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Nanotechnology: Applications in pharmaceutical drug delivery systems

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ABSTRACT

Nanotechnology has great benefits in the area of pharmaceutical researches and applications. It is used to create small features on software's and computers chips for last 25 years. The major principal that makes the nanomaterial differ from other material are the enhanced surface area and quantum effects; so that the properties like strength, reactivity, electrical behaviour etc. are enhanced. While the quantum effects affect the magnetic, optical and electrical behaviour of materials. In the pharmaceutical area nanotechnology has been widely used for the targeting drug delivery. Recently the developments in nanotechnology have shown that nanomaterials have a great potential as drug carriers. Their small sizes make them physiologically and biologically, a favourable material for biomedical applications. The present study reviews some of the recent biomedical applications of nanotechnology.

Keywords: Nanotechnology, Liposomes, National Nanotechnology Initiative (NNI), Blood Brain Barrier (BBB), Solid Lipid Nanoparticles (SLN)

INTRODUCTION

In 1974, the term "Nanotechnology" was used for the first time by Norio Taniguchi, who was the scientist at University of Tokyo [1]. One nanometre is equivalent to one-billionth of a meter, which is, 10^{-9} m. According to National Nanotechnology Initiative (NNI) definition nano-materials have the size range from 1- 100 nm in at least one dimension, but the prefix "nano" is used for materials that are up to several hundred nanometres in size range. The nanoscale materials also occur in natural world like nanosized proteins which regulate the biological activities of body like energy production, muscles flexing and cellular repairing functions etc.Nanosized materials used for biomedical field should have low toxicity profile and biocompatibility. Their undesirable effects mainly depends upon their size range, amount, shapes, route of administration, their surface chemistry, residence time in blood and the reaction of immune system [2].

Now a days many nanosystems are used in the medical field for the drug delivery like liposomes, nanoparticles, SLN (solid lipid nanoparticles), dendrimers, hydrogels etc. Polymeric nanoparticles are widely used for the controlled and targeted delivery of drugs. These are patient friendly system of drug delivery as the less frequent application of dose and more retention time of the drug in the biological system. The main goal of nanomaterial in drug delivery system is to maintain the therapeutic amount of drug at the targeted site in the body and maintain desired amount of drug in bloodstream. However some of the major key points which have to be kept in mind before drug delivery are the type of carrier used, the route of administration, the target of drug delivery and the strategy designed to enhance therapeutic efficacy of drug. These are the factors which can reduce the undesirable effects of the active pharmaceutical entity [1].

Drug Carriers Used in Nanotechnology:

There are several nanoscale materials which can be utilized for the targated and controlled delivery of drugs in the biological systems with very less undesirable effects. Nanoparticles, liposomes, hydrogels, nanosuspensions, nanoemulsions, nanospheres, SLNs etc. are the major nanocarriers used for the delivery of drugs at their targeted site in the body (Table 1). Liposomes are lipid vesicles containing aqueous core which have been widely used in ocular delivery for various drug molecules. Those drugs which have poor solubility, low partition coefficient, poor absorption and having high molecular weight are delivered by this method. The particle size of the nanosuspensions lies between 200 and 600 nm which is less than one micron [3]. Nanosuspension is preferred for the compounds which have high partition coefficient (log P) value, insoluble in water, but soluble in oil, having high doses and high melting point.

The uniform particle size is key factor for the stability of the nanosuspensions. Nanaosuspensions can be formulated for drugs which are insoluble in both aqueous and organic solvents.Drugs which are hydrophobic in nature can also be formulated as nanosuspensions such as clofazomine, naproxen,mitotane, amphotericin B, omeprazole and spironolactone [4].

Table 1. Applications of different types of nanocarriers

Nanocarriers	Applications
1. Liposomes	Neurosonography, antiarthrites and anticancer drug delivery [5]
2. Nanoparticles	Ocular drug delivery, gene delivery, drug delivery of poor water soluble drug, enhancing residence time of drugs having short half-lives [6]
3. Hydrogels	Used formanufacturing contact lenses, hygiene products, tissue engineering scaffolds, drug delivery systems and wound dressings [7]
4. Dendrimers	Used for protein drug delivery, antimicrobial and anticancer drug delivery, ocular and gene drug delivery, used in Magnetic Resonance Imagine for diagnosis purpose [8]
5. Solid Lipid Nanoparticles	Used for CNS drug delivery, for topical drug delivery, used in cosmetics mainly sunscreen creams, for enzymes encapsulation, for tuberculosis chemotherapy [9]

