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# Nanoparticles as 'smart' pharmaceutical delivery

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## 1. ABSTRACT

Pharmaceuticals in conjunction with nanoparticle delivery systems are growing towards new heights. The aim of this review is to gain a thorough understanding of different types and characteristics of nanoparticle based delivery systems, important properties of delivery systems, pharmaceutical ingredient loading and release in the nanoparticle delivery systems. In this review, we have also highlighted about the promising pharmaceutical deliveries like brain targeted delivery, ocular delivery, oral delivery, dermal and transdermal delivery, cancer chemotherapy, vaccine delivery, nucleic acids delivery and delivery system coupling to implants. A snapshot of the

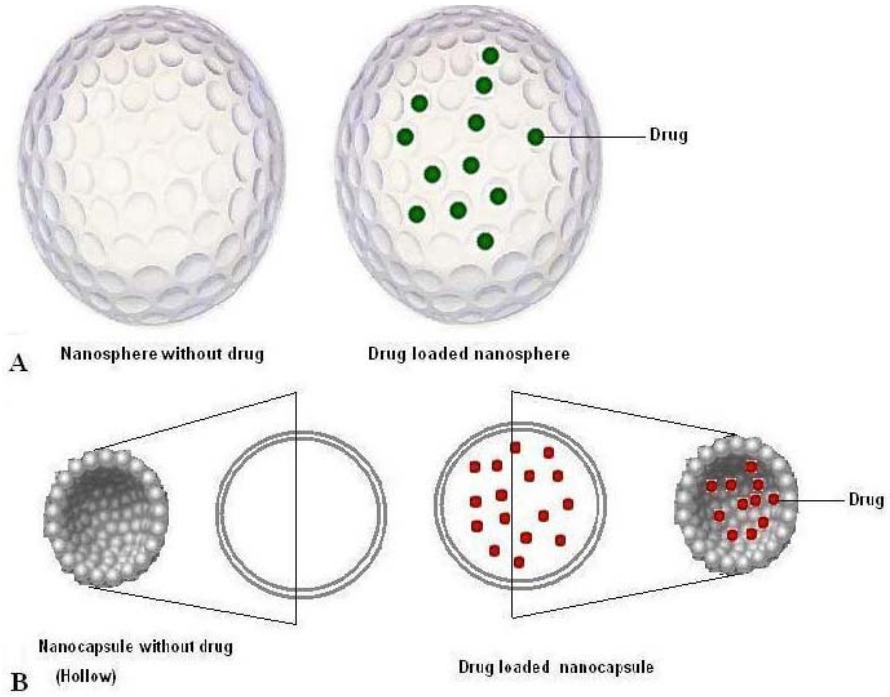


**Figure 1.** Biodegradable nanoparticle based drug delivery system. (A) nanosphere ( B) nanocapsule

nanoparticle mediated drug deliveries which are commercially available and ongoing clinical trials have been provided.

## 2. INTRODUCTION

Drug delivery technologies play a vital role in pharmaceutical industry. The efficiency and marketability of drugs depends on the mode of delivery. Currently, industries are moving to new delivery systems to effectively and safely deliver novel products and formulations. Several products derived from new delivery systems are generating interest in the medical practice in recent years causing several pharmaceutical companies to pioneer drug delivery system development (1, 2). With the help of a new drug delivery system, an existing drug candidate molecule obtains a new chance. Its market price, competitiveness and patent life are increased (3). On the other hand, patent expiration is one of the biggest current concerns for the pharmaceutical industry. To go around this, a new drug delivery system can give an existing drug a new marketability. Henceforth, the development of novel delivery systems is a high priority for the pharmaceutical companies especially because the global market for drug delivery systems in 2010 was recorded at $131.6 billion and will hold $137.8 billion by the end of 2011 and $175.6 billion by 2016 end. Therefore, the sell is expected to rise at a compound annual growth rate (CAGR) of 5% (4).

Nanotechnology is an exhilarating area for the development of drug delivery systems using nanoparticles, with dimension range of 1-100 nm (5, 6). Nanoparticles have the ability to deliver an ample range of molecules to varying areas of the body and for sustained periods of time. For a nanoparticle based delivery system, the key objectives are size of particles, surface properties as well as discharge of drugs or the active ingredients to accomplish highest efficacy (7, 8). During the early 1980s, a number of delivery systems were formulated to get better the effectiveness of drug active agents and to reduce toxic side effects (9). During that time, micron sized particles or microparticles were formulated; but there was a size limit. Conversely, for the pharmaceutical industry, drug-loaded particles were comparatively less efficient due to rapid phagocytosis particularly after intravenous administration (10). Nowadays, this problem has been resolved through the surface modifications of the delivery particles.

In this review paper, we highlight the different varieties and properties of nanoparticle based drug delivery systems and different promising pharmaceutical delivery systems. Further, we discuss the toxicological effects, commercial applications and future direction of nanoparticle based delivery systems.

## 3. NANOPARTICLES-BASED DELIVERY SYSTEMS: TYPES AND PROPERTIES

Delivery technologies represent an important broader part of science, which engages multidisciplinary methodical improvement. Usually, delivery systems are associated with a carrier. In nanoparticle based delivery systems, the active compound is dissolved or entrapped or encapsulated in the carrier; in addition, the active compound could be adsorbed or attached to the nanoparticle (11). Often the drug is attached with the nanosphere and encapsulated in nanocapsule (Figure 1). There are several advantages of nanoparticles as delivery

systems. First, the particle size, particle morphology and surface charge of nanoparticles can be easily controlled (12). Second, controlled and sustained discharge of the active molecule in the time of the delivery and at the location of localization. Third, particle degradation properties can change with a modified carrier. Lastly, the site-specific delivery can be carried out in nanoparticle based delivery systems that can be used for various routes of drug deliveries like oral, nasal, parenteral, etc. Based on the importance, the development of nanoparticle based delivery systems is rapidly growing using proteins, natural polymers, synthetic polymers, and fullerenes.

### 3.1. Protein based delivery systems

Several nano-sized protein based delivery systems are available (Figure 2A). Albumin, gelatin, gliadin and legumin are the protein based nanoparticles which play a vital role in drug delivery. Among these proteins, albumin, gelatin are animal based; gliadin and legumin are plant based.

