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APPLICATIONS OF NOVAL NANOPARTICLES IN PHARMACY

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ABSTRACT

The challenge of nanotechnology is to develop nanoparticles for biomedical and biotechnology applications to deliver the pharmaceutical in the right place at the right time drug. This can be achieved by using nanoengineered devices for target cells at molecular level .Different types of particulated drug delivery systems, microspheres, nanoparticles, liposomes, niosomes, resealed erythrocytes etc.Among these carriers liposomes and nanoparticles have been the most extensively investigated. Among these carriers liposomes and nanoparticles have been the most extensively investigated. Polymeric nanoparticles offer some specific advantages over liposomes. The important technological advantages of nanoparticles used as drug carriers are high stability, high carrier capacity, feasibility, incorporation of both hydrophilic and hydrophobic substances, and feasibility of variable routes of administration, including oral application and inhalation. These properties of nanoparticles enable improvement drug bioavailability and reduction of the dosing frequency, and may resolve the problem of nonadherence to prescribed therapy.Nanaparticles used for antibiotics, antiviral, antiparasitic drugs, cytostatics, protein and peptides.

Keywords: Nanotechnology,Nanoparticles,Types,Drug delivery systems,Polymeric Nanoparticles,Applications.

Introduction

Drug delivery to the body can be divided into two broad groups local and Systemic. The local delivery of drugs is available only for the external sites of the body while drug delivery to the internal sites is usually systemic[1]. Several recent reviews have emphasized an important aspect of pharmaceutical delivery, namely the

accurate targeting of the pharmaceutical to cells or tissue of choice[2]. The challenge of nanotechnology is to develop nanoparticles for biomedical and biotechnology applications to deliver the pharmaceutical in the right place at the right time[3]. Drug delivery approach is aimed at developing nanoscale particles or molecules to improve the bioavaialability of the drug[4]This can be achieved by using nanoengineered devices for target cells at molecular level[5].Drug carrier can be engineered to slowly degrade, react to stimuli and be site specific[6].Delivering drug at controlled rate, slow delivery, targeted delivery are other very attractive methods and have seen pursued vigorously[7].Different types of particulated drug delivery systems ,microspheres, nanoparticles, liposomes, niosomes, resealed erythrocytes etc[8]. Among these carriers liposomes and nanoparticles have been the most extensively investigated[8]. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability[9]. Polymeric nanoparticles offer some specific advantages over liposomes[10]. These are stable, solid colloidal particles consisting of biodegradable polymer, lipids and size range 10-1000nm[11].Nanoparticles are commonly polymeric colloidal carriers of drugs where as solid lipid nanoparticles are lipid carriers of drugs[12].A nanometer is one billionth of a meter, which is 250 millions of an inch. On this scale, materials exhibit properties remarkably different from properties of the bulk material[13]. These systems were developed in the early 1970s[14]. Due to extremely small size of nanoparticles they are costly and more readily taken up by the human body. Biological membranes and access cells ,tissues and organs are recognized for entrance of nanoparticles[15].these cells are not able for cross by the larger sized particles.One can distinguish two types of nanoparticles ;nanospheres, which are matrix systems; and nanocapsules, which are reservoir systems composed of a polymer membrane surrounding an oily or aqueous core[16]. They consist of macromolecular materials in which the active principle(drug or biologically active material) is dissolved, entrapped, or encapsulated, and/or to which the active material is adsorbed or attached[17] .The macromolecular material from which they aremade, can be of synthetic or natural origin.Some