Polymers used for nanomaterials preparation:

Nanoparticles comprise of various biodegradable or non-biodegradable polymers, lipids, phospholipids or metals. These are prepared by different bio-adhesive polymers like chitosan, PEG, PLGA etc. These polymers enhance the residence time of drug in the body and lead to better bioavailability of drug than the conventional drug delivery methods (10).Various types of polymers are being used for the preparation of polymeric nanocarriers, some of which are naturally occurring and others are synthetic polymers. For the selection of polymer to be used for nanomaterial preparation, some points should be kept in mind such as nontoxicity, biocompatibility and biodegradability of the polymers.

Following is the list of polymers commonly used for polymeric nanocarriers preparation:

Natural Polymers :- Chitosan, Albumin, Sodium alginate, Gelatin, Cellulose ether, Xanthan gum, Scleroglucan, Gum Arabica, Tamarind seed polysaccharide, Locust bean gum (Table 2).

Table 2. Applications of natural polymers

POLYMERS	APPLICATIONS
1. Chitosan	For treatment of high cholesterol, osteoporosis, obesity, Crohn's disease, acne [11]
2. Alginate	thickening agent, gelling agent, emulsifier, stabilizer, Textile Printing disintegrater moisture [12]
3. Albumin	Breast cancer surgery, nanoparticulate drug delivery [13]
4. Gelatin	Brittle bones (osteoporosis). Strengthening bones and joints. Strengthening fingernails. Improving hair quality. Weight loss [14]
5. Cellulose ether	coatings, inks, binders, controlled-release drug tablets [15]
6. Tamarind Seed Polysaccharides	stabiliser, thickener, binder, release retardant, modifier, emulsifying agent [16]

Synthetic Polymers :-Polylactides(PLA), Polyglycolides(PGA), Poly(lactide co-glycolides) (PLGA), Polyanhydrides, Polyorthoesters, Polycyanoacrylates, Polycaprolactone, Poly glutamic acid, Poly malic acid, Poly(N-vinyl pyrrolidone), Poly(methyl methacrylate), Poly(vinyl alcohol), Poly(acrylic acid), Poly acrylamide, Poly(ethylene glycol), Poly(methacrylic acid).

Advantages of nanomaterials:

Nanotechnology offers various advantages over conventional drug delivery systems. Cell specific targeting can be achieved by attaching the drug with specifically designed nanocarrier. Nanomaterials like nanoparticles, liposomes, nanospheres, nanoemulsionsetc. have a great potential as drug carriers. Due to their small size and structure, they

exhibit unique biological and physiological properties like enhanced surface area and enhanced ability to cross the biological membranes and barriers[2]. Followings are some of the properties which make them favourable for application in biomedical field [4]:

1. These materials provide a significant improvement over the traditional drug administration method in terms of therapeutic efficacy and effectiveness.
2. Provide targeted and controlled drug delivery to the desired site of action.
3. These are ideal choice for drug delivery in case of cancer therapy, gene delivery, vaccines delivery and delivery of targeted antibiotics
4. Suitable candidates for the tissue engineering.
5. Enhance the stability issue of volatile material fabricated by multitude of methods.

Applications of nanotechnology in drug delivery systems:

1. Nanocarriers drug delivery of protein and peptides:

Traditionally proteins and peptides were delivered through injections i.e subcutaneously, intravenously or intramuscularly. Although their bioavailability was high but fail to maintain sustain plasma concentration. So introduction of nanoparticulate system for the delivery of proteins and peptides maintain the drug release over extended time period and lead to less frequent administration of dose (1).Rodrigues *et al.*studied on lectinnanocarrier conjugate. The study was performed by using dextran/poly(e-caprolactone) polyester polymers and conjugated with three different proteins, lectins from leaves of Bauhinia monandra and Lens culinaris, and bovine serum albumin (BSA) [17].

Yoo and Park studied salmon calcitonin containing PLGA nanoparticles using salmon calcitonin oleate complexes. These complexes were prepared by hydrophobic ion pairing. Theses nanoparticles were quickly taken up by Caco-2 cells and salmon calcitonin is transported to Caco-2 monolayer in vitro. In vivo studies showed salmon calcitonin was orally absorbed [18]. Vranckx*et al.,* also showed almost similar results when they used nanocapsules formulation with hydrophilic core for delivering salmon calcitonin in rats [19].