#### 3.1.1. Albumin

Albumin is a versatile protein carrier, and extensively used to construct nanospheres and nanocapsules (13). Albumin is a plasma protein which is well accepted due to its harmless in nature such as non-hazardous, non-immunogenic, biocompatible and biodegradable nature (14). Several nanotechnological methodologies such as desolvation, emulsification, thermal gelation, nano-spray drying and self-assembly are used quite often for fabrication of albumin nanoparticles especially from bovine serum albumin (BSA) as well as human serum albumin (HSA) (15,16). Albumin carries different reactive groups such as thiol, amino, and carboxylic groups. These groups can be applied for ligand binding or other surface alterations. Albumin has a tendency to accumulate on solid tumors (17) and therefore, this property has been explored for site-specific delivery of anti-tumor drugs. For example, noscapine, a benzylisoquinoline alkaloid from plants of the papaveraceae family has been recently delivered to tumor cells to see its efficacy as anticancer agent using HSA nanoparticle carrier. Here, optimal ranges (150-300 nm) of HSA nanoparticle size and drug-loading effectiveness (85%-96%) have been achieved (18). Therefore, albumin nanoparticle is particularly useful for efficient delivery of chemical and pharmaceutical active ingredients.

#### 3.1.2. Gelatin

Gelatin comes from collagen which is a fundamental component of animal skin, bones or connective tissue and used in the production of nanoparticle delivery systems. Stringy collagen, an insoluble protein, is hydrolyzed to prepare gelatin (19). It is a biodegradable and non-toxic nanoparticle that is easy to crosslink (20). As such, there is an enormous scope for the research of colloidal drug delivery using gelatin (21, 22). Gelatin molecule contains amino acids such as glycine, proline and alanine; and these amino acids are accountable for the helical arrangement especially triple helical structure of this molecule (23). Sometimes, chemical modifications can be performed in the process of preparing the nanoparticles for the development of a drug delivery system (24).

Recently, a study by Lee *et al.* (25) loaded three dissimilar drugs (tizanidine hydrochloride, gatifloxacin and fluconazole) in gelatin nanoparticles. This group reported that gelatin nanoparticle filled with tizanidine hydrochloride, blank nanoparticles and gatifloxacin- filled nanoparticles, under crosslinked situation, 59.3, 23.1 and 10.6% yield of drug loaded gelatin. In another study by Zhao *et al.* (26), they used gelatin nanoparticles with insulin used for diabetes treatment through pulmonary administration. These findings reflect the better bioavailability, speedy and stable hypoglycemic outcome. Several reports on the applications of gelatin nanoparticle based drug delivery systems include ocular delivery (27), anticancer drug delivery (28), etc. In gelatin drug delivery system, the outer of layer gelatin capsule (hard and soft ) has a tendency to form inter or intra-molecular cross-link that is dependent on time, temperature and humidity; because of this trend, the use of gelatin in pharmaceutical formulations is debated (29).

#### 3.1.3. Gliadin

Gliadin, a plant based protein, is suitable for the construction of mucoadhesive nanoparticles. It can be extracted from wheat and vicillin (30). Based on the natural origin, biodegradability, and biocompatibility, this nanoparticle is used in various drug deliveries. This drug delivery is used for controlled release of pharmaceutical ingredients (31). To evaluate its bioadhesive properties, gliadin nanoparticle was added to carbazole in two forms i.e. non-hardened gliadin nanoparticles (NPs) as well as cross-linked gliadin nanoparticles (CL-NP). Both of these nanoparticles showed a good absorption at the upper gastrointestinal regions, especially in the stomach mucosa (32). When gliadin nanoparticles were used for the oral delivery of tetanus toxoid, the results showed 50% w/w antigen stability over 3 weeks of testing (33). Thus, it has greater potential for the delivery of active molecules in targeted therapy of upper gastrointestinal tract and possibly for other targeted delivery systems.

#### 3.1.4. Legumin

Legumin is a protein from pea and a source of sulfur-containing amino acids. Legumin-based nanoparticle delivery systems can be made following aggregation and chemical cross-linkage with glutaraldehyde (34). Irache *et al.* (35) prepared legumin nanoparticles of approximately 250 nm diameter using the pH-coacervation method and chemical cross-linking with glutaraldehyde. However, one study with legumin immunized rats robustly expressed antibodies against this protein. This may be due to the reduction of antigenic epitopes of is protein bring on the glutaraldehyde employed throughout the cross-linking (34).

### 3.2. Natural polymers and their derivates

Nanoparticle based delivery systems can be prepared from different natural materials. Chitosan, dextran, starch, liposome (Figure 2B) etc. are such nanoparticle based drug delivery systems.