Macromolecular Materials Employedas Nanoparticular Carriers:-Natural – Serum albumin (Human, Bovine,Rabbit, Egg), Gelatin, Lecithin, Collagen,Iron oxide, Casein, etc.Synthetic – Polymethyl metha acrylate(PMMA), Poly alkyl cyano acrylate (PACA),Poly methyl cyano acrylate (PMCA), Poly(D, L-Lactide), Polyarylamide, Ethylcellulose, Eudragit, etc[18]. Nanoparticles from the biodegradable polymer ,from vectors ,lipids are now being developed for further application given as enzyme statinization,immobilization and DNA transactions[19]. The particles formed were stable and easily freeze-dried[20]. Due to these reasons, nanoparticles made of biodegradable polymers were developed for drug delivery[21].Nanoparticles were able to achieve with success tissue targeting of many drugs (antibiotics, cytostatics, peptides , proteins,antiviral , antiparasitic drugs[22], nucleic acids, etc.). Nanoparticles were able to protect drugs against chemical and enzymatic degradation and were also able to reduce side effects of some active drugs[23].Nanoparticle based drug delivery systems have considerable potential for the treatment for tuberculosis, treatment of intracellular infections[24]. The important technological advantages of nanoparticles used as drug carriers are high solubility,high carrier capacity,prolong the exposure to the pharmaceuticals by controlled release from the matrix, their stability ,to cross membrane barrier particularly in CNS & gastro intestinal tract. Capability of incorporation of the both hydrophyllic and hydrophobic substance and friability of various routes of administration,including oral application , inhalational, provide protection against agents which cause degradation[25]. Main disadvantages of the nanoscaled particles are difficult sterilization on large scale, storage and administration because in many cases, the penetrability and the drug concentration in the organ are unknown[26]. major goals in designing nanoparticles as a delivery system are to control particle size ,surface properties and release of pharmacologically active,in order to achieve the site – specific action of the drug at the therapeutically optimal rate and dosage regimen[27]Today nanoindustry is a big industry with about 200 companies involved and 10 billian dollars are being invested in research and development every year ,nanomedicin is credited with bicorporation of more than 3billion dollars worth of manufactured goods world wide .This figure was estimated to 1 trillion dollars by2015[28].

Applications

Depending on the application of interest, nanoparticles may be known by a number of alternative and trade-specificnames, includingparticulate matter, aerosols, colloids, nanocomposites, nanopowders, and nanoceramics.[29]Nanoparticles application for the design of drug delivery systems was made available by the use of biodegradable polymers that were considered to be highly suitable for human applications.[30] Nanoparticles can also be designed to allow controlled (sustained) drug release from the matrix.The important technological advantages of nanoparticles used as drug carriers are high stability, high carrier capacity, feasibility of incorporation of both hydrophilic and hydrophobic substances, and feasibility of variable routes of administration, including oral application and inhalation. These properties of nanoparticles enable improvement of drug bioavailability and reduction of the dosing frequency, and may resolve the problem of nonadherence to prescribed therapy.[31]Nanaparticles used for antibiotics, antiviraland antiparasitic drugs, cytostatics, protein andpeptides.

Resipiratory infections

The most common cause of a respiratory tract infection is one of over 200 viruses. However, a bacteria or fungus can be its cause as well. Viruses causing respiratory infections are highly contagious. And they disperse readily via direct contact. [32]. Recent advances have led to the development of functionalized nanoparticles (NPs) that are covalently linked to biological molecules such as antibodies, peptides, proteins, and nucleic acids. These functionalized NPs allow for development of novel diagnostic tools and methods, particularly for pathogens. Ralph A Tripp et al showed that functionalized NPs conjugated to monoclonal antibodies can be used to rapidly and specifically detect respiratory syncytial virus in vitro and in vivo. Suk et al works suggests that recent improvements in surface chemistry have augmented the ability to make functionalized NPs to create bioconjugated NPs that allow for specific targeting or signal enhancement .[33]The many conventional forms were used to trate the respiratory infections. Recently, however, nanoparticle-based detection strategies have been employed in an effort to develop detection assays that are both sensitive and expedient for

respiratory infections.Gold nanoparticles (AuNPs) have been functionalized with virus specific antibodies or oligonucleotides. In each of these constructs, AuNPs act as both an easily conjugated scaffolding system for biological molecules and a powerful fluorescence quencher. The development of these nanoparticle-based detection strategies holds the potential to be a powerful method to quickly and easily confirm respiratory virus infection.[34]

