of the drug, so that the patient can take a smaller dose, and yet have the same benefit, Deliver the drug to the right place in the living system, Increase the local concentration of the drug at the desired site and limit or eliminate side effects. In nanotechnology by using very small channels, only nanogram quantities of analytes and reagents are required. Throughput can increase while cost decreases. Such devices could dramatically change the care model by making sophisticated tests widely and immediately available at lower cost in office settings, at home, or at a patient's bedside. Some of the concerns were also discussed but with proper care these problems can be avoided. So drugs that have side-effects due to triggering an immune system response can be wrapped in nanoparticle coating and prevent immune system from recognizing and reacting to a foreign substance. It is an ideal targeting system should have long circulating time, it should be present at appropriate concentrations at the target site, and it should not lose its activity or therapeutic efficacy while in circulation.

REFERENCES

[1] R.H. Muller, C.M. Keck, *J Biotechnol*, **2004**, 113(13), 151–170.
[2] V.B. Patravale, A.A. Date, R.M. Kulkarni, *J. Pharm. Pharmacol*., **2004**, 56 (7), 827–840.
[3] T. Venkatesh, A.K. Reddy, J.U. Maheswari, M.D. Dalith, A. Kumar, *Der Pharmacia Lettre*, **2011**, 3(2), 203-213
[4] R.H. Muller, R. Becker, B. Kruss, **1999** US Patent 5858410. USA.
[5] M. Hamidi, P. Rafiei, A. Azadi, S. Mohammadi-Samani, *J. of Pharm. Sci*., **2011**, 100, 1702–1711.
[6]H. S. Yoo, T.G. Kim, T.G. Park, *Adv. Drug Del. Rev*., **2009**, 61, 1033-1042

[7]A. Hanafy, H. Spahn-Langguth, G. Vergnault, P. Grenier, M.T. Grozdanis, T. Lenhardt, P. Langguth, *Adv.DrugDel.Rev*.,**2007**,59(6),419-426
[8]Y. Liu, K. Li, B. Liu, S. Feng, *Biomaterials*, **2010**, 31, 9145-9155
[9]J. Araujo, E. Gonzalez, M.A. Egea, M.L. Garcia, E.B. Souto, *Nanomed.*, **2009**, 5, 394-401
[10] A.A. Badawi, H.M. El-Laithy, R.K. Qidra, H.E. Mofty, M.E. Dally, *Archi. of Pharmacal Res*., **2008**, 8, 1040-1049
[11] A.V. Il'ina, A.N. Levov, N.M. Mestechkina, N.N. Drozd, V.N. Orlov,Nanotechnologies in Russia, **2009**, 4, 244-252
[12] D. Sahana, G. Mittal, V. Bhardwaj, M.R. Kumar, *J. Pharm. Sci.*, **2008**, 97, 1530–1542.
[13]H. Gupta, M. Aqil, R.K. Khar, A. Ali, A. Bhatnagar, G. Mittal, *Nanomed.*, **2010**, 6, 324-333
[14]W. Di, X. Ren, H. Zhao, N. Shirahata, Y. Sakka, W. Qin, *Biomaterials*, **2011**, 32, 7226-7233
[15]D. Das, & S. Lin,S. Double-coated poly (butylcynanoacrylate) nanoparticulate delivery systems for brain targeting of dalargin via oral administration. *J. Pharm. Sci*., **2005**, 94, 1343–1353.
[16] J.S. Park, Y.S. Koh, J.Y. Bang, Y.I. Jeong, J.J. Lee,J.J. *J. Pharm. Sci.*, **2008**, 97, 4011–4019.
[17] F. Cui, A.J. Tao, D.M. Cun, L.Q. Zhang, K. Shi, *J. Pharm. Sci.*, **2007**, 96, 421–427.
[18] P. Couvreur, B. Kante, V. Lenaerts, V. Scailteur, M. Roland, P. Speiser, *J. Pharm. Sci.*, **1980**, 69, 199–202.
[19] Y.H. Sang & P.T. Gwan, *J. Pharm. Sci.*, **2004**, 93, 488–495.
[20] M.K. Rawat, A. Jain, S. Singh,S. *J. Pharm. Sci*., **2011**, 100, 2406–2417.
[21] K. Margulis-Goshen, M. Weitman, D.T. Major, S. Magdassi, *J. Pharm. Sci*., **2011**, 100, 4390–4400.
[22] A. Dalpiaz, E. Vighi, B. Pavan, E. Leo,. *J. Pharm. Sci*., **2009**, 98, 4272–4284.
[23] W. Tiyaboonchai, J. Woiszwillo, C.R. Middaugh, *J. Pharm. Sci*., **2001**, 90, 902–914.
[24] C. Damge, M. Socha, N. Ubrich, P. Maincent, *J. Pharm. Sci*., **2010**, 99, 879–889.
[25] K.C. Choi, J.Y. Bang, C. Kim, P.I. Kim, S.R. Lee, W.T. Chung, W.D. Park, J.S. Park, Y.S. Lee, C.E. Song, H.Y. Lee, *J. Pharm. Sci*., **2009**, 98, 2104–2112.
[26] R.M. Mainardes, M.P.D. Gremiao, I.L. Brunetti, L.M. Da Fonseca, N.M. Khalil, *J. Pharm. Sci*., **2009**, 98, 257–267.
[27] M. Sun, Y. Gao, C. Guo, F. Cao, Z. Song, *J. Nanopart. Res*., **2010**, 12, 3111-3122
[28] S. Kommareddy & M. Amiji, *J. Pharm. Sci*., **2007**, 96, 397–407.
[29] N. Giri, P. Tomar, V.S. Karwasara, R.S. Pandey, V.K. Dixit, *Acta Biochim Biophys Sin*., **2011**, 43(11), 877-83
[30] F. Li, J. Sun, H. Zhu, X. Wen, C. Lin, D. Shi, *Biointerfaces*., **2011**, 88(1), 58-62.
[31] P. Calvo, C. Remunan-Lopez, J.L. Vila-Jato, M.J. Alonso, *J. Appl. Polymer Sci*., **1997**, 63, 125-132.
[32] R. Cavalli, a. Bisazza, R. Bussano, M. Tratta, A. Civra, D. Lembo, E. Ranucci, P. Ferruti, *J Drug Deliv*., **2011**, 58, 7604.
[33] S.c. Shen, W.K. Ng, Z. Shi, L. Chia, K.G. Neoh, R.B. Tan, *J. Mater. Sci. Mater. Med*., **2011**, 22(10), 2283-92.
[34] P.S. Pourshahab, K. Gilani, E. Moazeni, M.R. Fazeli, H. Jamalifar, *J Microencapsul*., **2011**, 28(7), 605-13.
[35] S. Pillay, V. Pillay, Y.E. Choonara, D. Naidoo, R.A. Khan, L.A. Toit, V.N.K. Ndesendo, G. Modi, M.P. Danckwerts, E. Sunny Iyuke, *Int. J. Pharm*., **2007**, 382, 277-290
[36] M. Adeli, M. Kalantari, M. Parsamanesh, E. Sadeghi, M. Mahmoudi, *Nanomed*., **2011**,7,806-817