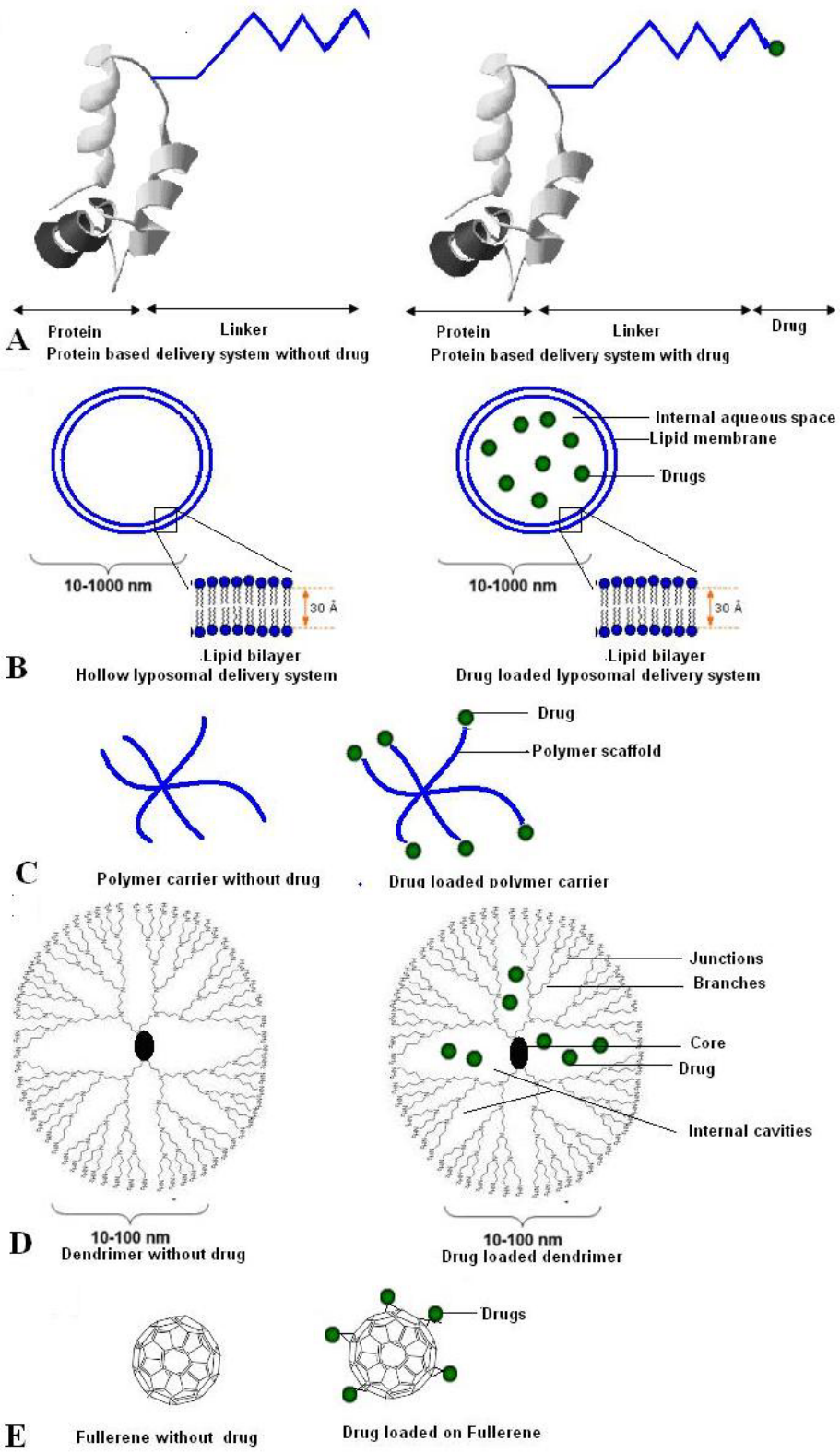


**Figure 2.** Different types of drug delivery system (A) protein based delivery systems (B) natural material based drug delivery system (liposamol drug delivery) (C) polymer drug carriers (D) dendrimer drug delivery system (E) fullerene drug delivery system

### 3.2.1. Chitosan

Chitosan, is a structural part within exoskeleton of subphylum crustaceans, can be formed commercially by deacetylation (36). It is biodegradable, safe, biocompatible, easily modified, no difficulty for DNA or protein composite formation, widespread accessibility, and low-priced which makes the chitosan a promising delivery system. It is of natural origin making it well accepted for the biological applications. Chitosan, a mucoadhesive polymer increases the cellular permeability, improves the bioavailability of orally delivered protein based drugs (37) and boosts the protein uptake (38-41). Oral delivery of chitosan DNA nanoparticles was examined for vaccine delivery and seems to be useful for inducing immune system against *Toxoplasma gondii* (42).

### 3.2.2. Dextran

Dextran is a complex, polysaccharide of D-glucose monomers linked by glycosidic bonds (43). Magnetite dextran nanoparticles can be developed from dextran. These particles have null zeta potential which contributes to high safety margin and efficacy (44). Presently, this polysaccharide nanoparticle is used as drug carrier system (45) in tumor targeted delivery (46), oral delivery of insulin (47), reticuloendothelial delivery (48) etc. It has been reported that chitosan-carboxymethyl dextran nanoparticles regulate cell proliferation and serum cytokine (49).

### 2.2.3. Starch

Starch is a natural polymer found in grains of plants like rice, corn, wheat, tapioca, potato etc. It is biodegradable and abundant biomass material in nature (50, 51). Nanocrystal (52), nanoparticles (53) and nanocolloids (54) were prepared from the starch. Several researchers have used starch as a drug delivery system. Cross-linked starch nanoparticles with hydrophobic end were used for drug delivery of indomethacin (55). Starch has been used as drug delivery system for tumor-targeted drug delivery (56), trans-dermal drug delivery (57) and brain tumor-targeted drug delivery (58). A starch microsphere is utilized as drug delivery for tissue engineering. This starch microsphere further loaded with definite growth factors and immobilized, and can be employed for delivery of encapsulate living cells (59).

### 3.2.4. Liposome

Liposome, made of lipid bilayer, is an extensively explored drug delivery system. Its diameter varies from 20 nm to more than a few hundreds of nanometers and width of the phospholipid bilayer is about 4–7 nm (60). Liposomes can be classified into three forms such as multilamellar vesicles (MLV), small unilamellar vesicles (SUV) and large unilamellar vesicles (LUV). MLV consists of a number of concentric bilayers in a particle and the diameter of this liposome may differ from hundred to thousands of nanometers. MLVs can be processed to produce unilamellar vesicles. According to size, unilamellar vesicles can be classified into two types such as small unilamellar vesicles (SUV) and large unilamellar vesicles (LUV). SUVs show a diameter lower than 100 nm, while LUVs have diameter bigger than 100 nm (61-63). In addition, there were several reports indicating the application of liposomes as dyes in textiles (64), pesticides for plants (65), food ingredients (66) and cosmetics to the skin (67) in areas other than drug delivery systems. Several drugs are in clinical trials, which use liposomal delivery systems (68). However, for targeted cancer drug and therapeutic protein delivery, liposome constructed with PEG (Polyethylene Glycol) is one of the sought after preferences for the delivery. It can increase the plasma stability and solubility property of the drug. Conversely, this increase properties help to decrease its immunogenicity and now PEGylated drugs in clinical practice. One example of PEGylated drug is Oncaspar (PEG–L-asparaginase) which familiar to treat acute lymphoblastic leukemia (68).

### 3.3. Polymeric carriers

Several polymer based carriers are available (Figure 2C) such as polylactic acid, block copolymers, polyethyleinemine, etc. These polymer carriers are significant in drug delivery systems.

### 3.3.1. Polylactic acid

Polylactic acid (PLA), thermoplastic aliphatic polyester, is promising biodegradable polyester (79). PLA is a member of the family of aliphatic polyesters. This family usually composed of α -hydroxy acids. Polylactic acid nanoparticles are used as colloidal drug delivery system for lipophilic drugs (70). This type of delivery system is regularly used for the cancer related drug delivery (71, 72). For example, PEG-coated polylactic acid nanoparticle was used for the delivery of Hexadecafluoro zinc phthalocyanine (ZnPcF16) for the mammary tumor therapy (71). Another example, cucurbitacin, was delivered using polylactic acid nanoparticles to oral cancer (72). Recently, PLA is used for the Plasmid DNA delivery. These results showed lower cytotoxicity compare to Lipofectamine 2000. PLA can transfer gene into HELA cells. From this we conclude that PLA can be a promising non-viral nano-device for cancer gene therapy (73).