Asthma

Pulmonary delivery is carried out in a variety of ways – via aerosols, metered dose inhaler systems, powders (dry powder inhalers) and solutions (nebulizers), which may contain nanostructures such as micelles, liposomes, nanoparticles, and microemulsions. Development of nanoengineered polymeric micellar formulations that can address the problem of drug resistance correspond to one focus of this drug targeting dosage form.[35]Mukesh Kumar et al reasoned that a non-viral intranasal IFN-γ gene delivery using chitosan nanoparticles may provide an effective approach for asthma treatment. Mukesh Kumar et al examined the effects of chitosan- IFN-γ pDNA nanoparticles (CIN) using a BALB/c mouse model of allergic asthma. The results show that CIN therapy significantly inhibits the production of IL-4, IL-5, ovalbumin (OVA)-specific serum IgE, airway inflammation, and hyperreactivity.[36]

Anti inflammatory

The severity of allergic asthma is dependent, in part, on the intensity of peribronchial inflammation. P-selectin is known to play a role in the development of allergen-induced peribronchial inflammation and airway hyperreactivity. The nanoparticles were shown to preferentially bind to selectins expressed on activated endothelial cells. [37]Systemic delivery of TNF-α-specific siRNA using cationic lipid-based nanoparticles show effective anti-inflammatory effects in arthritic mice.[38]. In the last years much interest has been focused on nanoparticles, as a drug delivery systems, due to their possibilities of increasing drug efficacy, reducing toxicity and controlling drug release. Seijo *et al.* reported a dexamethasone entrapment efficiency of 75% in PIBCA nanospheres prepared by the in situ polymerizationprocedure and Song *et al.* presented a drug entrapment of 79.6

% in PLGA nanospheres obtained using an emulsification/solvent evaporation technique. In addition, Fessi *et al.* usingnanodispersion of the preformed poly(DL-lactide) showed a drug entrapment of 40% in nanocapsules. [39]

Drug Delivery to Eye

Drug delivery to ocular region is a challenging task. Only 1-2% of drug is available in eye for therapeutic action, rest of the drug is drained out through nasolachrymal drainage system and other ocular physiological barriers.[40] Nanoparticles and nanosuspensions are showing a better application as compare to conventional delivery sysyems. Polymer nanoparticles proposed are reported to be devoid of any irritant effect on cornea, iris, and conjunctiva and thus appear to be a suitable inert carrier for ophthalmic drug delivery. Nanoparticles represent promising drug carriers for ophthalmic applications. After optimal binding to these particles, the drug absorption in the eye is enhanced significantly in comparison to eye drop solutions owing to the much slower ocular elimination rate of particles. Smaller particles are better tolerated by the patients than larger particles therefore nanoparticles may represent very comfortable ophthalmic prolonged action delivery systems. Biodegradable polymer nanoparticles have great potential as drug delivery devices for the eye.The major developmental issues in the case of nanoparticles include formulation stability, particle size uniformity, control of drug release rate, and large-scale manufacture of sterile preparations. Nanosystems having surface-segregated chitosan or polyethyleneglycolhavebeen found to be relatively stable and also efficient at overcoming mucosal barriers. Wood *et al* showed that PACA nanoparticles were able to adhere to the corneal and conjunctival surfaces, which represent their mucoadhesion property. PACA (polyacryl-cyanoacrylate) polymer has the ability to entangle in the mucin matrix and form a noncovalent or ionic bond with the mucin layer of the conjunctiva. 4. poly-caprolactone (PECL) nanocapsules may serve as superior polymer systems for ocular drug delivery. [41]

In our present work, levofloxacin encapsulated poly(lactic-co-glycolic acid) nanoparticles were developed and evaluated for various parameters like particle size, zeta potential, in vitro drug release and ex vivo transcorneal permeation. The nanosuspension thus developed was retained for the longer time and drained out from the eye very slowly compared to marketed formulation as significant radioactivity was recorded in later in kidney and

bladder. The developed nanosuspension with a mean score of 0.33 up to 24 h in HET-CAM assay, showed the nonirritant efficacy of developed formulation.