Alphandary*et al.,* studied the crossing of insulin containing poly (alkylcynoacrylate) nanocapsules through intestinal epithelial barrier to blood compartment where it was absorbed by M-cell free epithelium [20]. Leach *et al.,*reveals that excipients free protein nanoparticles prepared through spray freezing into liquid technology can be prevented from burst effect by dispersing into PLA and PLGA microparticles [21].

2. Nanotechnology in ocular drug delivery:

Topical application of ophthalmic drugs shows poor absorption because of efficient protecting mechanism of eye from foreign materials. These mechanisms are reflex blinking, tear turnover, lachrymation, and drainage which leads to faster removal of drug from the eye. Another barrier for poor drug delivery is the tight epithelium of cornea which compromises the permeation of drugs into the eye. There are many drug delivery system for ophthalmics which are under investigation such as nanoparticles, liposomes, hydrogels, microparticles, collagen shields etc. Colloidal systems like nanosuspensions provides extended drug release in the eye and also enhance the penetration power through cornea, so that the frequency of dose administration and amount of drug both are reduced, which is very helpful and efficient for patient [22]. Adibkia*et al.,* prepared Eudragit RS100 loaded piroxicame nanoparticles for control the inflammatory symptoms in rabbits with endotoxins induced uveitis. The results shows that the non-invasive implementation of piroxicamenanosuspension as a safer controlled ocular delivery of anti-inflammatory agent for treatment of uveitis [23].

Kaur *et al.,* prepared tropicamide loaded carboxymethyl tamarind kernel polysaccharide nanoparticles for enhancement of corneal penetration. The study reveals that the nanoparticles show a better bioavalabilty and enhanced penetration through cornea [24].

3. Nanotechnology for central nervous system drug delivery:

In case of CNS, the blood brain barrier (BBB) plays a significant role in CNS drug delivery [25]. It creates a strict extracellular fluid environment which protects the brain parenchyma from blood composition variation and potential CNS toxic materials. So this barrier regulates the diffusion of drugs toward brain parenchyma and thus the drug diffusion is drastically declined. Conventionally intracerebral or intraventricular route of administration have to be adopted but these are risky and invasive techniques [26-27].

As per the pharmacokinetic, the percent of injected dose which is delivered per gram brain is directly proportional to the blood brain barrier permeability surface area product and the area under the plasma concentration curve [28]. For optimal efficiency nanocarriers administered IV should remain in blood compartment in order to reach brain vasculature and possess an appropriate blood brain barrier permeability surface area in order to deliver their content

beyond the BBB. Owing their size the nanocarriers cannot cross the endothelium of brain capillaries by passive diffusion through normal blood brain barrier. So deliver the drug efficiently in to the brain [29].

Straubinger *et al.,* studied the intravenously administered liposomes poorly spread within the tumor and lined the blood vessels. On repeated administration of Doxil^{R} liposomes, within the tumoran extensive region of haemorrhage occur, which shows the tissue vasculature destruction. The uptake efficiency and intracellular delivery of drug may be enhanced by designing the tumor specific nano drug delivery system [30].

4.Nanotechnology for GIT drug delivery system:
The aim of nanocarriers administration by oral route is basically to decrease the dose and number of dosing and also to enhance patient compliance. Some key point that should be kept in mind before selection of type of nanocarriers are to ensure sustained and controlled drug release from the nanocarrier [31].it should be biocompatible, biodegradable, stable at various chemicophysical environments, nontoxic and should have sufficient drug loading capacity. Mainly the targets in GIT are lymphatic targeting and colon targeting [32].

Peyer's patches are associated with lymphoid tissues which the most important structural units of gut. M- Cells are present over the lymphoid tissues which are specialized for endocytosis. Nanocarriers bind with apical membrane of M-cells and rapidly internalized and shuttled to lymphocytes. The absorption of drug through lymphatic absorption avoids presystemic metabolism by hepatic first pass metabolism [33].

The presences of lymphoid tissues in colon area are present in aggregate masses. So the presence of M-cell may lead to absorption of nanoparticles in the colon area. Basically proteins and peptides can be delivered through this route to protect them from proteolysis. Diseases of colon such as ulcerative colitis or Crohn's disease can be easily treated with colon targeting drug delivery system through nanotechnology. The nanocarriers used for GIT drug delivery are dendrimers. Polymeric nanoparticles, SLNs, and liposomes [34].