### 3.3.2. Block copolymers

Block copolymers, a type of copolymer, is made up of different polymerized monomers (74). Amphiphilic block copolymers encompass the capacity to bring together into multiple morphologies in solution (75). However, vesicle configuration of amphiphilic block copolymers depends on raise in total molecular weight and increasing bending modulus ($K$). A vesicular morphology is applicable in the fields of drug delivery (76). Amphiphilic linear-dendritic block copolymers (LDBC) have been developed for drug delivery (77). Further, synthesized LDBC was established to be a candidate for drug delivery due to some important characteristics such as relative stability, drug encapsulation and release property (78). *In vitro* release behavior of LDBC can be controlled by light which is a potential carrier for controlled drug delivery (79). Recently, biodegradable amphiphilic copolymer was used for cancer drug delivery (80, 81). Eg. Block copolymer COPY-DOX showed high anticancer efficacy in the course of some biochemical test such as MTT assays against cancer cells (80).

### 3.3.3. Polyethyleinemine

Polyethyleneimine, containing secondary amines, is a biodegradable polymer and widely used in the cell culture for the attachment of weakly anchoring cells (82). It is insoluble in cold water, benzene, etc. This polymer includes primary, secondary, and tertiary amino groups. Polyethyleneimine is also used in gene delivery (83, 84) and gene therapy (85). It is also used for drug delivery (86) especially to cross the blood-brain barrier (87). Extreme cytotoxic effect prevents its use from drug delivery (88).

### 3.4. Dendrimers

Dendrimers are branched polymers, presently used a significant drug carrier system (Figure 2D). Poly (amidoamine) spherical dendrimers, poly (Propylene Imine) dendrimers are similar type of nanoparticle.

### 3.4.1. Poly (amidoamine) spherical dendrimers (PAMAM)

Poly (amidoamine), is one of the well known dendrimers which conatin a diamine. This is commonly used in analytical chemistry in the separation science (89-91). These molecules are used in gene delivery (92). Gamma-Glutamyl PAMAM dendrimers are used as versatile precursor for dendrimer-based delivery of active pharmaceuticals (93).

### 3.4.1. Poly (propylene imine) dendrimers (PPI)

During the last few years, poly (propylene imine) dendrimers (regularly branched molecules) is popular due to their unique physical properties. Poly (propylene imine) dendrimers are the preeminent surveyed dendrimer systems (94-97). Numerous hybrid dendrimers have been prepared with different end groups with distinctive characters (97-100). Multifunctional dendrimeric systems derived from poly (propylene imine) dendrimers are used as targeted drug delivery systems to encapsulate the drug (101). In a study, antimicrobial activity was analyzed using this delivery system against Bacillus subtilis, Staphylococcus aureus and Escheriachia coli where exceptional inhibition capacity was reported against these bacteria. They used with silver nanoparticles as antimicrobial drug (102). Dendrimer is toxic due to its positively charged exterior part. However, this toxicity can be reduced by putting an outside layer these peripheral cationic groups with carbohydrate residues (103).

### 3.5. Fullerene

Fullerene, a hollow sphere or tube composed of carbon, can be used as a drug delivery system (Figure 2E). Buckyball clusters are examples of fullerene which have been studied for drug delivery.

### 3.5.1. Buckyball clusters

Buckyball clusters have hexagons and pentagons linked jointly in a coordinated manner and can develop a hollow ground with bonding strains composed entirely of carbon. All these molecules are used in delivery systems particularly for drugs (104,105).

### 3.6. Carbon nanotubes (CNTs)

Carbon nanotubes, covalently bonded fullerenes, are used as molecular anchors (106). These fullerenes have bigger inner volume which can be used as the active molecule container. Therefore, several molecules can be attached with this carrier which is readily taken up by the cell (107). CNTs are used in the drug delivery of several molecules, especially for cancer drugs (108,109). These can be applied as biological transporters as well an agent for some cancer cell destruction (108). *In vivo* distribution and tumor targeting of CNTs have been studied (109). Concerns about CNTs that prevents advancement in its drug delivery applications include lack of solubility, clumping and aggregation and 6.8h half-life (110**).** However, studies have demonstrated that functionalized CNTs are non-cytotoxic (111). CNT has fibrous contour which is needle-like and toxic property has been related with asbestos. One of the major concerns is that extensive application of CNT may lead to cancer especially lung cancer (253). However, to avoid excessive surface interactions, CNT can be used as nanocapsules shown its biocompatibility for intravenous drug delivery (254).

## 4. MAIN FACTORS FOR NANO BASED DELIVERY SYSTEMS

There are two main governing factors for the nanoparticle based delivery systems: particle size and surface charge.

### 4. 1. Particle size

Drug loading and its release is affected by particle size distribution (112). Higher intracellular uptake of nanoparticles has been recorded compared to micron sized particles. Nanoparticles can access wide collection of biological targets because of their tiny size and mobility (113). Delivery and distribution experiments have suggested that nanoparticles greater than 230 nm size can congregate in the organ especially in spleen due to the capillary size of this organ (113). Several *in vitro* studies have pointed out that particle size can also control the cellular uptake of nanoparticles (114, 115). Further, it has been found that particle size is significant for oral drug delivery (113,116). Topical application to the eye is the well established route (113,256**).** However, it has been found that small size differences may be of influence for the actual distribution and bioavailability (113,225).

Smaller nonoparticle has more surface area. So, the majority of the drug associated would close to the exterior part leading to rapid drug release (117). The large surface area causes the active ingredient to be coupled with in or near the particle exterior part, and this result in faster active ingredient release (117).

### 4. 2. Surface charge

Surface charge is another important nanoparticle drug delivery system property that can affect the outcome of particles. Surface charge of gold nanoparticles with PEG caused efficient internalization in endosomes and cytosol (118). Poly (DL-lactide-co-glycolide) nanoparticles were found to be ingested by cells by endocytosis (119, 120). It

is found that after entering, the nanoparticles get away from these endosomes into the cellular cytoplasm. This depends upon the change in surface charge especially from negative to positive (eg. the PLGA NP resulting in cytoplasmic delivery). It is hypothesized that the positive surface charge influences the escape of these nanoparticles from endosomes (119).

The blood-brain barrier (BBB) is an electrostatic barrier to boundary brain penetration of therapeutics. It has been reported that nanoparticle surface charge can alter blood-brain barrier permeability (121). When the particles are absorbed in the blood, their surface hydrophobicity is related with the amount of adsorbed blood components (122).

