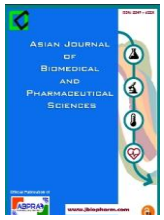
Asian Journal of Biomedical and Pharmaceutical Sciences
ISSN : 2249 - 622X



REVIEW ARTICLE

Received on: 23/12/2013
Accepted on: 19/02/2014
Published on: 20/02/2014

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QR Code for Mobile users

Conflict of Interest: None Declared !

Nanotechnology: A possible healer in drug delivery system

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Abstract
To obtain better therapeutic efficacy, nanotechnology based drug delivery system has been showing its endless possibilities and eventually bringing transformation in the perspective of upcoming medication system. Precision in developing biomaterial maintaining proper physicochemical properties and target specificity can unveil desired therapeutic outcome. Nanotechnology based drug delivery system provides some novel advantages like increased bioavailability, controlled drug delivery, target specification and reduced toxicity. Different nanotechnology based systems like liposomes, biodegradable nanoparticles and dendrimers are becoming potential healer in drug delivery system.

Keywords: Nanotechnology, Drug delivery, Biophysicochemical property, Targeted delivery, liposomes, biodegradable nanoparticles, Dendrimers.

Cite this article as:
Md. Moniruzzaman, Mohammed Monzur Morshed, Mohammad Arif Ashraf. Nanotechnology: A possible healer in drug delivery system. Asian Journal of Biomedical and Pharmaceutical Sciences; 04 (29); 2014; 1-6.

INTRODUCTION:

Nanotechnology is the science of material where engineering and manufacturing take place at atomic and molecular scale that give a range of 1-100nm size in at least one direction[2-4]. Nanoparticles used as drug delivery system consist of biodegradable materials like lipids, polymers or metals. They have the size of <100 nm in at least one dimension [7,8]. Nanotechnology is becoming popular in terms of application in diverse fields like agriculture, forensic science, textile and electronics [9-13]. Nanotechnology has its contribution in medical therapeutics [14,15]. Continuous efforts are being made to overcome the dreadful diseases like diabetes, cancer, AIDS through nanomedicine[16-18]. Biocompatible nanoparticles provide an excellent example of transport and delivery process where either attachment to the particle surface or integration to the matrix is possible. They exhibit unique physicochemical properties for optimum bioavailability and target specification [7,19,20].

Application of nanotechnology based drug delivery system may add something new to the arsenal of therapeutics for the fight against diseases with some inevitable advantages like:

i)target specificity [21],
ii) increased bioavailability [22],
iii) reduced dosing [23],
iv) reduced toxicity [24],
v) concurrent evaluation of in-vivo efficacy of therapeutics [25],
vi) visualization of drug delivery through integration of imaging techniques [26].

PROGRESSIVE WONDER INTO PRACTICE:

Meaning 'dwarf' according to the Greek derived word 'nano'; nanotechnology has its great involvement in terms of research and application to be exact.

It was none other than the American physicist Richard P. Feynman(1965 Nobel Laureate in Physics) who made the initial inspiration and later conceptual foundation through his lecture 'Plenty of Room at the bottom' in 1959 [27]. The idea of nanotechnology was explored in depth further by K. Eric Drexler. In succession, technological aspect was contributed by him for its nano-sizing and devices [28].

Drug delivery through nanotechnology is one of the key achievements where lipid vesicle was one to make the initial footstep [29]. To continue with the endeavor, attention was paid towards the exploration of feasible alternative materials and systems. Different organic and inorganic materials were developed for the purpose. Complex situation of then like optimization to pH change in order to trigger release of drug was a success after first ever controlled release of polymer system noted in 1976 [30,31]. The idea of long circulating chromosome was generated later and named as 'stealth liposome' [32]. It was necessary to increase the circulation time for liposomes and polymeric nanoparticles. Development of the use of polyethylene glycol (PEG) was a successful one in this regard [33]. As a succession towards most advantageous efficacy, new molecular entities (NME) are taken into consideration which eventually can lead to advancement in therapeutic perspective. These are found as biologically active but suboptimal in pharmaceutical perspective [2,34].

Biophysicochemical properties and targeting for desired destination:

It is already evident that the development and application of targeted drug delivery through properly assembled biocompatible material along with the optimization of physicochemical parameter can guide towards effective implementation of nanotechnology based drugs delivery system [35,36].

Properly designed biocompatible nanoparticles can be used in targeted drug delivery which may result in precision to a specific site and improved bioavailability [37,38]. Circulating half-life of nanoparticles and their biodistribution rely on biophysical properties of drug-vehicle. They are size, surface hydrophilicity, charge and nature of the ligands on the surface along with density [39,40]. Figure-1 depicts the size and shape dependence of nanoparticles.