Recombinant human epidermal growth factor containing liposomes coated with PGA administered to rats orally and area under curve was evaluated and compared to that of solution. The study shows 1.7 and 2.5 folds enhancement for phosphatidylcholine and dipalmitoylphosphatidylcholine liposomes respectively [35].

Calcitonin containing liposomes coated with chitosan effects were studied on rats' intestinal absorption. The study reveals that the efficacies of coated liposomes were more than double that of uncoated liposomes. But the absorption of calcitonin was poor because of its higher molecular weight and its enzymatic degradation in GIT [36].

5. Nanotechnology in transdermal drug delivery system:
Stratum corneum is the layer from where the transdermal drug delivery is started but it is a most important barrier for most of the nanoparticulate systems. Basically skin has irregular surface area which makes difficult for large particles to cross the skin barriers [37-38]. The nanotechnology is widely used in the cosmetic industry for manufacturing cosmetic products. But it is not necessary for nanoparticulates to be penetrated under stratum corneum, rather it is recommended these should be easily removed by turn-over period of stratum corneum. The drug to be delivered can be dissolved in a suitable liquid phase and spread over the skin but if such solvent is not available than nanoparticulate system comes into consideration. The SLN or polymeric nanoparticles encapsulates the drug and then these nanoparticulates are spread over the skin. After that the medium is evaporate or absorbed on the skin and the drug loaded nanomaterials produce a membrane over the skin which act as a patch. Now the drug concentration over the skin is highly elevated and due to concentration gradient the drug is delivered. The selection of drug candidate for such a nanoparticulate system depends on the molecular weight and hydrophilic properties of the drug [39-41].

6.Nanotechnology in parenteral drug delivery system:
In case of parenteral drug delivery system, the nanosuspensions are considered as the most important formulation approach. As a dosage form nanosuspensions are prepared for the drugs which are insoluble in aqueous medium [42]. Those drugs which have highly binding efficiency to the hydrophobic receptors and poor water solubility are the best candidates for nanosuspensions formulations. These nanosuspensions become the most suitable candidates for parentral drug delivery system as no solvent required; small particle size permits i.v. drug delivery and high entrapment efficiency [43-44]. There are two key factors which influence the nanoparticulate drug delivery, the vascular occlusion due to size and composition of nanoparticles, another factor is the monocyte phagocytic system.Nanoparticles having size more than 7µm are trapped in pulmonary vasculature. In case of lungs alveolar macrophages provide way for passing particles size less than 12 µm through capillary walls [45].

The nanoparticulate system have many application as a parentral drug delivery system such as regional anaesthesia, anticancer agent paclitaxel drug delivery, malignant hyperthermia, intrathecal delivery of drug etc. [46].

7. Nanotechnology in gene delivery:

Gene therapy is an important approach for treatment of genetic disorders like haemophilia, tumours, cystic fibrosis and AIDS. The delivery of genes at targeted site is still a formidable challenge. Genetic materials are labile to the biological environment as well as they don't cross the biological membranes efficiently. Conventionally gene delivery has been performed with viral vectors. In viral vectors, the potential to induce immune responses and the risk of insertional mutagenesis in host genome due to retroviral vectors make them unsuitable for gene delivery [47]. The nonviral vectors include liposomes, nanoparticles etc. are efficient and effective gene delivery vectors. These materials can be prepared by encapsulating genetic materials in polymeric nanoparticles as naked plasmid DNA, condensed with cationic polymers or in noncondensed form. PLA/PLGA nanoparticles containing plasmid DNA are very effective for gene delivery due to their nonimmunogenic nature. These nanoparticles are prepared through water-in-oil-in-water double emulsion solvent evaporation technique using PVA as an emulsifier. The efficiency of encapsulation depends upon the concentration of polymer, its molecular weight and concentration of emulsifier used [48].