## 5. PHARMACEUTICAL INGREDIENTS LOADED IN THE NANOPARTICLE DELIVERY SYSTEMS

One of the properties to be taken into consideration for a successful nanoparticle drug delivery system is its high loading capacity. This feature is necessary to reduce the volume of the carrier molecules required for administration. The loading of pharmaceutical ingredient in the delivery systems can be performed by two methods: i) Incorporation method: Integrate the drug at the time of nanoparticles production or polymerization in the presence of the drug. This technique is known as incorporation method. ii) Adsorption method: in this method, adsorbing the drug by particles can be performed by incubation in solution.

Drug adsorption is depended on the affinity of the drug to the polymer dispersed in the polymer matrix in the form of a solid solution (123). It has been recorded that the majority of drugs are being entrapped by the incorporation method (124, 125). Additionally, other than the above two methods, another new method of drug loading was proposed by Yoo et al. (126) for the water-soluble drugs. In this method, drug was placed into nanoparticles where doxorubicin-loaded PLGA nanoparticles were prepared for the experiment.

Drug loading is related with the amount of drug bound per mass (generally moles of drug per mg nanocarrier) and represented on a percentage basis. Drug loading is influenced by the type of surface-active materials and stabilizers (127) present. The adsorption of unlike psycho-pharmacological agents onto NPs of poly (isobutylcyanoacrylate), PIBCA, has been studied using different pH range (128). However, several studies demonstrated that the employment of ionic interface between the drug and matrix materials is one of the successful ways to boost the drug loading (129, 130). The ionic interaction is inversely relative to the distance between the two charged atoms, and also related to the nature of the environment. This enhances the effect of an ionic interaction. This interaction seems to be most important preliminary interaction as the drug enters the binding site. One example is mesoporous nano materials. It was found that mesoporous SBA-15 is more significant for the adsorption and release of BSA. This is because of the equilibrium of electrostatic interaction and hydrophilic interface between BSA and SBA-15 (256).

## 6. PHARMACEUTICAL INGREDIENT RELEASE FROM DELIVERY SYSTEMS

Pharmaceutical ingredient release from nanoparticles and consequent biodegradation are most vital for a new formulation. Pharmaceutical ingredient must be homogeneously spread or suspend in the matrix. If the dispersal of the drug is more rapid than delivery systems degradation, then the process of drug release occurs primarily by diffusion; or else it depends upon degradation. Thus, diffusion and biodegradation govern the process of drug release (131, 132). However, the release rates of pharmaceutical ingredients from delivery systems depend upon conditions such as i) desorption of the surface-bound /adsorbed drug; ii) diffusion of pharmaceutical ingredient from nanocarrier; iii) diffusion of drug through the nanocapsule wall (if the carrier is nanocapsule); and finally, iv) a combined erosion/diffusion process pharmaceutical ingredient and nanocapsules (131).

We can quantify *in vitro* drug release using various methods such as diffusion of cells with membranes, equilibrium dialysis method etc. (131, 133). These methods are useful to assess pharmaceutical ingredient release from the nanocarrier.

## 7. PROMISING PHARMACEUTICAL DELIVERIES

The market of drug delivery in the United States has shown a growth rate of 9% annually (134). Presently, this pharmaceutical delivery technology has incorporated nanotechnology in many frontiers. This advanced technology provides targeted delivery of various therapeutic agents. The unique property of nanoparticle based delivery systems is to deliver the drug in a particular tissue or organ. They have the capability to distinguish a diseased cell from a healthy one in the body (135). Such a mechanism will lead to a highly efficient, targeted delivery system, controlled delivery and optimum bioavailability.

### 7.1. Brain targeted drug delivery

One of the areas of medicine that can benefit from nanoparticle targeted drug delivery is the central nervous system (CNS). The treatment of CNS diseases is limited due to deficiency of the delivery of therapeutic agents. The main cause is the inefficient delivery of drugs which are unable to reach the desired targets. In order to achieve effective treatment for CNS disorders, it is necessary to transfer therapeutic agents across the blood–brain barrier (BBB) which is a very challenging task even today (136). Nanoparilcle based delivery system can solve this because it can cross the BBB. Additionally, this process may decrease drug leakage and can diminish peripheral toxicity (137, 138). Recently, paclitaxel, anti cancer dug, has been used efficiently for brain cancer using glutathione-coated nanoparticles (139) whereas; paclitaxel alone cannot cross the BBB. It has been noted that aptamer-functionalized PEG-PLGA nanoparticles can improve anti-glioma drug delivery (140). Other than cancer, active therapeutic molecules have been delivered in CNS diseases such as prion disease (141), Alzheimer's disease (142), and antioxidants for the treatment of

neurodegenerative diseases (143). However, nanoparticles based delivery systems can cross BBB easily which are creating a lot of hope for the treatment of specific CNS diseases that currently have no cure.

### 7.2. Pulmonary drug delivery

Pulmonary drug delivery is an important route of administration for delivery of therapeutic agents especially for peptides and proteins. Several advantages make the lung as an efficient route for drug delivery. The advantages are i) Large absorptive surface area; ii) Human lung is extremely thin, and it is recorded between 0.1 μm – 0.2 μm; iii) It provides an absorptive mucosal membrane; iv) Lung is highly vascular with good blood supply, and lastly v) this delivery system can eliminate injection. Therefore, pulmonary route of drug delivery shows great promise (144, 145) utilizing two techniques: aerosol inhalation technique and intratracheal instillation (146). Several nanoparticles based delivery systems are being developed for administration by pulmonary route. Eg. a sildenafil-loaded nanoparticle is a promising drug for the therapy of pulmonary arterial hypertension (147). For pulmonary fibrosis and exacerbated lung disease, CNTs allow extensive functionalization and loading of drugs (148). Spray-dried aqueous PLGA nanosuspensions were developed for pulmonary drug delivery which can access the alveolar tissue (149). Antitubercular drugs were encapsulated in poly (DL-lactide-co-glycolide) nanoparticles suitable for nebulization which shows better bioavailability and reduction of dose incidence for better management of pulmonary tuberculosis (150). Presently, pulmonary nanoparticle drug formulations have generated great interest in the pharmaceutical industry, but this is a challenging route of drug administration for new drugs.