Antiviral agents

Using nanoparticles as a drug carrier system could improve the delivery of antiviral agents to the mononuclear phagocyte system in vivo, overcoming pharmacokinetic problems and enhancing the activities of drugs for the treatment of HIV infection and AIDS.In acutely infected cells, an aqueous solution of saquinavir showed little antiviral activity at concentrations below 10 nM, whereas the nanoparticulate formulation exhibited a good antiviral effect at a concentration of 1 nM and a still-significant antigen reduction at 0.1 nM (50% inhibitory concentrations 5 4.23 nM for the free drug and 0.39 nM for the nanoparticle-bound drug). At a concentration of 100 nM, saquinavir was completely inactive in chronically HIV-infected macrophages, but when bound to nanoparticles it caused a 35% decrease in antigen production. [42]*In vitro* studies have demonstrated that polyvinylpyrrolidone coated silver nanoparticles (PVPcoated AgNPs) have antiviral activity against HIV-1 at non-cytotoxic concentrations. These particles also demonstrate broad spectrum virucidal activity by preventing the interaction of HIV-1 gp120 and cellular CD4, thereby inhibiting fusion or entry of the virus into the host cell. In this study, Humberto H Lara et al evaluated the antiviral activity of PVP-coated AgNPs as a potential topical vaginal microbicide to prevent transmission of HIV-1 infection using human cervical culture, an *in vitro* model that simulates *in vivo* conditions.[43]Using nanoparticles as a drug carrier system could improve the delivery of antiviral agents to the mononuclear phagocyte system in vivo, overcoming pharmacokinetic problems and enhancing the activities of drugs for the treatment of HIV infection and AIDS.[44]Pamela R.Hall et al used carboxyl linkages to conjugate selected cyclicpeptides to multivalent nanoparticles and tested infection inhibition and found that multivalent inhibitors may disrupt polyvalent protein-protein interactions, such as those utilized for viral infection of host cells, and may represent a useful therapeutic approach.[45]

Humberto H Lara et al data suggest that silver nanoparticles exert anti-HIV activity at an early stage of viral replication, most likely as a virucidal agent or as an inhibitor of viral entry.[46]

Diabetes

Polymeric nanoparticles have been used as carriers of insulin. These are biodegradable polymers, with the polymer–insulin matrix surrounded by the nanoporous membrane containing grafted glucose oxidase. This can cause an increase in the swelling of the polymer system, leading to an increased release of insulin. The polymer systems investigated for such applications include copolymers such as *N*, *N*-dimethylaminoethyl methacrylate and polyacrylamide . The development of improved oral insulin administration is very essential for the treatment of diabetes mellitus to overcome the problem of daily subcutaneous injections. In one such study, calcium phosphate–poly (ethylene glycol)–insulin combination was combined with casein (a milk protein) . The casein coating protects the insulin from the gastric enzymes. Due to casein's mucoadhesive property, the formulation remained concentrated in the small intestine for a longer period, resulting in slower absorption and longer availability in the bloodstream. Temperature sensitive nanospheres made from poly (*N*-isopropylacrylamide) and poly (ethylene glycol) dimethacrylate were shown to protect the loaded insulin from high temperature and high shear stress; such a polymeric system can be an effective carrier forinsulin. P.S. SONA* combined dextran sulphate with polyethylenimine nanoparticles was shown to exhibit a high level of insulin entrapment and an ability to preserve insulin structure and biological activity in vitro. Poly (methacrylic acid)–based nanoparticles that are encapsulated in cyclodextrin–insulin complex have also been reported as an effective oral delivery system . These approaches substantiate the potential use of polymeric nanoparticles in oral administration of insulin, thereby bypassing the enzymatic degradation in the stomach. Insulin molecules can be encapsulated within the nanoparticles and can be administered into the lungs by inhaling the dry powder formulation of insulin. Preclinical studies in guinea pig lungs with insulin-loaded poly (lactide-co-glycolide) nanospheres demonstrated a significant reduction in blood glucose level with a prolonged effect over 48 hours when compared with insulin solution . Insulin-loaded poly (butyl cyanoacrylate) nanoparticles when delivered to the lungs of rats were shown to extend the duration of hypoglycemic effect over 20 hours when compared with pulmonary administration of insulin solution .[47]The insulin loaded NPs coated with mucoadhesive CS may prolong their residence in the small

intestine, infiltrate into the mucus layer and subsequently mediate transiently opening the tight junctions between epithelial cells while becoming unstable and broken apart due to their pH sensitivity and/or degradability.[48]Orally delivered nanoparticles lowered basal serum glucose levels in diabetic rats around 35% with 50 and 100 IU/kg doses sustaining hypoglycemia over 24 h.[49]