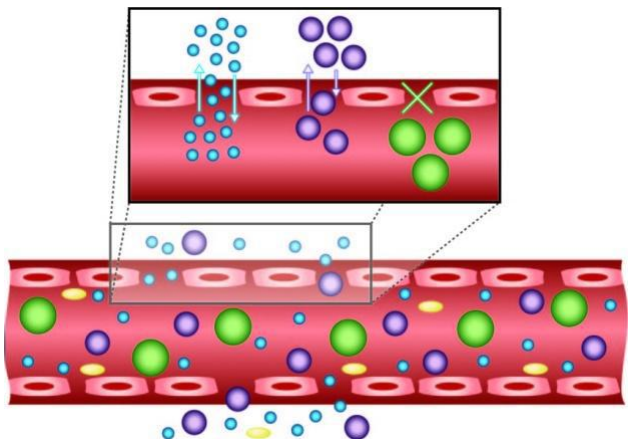

Figure-1: Size and shape are important determining factors for the efficacy of nanoparticles as delivery vehicles. The size determines their movement in and out of the vasculature. Shape determines the margination of particles to vessel wall. Figure is adapted from [2]

Targeted delivery vehicle provides a mentionable aid for the delivery of therapeutics with intracellular sites of action. RNAi or antisense therapeutics is an example for such issue.

Choice of therapeutic for targeted delivery hence plays important role [41,42]. For the therapeutics that needs intracellular delivery to obtain bioactivity, optimization of ligand density can serve as a possible solution. This optimization is done on drug delivery surface tissue

and helps in balance between tissue penetration and cellular uptake and ultimately provides therapeutic efficacy [41,43,44] . A comparative representation of untargeted and targeted drug delivery systems is shown in Figure-2.

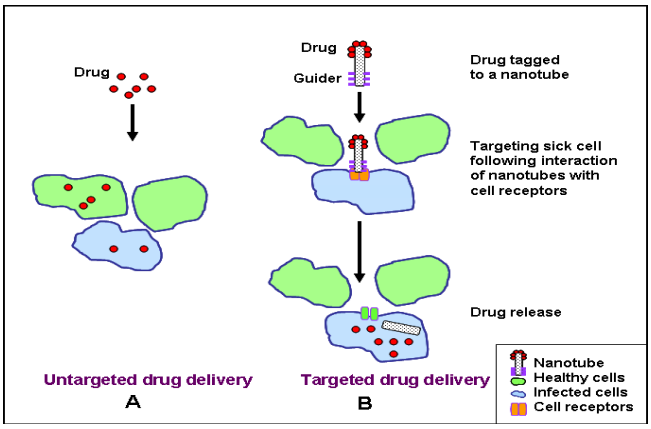

Figure-2: A simplified illustration of untargeted and targeted drug delivery systems. Figure is adapted from[1]

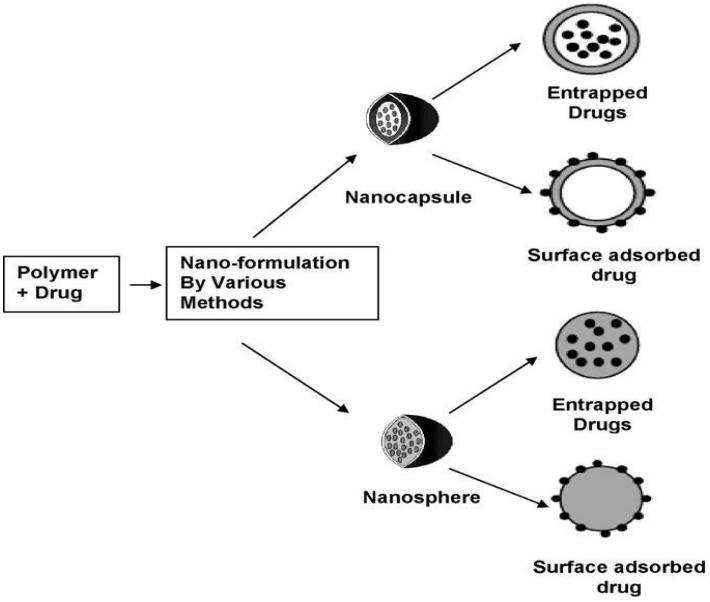

Figure-3: Type of biodegradable nanoparticles. They are distinguished as nanocapsule and nanosphere based on the structural organization. Drug molecules can be either surface adsorbed or entrapped inside. Figure is adapted from [5,6].

LIPOSOMES FOR DRUG DELIVERY:

Liposomes, previously mentioned as lipid vesicles were among the first nanotechnology based drug delivery systems reported in 1960s [29] .