### 7.3. Ocular drug delivery

The efficacy of ocular drug delivery is influenced by the corneal contact time (151, 152). Therefore, the major challenge for ophthalmic drugs is controlled and sustained delivery (153). Presently, solutions, suspensions and ointment are the most common topical form of drugs which are used regularly for ocular infections. These conventional dosages are used in people suffering from problems such as poor ocular bioavailability due to anatomical and pathophysiological obstruction existing in the eye (154). Currently, dilutable nanoemulsions are powerful drug delivery vehicles for ocular diseases (155,160). Its sustained effect, high penetration ability into the deeper layers of eye makes a better delivery system. Using nanoemulsion, dorzolamide hydrochloride is used for the treatment of glaucoma (155). Nanosuspensions may be included in a hydrogel base or mucoadhesive base or even in ocular inserts. An experiment has been performed to achieve the desired action of polymeric nanosuspensions loaded with the drug. The result shows better sustainability for the release of the drug (156). A polymeric nanosuspension of flurbiprofen and ibuprofen have been successfully formulated using acrylate polymers such as Eudragit RS 100 and Eudragit RL 100 (157-159). Another approach is to immobilize the drug with the help of the nonovehicle (such as liposome) on the exterior of marketable contact lenses (160). Immobilized of levofloxacin liposome's on NeutrAvidin-coated Hioxifilcon-B contact lenses have been released in this direction. It was noted that approximately 70% drug was free within the initial five hrs and remaining 30% drug discharge occurred over the subsequent 6 days (161). To date, nanoparticle based delivery systems emerged to be an exclusive and so far commercially viable way to combat problems such as reduced bioavailability or other issues of ophthalmologic drugs.

### 7.4. Oral delivery

Presently, an important research has been performed using nanoparticles as oral drug delivery carriers. Oral delivery of drugs using nanocarriers has revealed better delivery in terms of bioavailability and biodistribution (162). For example, insulin-loaded nanoparticles have conserved insulin activity and decrease in blood glucose level in diabetic rats for up to 14 days following the oral delivery (163). Using lactic-co-glycolic acid nanoparticle, salmon calcitonin (sCT)-loaded oral drug delivery system has been evaluated *in vitro* and *in vivo* (164). But, oral protein or peptide delivery still remains to be an issue today because of their poor oral bioavailability.

Nanoparticles can be engineered to distribute a drug directly to the basis for gastrointestinal uptake. These drugs need to be protected from low pH as well as enzymes present in the stomach. The pH-sensitive nanoparticles can be developed from a copolymer (methylacrylic acid and methacyrlate). It may provide a better result for the oral bioavailability of drugs like cyclosporine-which has specific pH inside the gastrointestinal tract. The pH sensitive nanoparticles help the drugs absorption through the Peyer's patches (165).

### 7.5. Dermal and transdermal delivery

Nanocarriers are the promising dermal and transdermal pharmaceutical delivery systems. Most prominent nanocarriers such as microemulsions, liposome's, micron sized, and nanoparticles are in use for dermal and transdermal applications (166). Several nanotechnology based dermal products such as medicated moisturizers, sunscreen are available in the market. The major compounds used for dermal applications are titanium dioxide and zinc oxide. Also, liposomes and niosomes are used in the cosmetic industry as delivery vehicles (167, 168). In addition, nanoemulsions are also used for dermal delivery. Nanoemulsions are nanoscale droplets of one liquid within another (169). From nanoemulsions, we can produce water-like fluids or gels, because emulsions are metastable systems (170). There are several advantages of these gels/water-like fluids, such as i) It can be stabilized to enhance the time before creaming occurs, and therefore, in this way increase the shelf life (171); ii) They are transparent and have bigger surface area because of the tiny particle size, and iii) nano scale dimension of the emulsion has high stability and better suitability to carry drugs (172). Several companies are producing stable nanoemulsions for dermal delivery such as Nanocream® from Sinerga (www.sinerga.it) and NanoGel from Kemira (www.kemira.com). Using lipid nanoparticles, several companies are manufacturing products for increased skin penetration. Muller *et al.* (173) and Pardeike *et al.* (174)

have listed commercially available products and their ingredients in dermal delivery. Several drugs in this area have a number of limitations due to problems relating to controlled drug release and achieving therapeutic efficacy. Lipid nanocapsules and solid lipid nanoparticles (SLNs) have been developed with increased efficacy. Lipid nanocapsules (LNC) are colloidal carriers which can offer controlled release property as well as better bioavailability for dermal delivery (175). Solid lipid nanoparticles (SLNs) are investigated due to their potential topical delivery, possible skin compartments targeting and controlled release in the skin. It is also reported that in Fluconazole, an antifungal ingredient, nanoparticles optimize the drug retention in the skin (176).

**7.6. Cancer chemotherapy**

Conventional chemotherapy in cancer suffers from drawbacks of toxicity and nonspecificity. Nanoparicles are potential carriers for cancer drugs because of the ability to specifically target and hit the cancer cells. Gadolinium neutron-capture therapy (Gd-NCT) for cancer was evaluated by Tokumitsu *et al.* (177) using gadolinium-loaded nanoparticles. The tumor growth in the nanoparticle governed bunch was considerably suppressed related to that in the gadopentetate solution-administered bunch. Glutaraldehyde cross-linked with chitosan having mitoxantrone antitumor activity was estimated using carcinoma in mice. Mean survival was increased to 50 days (178). Nanoparticle carrier with doxorubicin has been delivered to tumor cell successfully (179-181). An albumin-bound structure was added in doxorubicin where metalloproteinase-2 has been included and new matrix was developed (182) which is a targeted delivery in the unique microenvironment surrounding the tumor cells. This important nanoparticle carrier drug is in clinical trials **(**183**).** Another example is **c**olloidal gold nanoparticles, a sol comprised of nanoparticles of Au (0), which represents a new tool in the field of particle-based tumor-targeted drug delivery (184). Several other delivery systems have been developed such as liposomes, polymeric micelles, dendrimers, superparamagnetic iron oxide crystals, and colloidal gold etc. These carriers utilize both passive and active targeting strategies (185). Drug resistance appears to be one of the main limiting factors for the chemotherapeutic agents, and P-glycoprotein related drug resistance is well understood (186). However, nanoparticle carrier of drugs can solve the P-glycoprotein–mediated resistance problem (187). It is anticipated that the nanoscale drug delivery systems can solve several problems and provide better cancer chemotherapy.