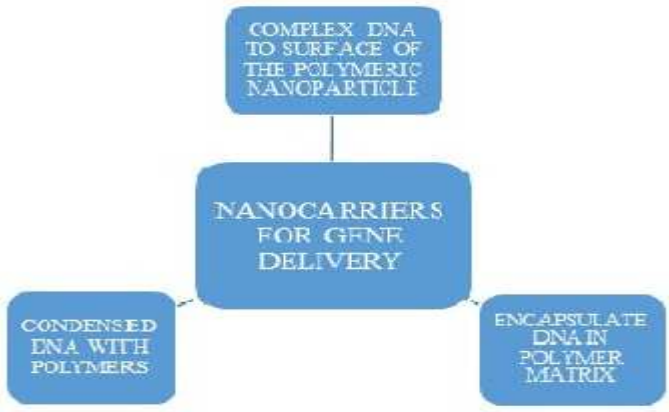

Figure 1. Nanocarriers for gene delivery

8. Nanotechnology in nano-fiber based drug delivery system:

The electro-spinning nanofiber technology was developed in around 1930s, but did not receive much attention. In this technique the drug and polymer of interest is dissolved in an appropriate solvent. This liquid is then filled in a syringe and high voltage is applied. The polymer in small quantity comes out, forming a Taylor cone. By increasing the voltage, the charged fluid jet initiated. To get a stable jet, the charge run above a critical voltage. The molecular entanglements present in the polymer solution prevent the jet from breaking into droplets. This process lead to formation of nanometer to micrometer sized fiber [49].

This technique is very useful for enhancement of drug dissolution of poorly soluble drugs, for wound dressing and sustain release of drug. The polymers like polyglycolide, polylactic acid or polycaprolactone can be used to sustain the release of drug from multiple days to months. However the selection of polymer is important because drug polymer compatibility play a key role [50].

9. Nanotechnology in lipid based nanoparticulate drug delivery system:

Cholesterol, phospholipids and triglycerides are the main components in lipid nanoparticulate drug delivery systems like liposomes and lipid nanoparticles. Phospholipids upon hydration form bilayer membrane vesicles. These systems are highly biocompatible as these are natural components of biological membranes. Drugs are incorporated in these vesicles through electrostatic complexation, conjugation or lipid phase solubilisation [51].

Liposomes are basically phospholipids bilayers with entrapped aqueous volume. These are classified as multilamellar vesicles (>200 nm), large unilamellar (100-400 nm) and small unilamellar (< 100 nm). These are designed to possess the characteristics like long systemic circulation, pH and environmental reductive sensitivity, targeted drug delivery and temperature sensitivity [1].

Wang *et al.*, coencapsulated doxorubicin and verapamil in liposomes and studied there in vitro cytotoxicity. The study demonstrated effective reversal of multidrug resistant in doxorubicin resistant cell lines [52].

10. Nanotechnology in anticancer drug delivery:

Nanocarriers are very important drug delivery systems, transferring conjugated paclitaxel loaded nanoparticles, nanovaccines, magnetic PBCA nanospheres with aclacinomycinA in gastric cancer, Adriamycin loaded nanoparticles for hepatoma treatment, polypropyleniminedendrimer nanoparticles for oligonucleotides, temoxifen nanoparticles for breast cancer treatment [1].

Yoo& Park have report a study of folate receptor targeted anticancer therapy using doxorubicin PEG folate nanoconjugates. *An in vivo study shows* a significant reduction in tumour volume in a human tumour xenograft nude mouse model [53].

CONCLUSION

Nanocarriers are designed to enhance the therapeutic and pharmacological properties of drugs. The entrapment of drug in these nanosystems enhance the stability of drug, increase the residence time in the systemic circulation and decrease the dose of drug as well as number of dosing. The targeted and controlled drug release can be achieved by nanoparticulate system which is a positive prospective in case of gene delivery and anticancer therapy. Because of their small size range, they can easily cross the blood brain barrier (BBB) which is beneficial in CNS drug delivery system. In comparison to conventional drug delivery systems, nanocarriers drug delivery is more selective and efficient. The toxicity and adverse effects are drastically reduced in case of nanocarriers drug delivery. With the several benefits, there are some drawbacks of nanocarriers such as handling difficulty due to smaller size and large surface area can lead to aggregation of nanocarriers. Due to phagocytosis by cells the nanocarriers drug conjugates get destroyed, whereas their intracellular degradation may cause cytotoxicity. Other drawbacks are low loading capacity and efficiency, poor ability to control the size range and lack of technology methods to produce nanocarriers with high quality.

Due to presence of several functional groups on the surface of nanocarriers, drugs can be attached them only in stoichiometric ratio. The conditions like inflammation and oxidative stress in cells have been reported as toxic mechanisms of various nanomaterials. Nanocarriers of size less than 10 nm remain in cells and induce chronic inflammation.

Conclusively, nanosystems may contribute to achieve a controlled and targeted drug delivery system with high therapeutic efficiency. The main biomedical application of nanotechnology are inthe fields of diagnosis and targeted therapy, however, there development are in the embryonic stage. A long journey has yet to be covered to exploit the benefits of nanotechnology in this sphere.

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