Tuberculosis

The pharmacokinetics and antibacterial effect of the nanoparticlebound anti-TB drugs administered via respiratory route was investigated in guinea pigs. A single nebulization of RMP, INH, and PZA coencapsulated in PLG nanoparticles to guinea pigs resulted in sustained therapeutic drug levels in the plasma for 6 to 8 d and in the lungs for up to 11 d.Nanoparticle-based systems have significant prospective for diagnosis, treatment and prevention of tuberculosis (TB). The development of aerosol vaccine is undergoing which could provide a great potential in prevention of tuberculosis infection. Scientific community believe that nanotechnology offers new ways to address residual scientific concerns for *Mycobacterium tuberculosis* (TB). Chemotherapy of TB is complex due to the requirement of multi drug regimens that need to be administered over long periods. Gelperina *et al.* summarizes major data on nano-particulate formulations of the anti-TB drugs Nanotechnology has provided a huge improvement to pharmacology through the designing of drug delivery systems able to target phagocytic cells infected by intracellular pathogens, such as mycobacteria. The increased therapeutic index of anti-mycobacterial drugs; the reduction of dosing frequency; and the improvement of solubility of hydrophobic agents, allowing the administration of higher doses, have been demonstrated in experimental infections. The Rising rates of tuberculosis and drug-resistant disease in developing countries have also amply illustrated the need for better diagnostic tools and effective vaccines.[50] We evaluated the efficacy of nanoparticle-encapsulated antituberculosis drugs administered every 10 days versus that of daily nonencapsulated drugs against *Mycobacterium tuberculosis* aerosol infection in guinea pigs. Both treatments significantly reduced the bacterial count and lung histopathology, suggesting that the nanoparticle drug delivery system has potential in intermitted treatment of tuberculosis.[51]

Tumours

Nanodelivery has shown tremendous promise in targeting drugs at tumors. Tumor microvasculature typically contains pores 100-1,000 nm in diameter, while healthy heart, brain and lung tissue is 10 nm or less. So by manufacturing nanoparticle-based drug molecules between 75-900 nm, researchers and manufacturers have been able to create compounds that selectively target only malignant tissue.[52] The rationale of using nanoparticles for tumor targeting is based on 1) nanoparticles will beable to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or activetargeting by ligands on the surface ofnanoparticles;2) nanoparticles will reduce thdrug exposure of health tissues by limiting drugdistribution to target organ.[53]Recently gold nanoshells used to detect and treat cancerous tumors. The nanoshells are imaging agents that also function as therapeutic agents.[54]

Cancers

The binding capacity of these nanoparticles to dactinomycin (90%), vinblastin (36–85%) and methotrexate (15–40%) exceeds that of these drugs incorporated in liposomes.[55] It is widely known that nanoparticles are beneficial tumor targeting vehicles due to their passive targeting properties by the enhanced permeability and retention (EPR) effect, whereby the added advantage of stealth shielding the particles with a poly ethylene glycol/oxide (PEG/PEO) surface modification avoids uptake by the reticuloendothelial system, thereby improving circulation time of the nanoparticles .Hyaluronic acid–coupled chitosan nanoparticles bearing oxaliplatin (L-OHP) encapsulated in Eudragit S100–coated pellets were developed for effective delivery to colon tumors . SLN have been proposed as new approach of drug carriers. SLN carrying cholesteryl butyrate (chol-but), doxorubicin and paclitaxel had previously been developed. [56]The use of solid lipid nanoparticles in medicine and more specifically drug delivery is set to spread rapidly.Gold nanoparticles are considered potential anti-cancer drug carriers for a number of reasons. In this research, we investigated gold's potential to deliver the inflammatory cytokine tumor necrosis factor-alpha (TNF-α) to augment thermal injury selectively in tumor cells. Both freezing and laser

heating were used to induce thermal injury.[57] Currently many substances are under investigation for drug delivery and more specifically for cancer therapy technology is the latest trend in the cancer therapy.

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