**7.7. Vaccine delivery**

Nanoparticles (NPs) have gathered increased attention for their ability to serve as a viable carrier for site specific delivery of vaccines**.** Several methods now exist for synthesizing different sets of nanoparticles based on the type of vaccines used and delivery mechanism selected (188). As an example, nanocarriers are used for the systemic and mucosal delivery of vaccine (189). In fact, mucosal vaccine delivery started because mucosal exterior signify the main point of entry for a lot of pathogens (190). This route offer simplified and cost-effective protocol for vaccination with anticipation for improved patient compliance. For mucosal immunization, PLGA nanoparticles have been developed against hepatitis B (191). It is reported that antigen-loaded nanocarriers are able of being dynamically absorbed by antigen-presenting cells which have shown the potential for cancer immunotherapy (192). Recently, several strategies have been developed which can initiate antigen-specific immune responses. An antibody-mediated delivery of nanoparticle vaccines has been developed for human dendritic cells (193). New technologies are developed for parasite and viral vaccine as well. Viral vaccines using nanoparticle carriers for H6N2 avian influenza virus and HIV vaccine was investigated using poly (2-hydroxyethyl methacrylate) i.e. pHEMA nanoparticle. This work suggests that by means of 100 µg of pHEMA nanoparticles showed decline in virus shedding and improved the immune response (194). In HIV, disease engages the interaction among the viral envelope-protein gp120 and cell receptor CD4. A study has been performed to demonstrate the interaction of HIV-1 gp120 protein to silica NP (195). This study demonstrated that CD4 bound to silica particles recognized and retained high binding affinity for HIV-gp120 (195). For the effective malarial vaccine, recombinant malarial antigen i.e. merozoite surface protein 1 (rMSP1) has been covalently conjugated to polymer-coated quantum dot CdSe/ZnS nanoparticles (QDs) via surface carboxyl groups forming rMSP1-QDs. This shows promising results to improve the immunogenicity of the polypeptide antigens in adjuvant-free immunizations (196). These novel vaccine platforms utilize engineered nanoparticle delivery system which is more efficient and safer than the previous vaccines.

**7.8. Therapeutic nucleic acids**

Nucleic acids as drugs have a great future in molecular medicine for gene therapy. Using these therapies, it has been projected that several serious diseases can be treated such as genetic diseases, viral infections or cancer (197). Liposome's (198), dendrimers (200), biodegradable polymeric nanoparticles (201) and gold nanoparticles (202) have been used for gene therapy. There are generally two ways of nucleic acids delivery such as encapsulation and conjugation. Nucleic acids like plasmid DNA, RNA, and siRNA can be encapsulated with a nanoparticle (203) or conjugated with the nanoparticle (204-206). One way to link nucleic acids to a nanoparticle, especially DNA, is to modify the surface of the nanoparticle to bring a positive charge. The positive charge of the nanoparticle can bind easily with the negative charge of the DNA. This mechanism is used for liposome and other polymer-mediated nucleic acid transfer (207, 208). Recently, Mendez-Ardoy *et al.* (209) have developed polycationic amphiphilic cyclodextrin-based nanoparticles which are used for therapeutic gene delivery (IL-12). For siRNA therapeutic delivery, Beloor *et al.* (210) used arginine-engrafted biodegradable polymer which enhanced accumulation of carrier-siRNA complexes in the tumor tissue. However, there is an urgent need for the generation of a common platform on nanoparticle based delivery systems which can be modified easily to deliver different types of nucleic acids.

**Table 1.** Approved drugs with nanoparticle-based delivery system which are commercially available

| Sl.No | Product name and company name | Nanoparticle based delivery system and Pharmaceutical ingredient | Indication | Delivery route | Reference |
|---|---|---|---|---|---|
| 1 | Abelcet (Enzon ,USA) | Delivery system: Lipid complex<br>Ingredient: Amphotericin B | Fungal infections | Injection (Intravenous route) | 221 |
| 2 | AmBisome (Gilead Science, Japan) | Delivery system: Liposome<br>Ingredient: Amphotericin B | Fungal and protozoal infections | Injection (Intravenous route) | 222 |
| 3 | DaunoXome (Gilead Science, Japan) | Delivery system: Liposome<br>Ingredient: Daunorubicin | Kaposi sarcoma | Injection (Intravenous route) | 223 |
| 4 | Doxil/Caelyx (Ortho Biotech, USA and Schering-Plough,USA) | Delivery system: Liposome<br>Ingredient: Doxorubicin | Cancer, Kaposi sarcoma | Injection (Intravenous route) | 224 |
| 5 | DepoCyt (SkyePharma, UK) | Delivery system: Liposome<br>Ingredient: cytarabine | Cancer | Injection (Intravenous route) | 225 |
| 6 | Epaxal Berna (Berna Biotech, Switzerland) | Delivery system: virosome<br>Ingredient: Hepatitis A Vaccine | Hepatitis A | Injection (Intravenous route) | 226,227 |
| 7 | Visudyne (QLT Canada and Novartis AG, Switzerland) | Delivery system: Liposome<br>Ingredient: Verteporfin | Age-related macular degeneration | Injection (Intravenous route) | 228 |
| 8 | Neulasta (Amgen, USA) | Delivery system: Polyethylene glycol (PEG)<br>Ingredient:Granulocyte colony-stimulating factor (GCSF) | neutropenia | Injection (Intravenous or subcutaneous route) | 229 |
| 9 | Pegasys (Nektar, USA and Hoffmann-La Roche Switzerland) | Delivery system: Polyethylene glycol (PEG)<br>Ingredient: interferon-α 2a | Hepatitis C | Injection (Intravenous or subcutaneous route) | 230, 231 |
| 10 | PEG-Intron | Delivery system: Polyethylene glycol (PEG)<br>Ingredient: Interferon-α 2b | Hepatitis C | Injection (Intravenous or subcutaneous route) | 232 |
| 10 | Renagel (Genzyme,USA) | Delivery system: Crosslinked poly(allylamine) resin<br>Ingredient: Sevelamer HCL | Chronic kidney disease | Oral delivery | 233 |
| 11 | Tricor (Abbott Laboratories, USA) | Delivery system: Nanocrystalline<br>Ingredient: fenofibrate | Lipid regulation | Oral delivery | 234 |
| 12 | Abraxane (Abraxis BioScience, USA and AstraZeneca,UK) | Delivery system: Albumin Nanoparticles<br>Ingredient: paclitaxel | Cancer | Injection (Intravenous route) | 235 |
| 13 | Copaxone (TEVA Pharmaceuticals,USA) | Delivery system: L-Glutamic acid, L-alanine, L-lysine, and L-tyrosine copolymer<br>Ingredient: Glatiramer Acetate | Multiple sclerosis | Injection (Intravenous route) | 236 |
| 14 | Estrasorb (NovavaxInc. USA) | Delivery system: micellar nanoparticle<br>Ingredient: estradiol emulsion | Menopausal therapy | Topical | 237,238 |

### 7.9. Delivery system coupling to implants

Presently, various implant devices have been prepared which are attached to smart drug delivery systems. Examples of implant devices are biosensors, pacemakers and stents (211). Several intra-ocular devices have been prepared for the delivery of ocular drugs (212). The coupling of drug delivery to sensors has been used for the treatment of diabetes (213) and also to measure oxygen pressure (214). Several scientists are working in this field to develop engineered nanoparticles for the development of the delivery systems coupling to implants.