Liposomes are lipid vesicular systems. They are small vesicles and can be obtained from natural non-toxic phospholipid and cholesterol. Liposomes have aqueous core enclosed by phospholipid bilayers. Hydrophilic drugs can be encapsulated through the aqueous core. Besides, within the phospholipid bilayers, hydrophobic and amphiphilic drugs can be solubilized. Liposomes can be distinguished in three different categories based on the structure of the lipid bilayers. They are i) small unilamellar vesicles (SUV) ii) large unilamellar vesicles (LUV) and iii) multilamellar vesicles [MLVs) [29,45].

Modification on liposome surface can be done by attaching polyethylene glycol (PEG)-units to the bilayer (named as stealth liposomes) to develop their circulation time in the bloodstream. Liposomes can facilitate the increase of target-specific drug therapy as they can be conjugated to antibodies or ligands [46,47]. Some liposomes and their uses are mentioned in table1.

Liposome type	Therapeutics	Indication	Reference
PEG-Liposome	Topotecan+ Vincristine	Brain cancer	[48]
PEG-Liposome	siRNA + Doxorubicin	MDR-breast cancer	[49]
Transferrin- (Tf-) Conjugated PEG-Liposome	Doxorubicin+ Verapamil	MDR-leukemia	[50]

Table-1: Liposomes for drug delivery

BIODEGRADABLE NANOPARTICLES FOR DRUG DELIVERY:

Biodegradable nanoparticles are considered as feasible and promising approach for health and biopharmaceutical industry. In terms of both bioavailability and reduced toxic properties, they stand as budding option. They are used recurrently for the betterment of therapeutic value of different water soluble and insoluble medicinal drugs[51].

Biodegradable nanoparticles can be classified based on the structural organization. They are nanocapsule and nanosphere. Drug molecules are either entrapped inside or adsorbed on the surface [6,52,53].Some biodegradable nanoparticles used for drug delivery are reported in table2.

Polymer	Encapsullant (Encapsulant Efficiency)	Therapeutic Improvement	Target cells /Indications/ Functions	Reference
Poly-d,l-lactide-co-glycolide (PLGA)	Taxol (100%)	Slow release of the drug up to 20 days	Cancer	[6,16]
Polylactic acid (PLA)	Haloperidol (30%)	Slow release of drug up to 4 days	Schizophrenia/ Antipsychotic	[54]
Poly-epsiv-caprolactone(PCL)	Docetaxel (90%)	Higher antitumor effect	malignant melanoma	[55]
Chitosan	Cyclosporin A (73%)	Achieving therapeutic concentration in external ocular tissues	Inhibition of T-cell activation; Nephrotic syndrome, Refractory myasthenia gravis	[56]

Table-2: Biodegradable nanoparticles for drug delivery

Dendrimers for drug delivery:

With the advantage of the comparative easiness of incorporation of targeting ligand, Dendrimers have emerged as potential choice in drug delivery system since its first discovery in early 1980s. Dendrimers are highly branched macro molecular compound with surface active groups [57,58].

Dendrimers are small (<100 nm) monodisperse symmetric macromolecules. They can be built from ABn-type monomers with each layer around a small molecule or in a linear polymer core using connectors and branching units[59,60]. Dendrimers can be synthesized in both ways- (divergent synthesis and convergent synthesis) like as central core is the initializing point and working out toward the periphery or starting from the outermost residues that follows a top-down approach [61,62].

Dendrimers have some very convincing unique features. They have three different topological sites like i) polyfunctional core ii) interior layers and iii) multivalent surface. Having globular shape and internal cavities, Dendrimers provide the possibility of encapsulation of therapeutic agents within the macromolecule interior and attachment to the surface groups as well[63,64]. Few examples of dendrimers in drug delivery are mentioned in table3.

Dendrimers	Drugs/ Therapeutics	Target cells/Indications/ Functions	Reference
G3.5 PAMAM Dendrimers	SN38	Hepatic colorectal cancer cell	[65]
Angiopep-carrying PEGylated PAMAM Dendrimers G5.0	Plasmid pEGFP-N2	Encode green fluorescence protein	[66]
2,2 bis [hydroxymethyl) propanoic acid based Dendrimers	Doxorubicin	Colon carcinoma cells of rat	[67]
Tuftsin-conjugated PPE dendrimers	Efavirenz	HIV	[68]
Amino-terminated carbosilane Dendrimers	siRNA	Lymphocytes	[69]

Table-3: Dendrimers for drug delivery

CONCLUSION:

Nanotechnology has revolutionized the health sector including drug delivery system through its successive evolution in a conquering manner. Maintaining precision about the target and increasing bioavailability, nanotechnology is emerging as a healer for conventional therapeutics in drug delivery system. Redefining the forecast of pharmaceutical practice is the good news for the patients suffering from various diseases. From laboratory research to clinical application, nanotechnology can gift us with a novel class of therapeutics unfolding great features with its minute size.

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