## 8. COMMERCIAL MARKET

A huge progress has been found in the past two decades for commercially available nanoparticle-mediated therapeutic products. A survey has been conducted by the European Science and Technology Observatory which reported that over 150 companies are developing nanoparticle based therapeutics. Several therapeutic products in this line have been approved for clinical use and with total sales value is reported to be more than $5.4 billion. Many products have been approved in the past 20 years (Table 1). In 1995, the nanoscale delivery system called “Doxil” was the first approved drug by the US-FDA for the treatment of AIDS associated with Kaposi’s sarcoma (215). Simultaneously, AmBisome (amphotericin B liposomes), DaunoXome (daunorubicin liposomes), DepoCyt (cytarabine liposomes), Visudyne (verteporfin liposomes), etc have been approved and marketed (216). Therapeutics like Doxorubicin, Daunomycin, Docetaxel, Efavirenz and Chloroquine phosphate with nanoparticle mediated delivery system (Table 2) are in Phase-I/II/III clinical trial. These products have opportunity to be approved in the near future.

## 9. TOXICOLOGICAL EFFECTS OF NANOPARTICLE MEDIATED DRUG DELIVERY

Safety and toxicological issues are the most important issues for a drug delivery system. Safety is an obvious concern for the fast growth of nanoparticles mediated drug delivery. Different nanoparticle based delivery systems are being developed for pharmaceutical ingredients deliveries should be examined properly from the point of toxicity. Therefore, study design related to toxicity testing is required. It has been noted that the use of nanoparticles as drug transporter may decrease the toxicity of the incorporated drug. However, toxicity of the “vacant” non-drug loaded particles should be evaluated properly (217).

Some studies of nanoparticle mediated drug delivery related to toxicological effects *in vitro* model have been performed (218). Conversely, it is found that the decrease in size due to the nanocarrier can cause variation in the physicochemical and structural properties of produced nanoparticles that can be accountable for numerous material interactions that may produce toxic effects (219). However, there is a huge gap among research exploration on toxicology and nanoscaled pharmaceutical ingredient delivery (220) and proper extensive research should be initiated to fill the gap.

**Table 2.** Nanoparticle-mediated drugs which are in clinical trial

| Sl.No | Product and company name | Nanoparticle based delivery system and Pharmaceutical ingredient | Clinical trial status | Indication | Delivery route | Reference |
|---|---|---|---|---|---|---|
| 1 | L-Annamycin(Callisto Pharma, USA) | Delivery system: LiposomeIngredient: annamycin | Phase II | Acute lymphocytic leukemia,acute myeloid | Injection (Intravenous route) | 239 |
| 2 | SLIT Cisplatin(Transave, Inc, USA) | Delivery system: LiposomeIngredient: cisplatin | Phase I | Progressive osteogenicsarcoma metastatic tothe lung | Pulmonary delivery | 240 |
| 3 | SP1049C(Supratek Pharma, Canada) | Delivery system: Pluronic block-copolymerIngredient: doxorubicin | Phase II | Esophageal carcinoma | Injection (Intravenous route) | 241 |
| 4 | CT-2106(Cell Therapeutics, Inc.,USA) | Delivery system: Polyglutamate-nanoparticleIngredient: camptothecin | Phase II | Colorectal and ovariancancers | Injection (Intravenous route) | 242 |
| 5 | Transdrug(BioAlliance Pharma, Paris) | Delivery system: Poly(iso-hexyl-cyanoacrylate)Ingredient: doxorubicin | Phase II | Hepatocellular carcinoma | Injection (Intra-arteria route) | 243 |
| 6 | BioVant(BioSante Pharma,USA) | Delivery system: Calcium phosphate nanoparticleIngredient: vaccine adjuvant | Phase I | Vaccine adjuvant | Injection (subcutaneous route) | 244 |
| 7 | NB-001(NanoBio, USA) | Delivery system: NanoemulsionIngredient: NB-001 | Phase II | Herpes labialis | Topical | 245 |
| 8 | AI-850(Acusphere Inc.USA) | Delivery system: nanoparticles in porous, hydrophilic matrixIngredient: Paclitaxel | Phase I | Solid tumors | Injection (Intravenous route) | 246,247 |
| 9 | Basulin(Flamel Technologies, France) | Delivery system: L-Leucine, L-glutamate copolymer,Ingredient: insulin | Phase II | Type I diabetes | Injection (subcutaneous route) | 248 |
| 10 | VivaGel(Starpharma,UK) | Delivery system: Poly-L-lysine dendrimerIngredient: SPL7013 | Phase II | Antimicrobial protectionfrom genital herpesand HIV infection | Topical | 249 |
| 11 | Panzem NCD(Elan, USA ) | Delivery system: Nano-crystalIngredient: 2-methoxyestradiol | Phase II | Several type cancers | Oral | 250 |
| 12 | ProLindac(AccessPharma, USA) | Delivery system: HPMA copolymerIngredient: DACH platinate | Phase II | Ovarian cancers | Injection (Intravenous route) | 251 |
| 13 | CYT-6091 (Aurimmune) (CytoImmune Science, USA) | Delivery system: PEGylated colloidal gold nanoprticle Ingredient: TNF alpha | Phase II | Solid tumar | Injection (Intravenous route) | 252 |

## 10. CONCLUSION

Nanotechnology has been demonstrated to be exceptionally significant for future medicine. Several nanoparticle-based therapeutic and diagnostic agents have been developed for the treatment of cancer, HIV related Kaposi's sarcoma, diabetes, pain, asthma, allergy, hepatitis, hypertension, influenza etc. Currently approved nanoparticle mediated drug carrier systems can reach extended circulation time, little immunogenicity, superior biocompatibility, selective targeting, and the competent penetration of barriers in human body such as BBB as well as vascular endothelium and helps self-determining drug discharge. Drugs incorporating nanocarriers are available in the market have shown reduced toxicity improving the therapeutic index of the drugs. In the future, there is a possibility that the next generation of nanoparticle mediated delivery systems with drugs like antibodies, peptides, etc may also improve drug efficacy or reduce drug toxicities.

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