Recent advances in pharmaceutical nanocarriers –current trends and future challenges.

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ARTICLE INFO	ABSTRACT
	Nanotechnology, involving the development of nanoscaled pharmaceutical delivery devices. The micelles, liposomes, solid lipid nanoparticles, polymeric nanoparticles, vesicles, Nanogel, nanocrystals, dendrimers, nanotubes and have been used as strategies to deliver conventional pharmaceuticals or substances such as peptides, recombinant proteins, vaccines and nucleotides. Nanocarriers and other colloidal pharmaceutical delivery systems modify many physicochemical properties, thus resulting in changes in the body distribution and other pharmacological processes. These changes can lead to pharmaceutical delivery at specific sites and reduce side effects. Therefore, Nanocarriers can improve the therapeutic efficiency, being excellent carriers for biological molecules, including enzymes, recombinant proteins and nucleic acid. This review discusses different pharmaceutical carrier systems, and their potential and limitations in the field of pharmaceutical technology. Products with these technologies which have been approved by the FDA in different clinical phases and which are on the market will be also discussed.

Introduction

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity.

The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and or mesogenic properties Current applications of Nanocarriers in pharmacy are development of nanomedicine, tissue engineering, nanorobots, advance diagnostic, as carrier of diagnostic and therapeutic modalities and as biosensor, biomarker, image enhancement device, implant technology, bioactive surfaces etc. A large number of nanosystems, which have been investigated in pharmacy to date, are liposomes, dendrimers, metallic nanoparticles, polymeric nanoparticles, carbon Nanotubes, etc.

Figure 1. Pharmaceutical Nanocarriers

Advantages of pharmaceutical drug Nanocarriers;

➢ Decreasing the non-specific delivery of the drug to nontarget tissues.
➢ Increasing the drug concentration at its site of action.
➢ Prolonging the residence time of the drug at its site of action by reducing clearance.
➢ Decreasing toxicity due to high initial doses of the drug.
➢ Improving the stability of the drug in vivo.
➢ Decreasing irritation caused by the drug.
➢ Improving taste of the product.
➢ Improving shelf life of the product.

Micelles

Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions are of great interest for drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water- solubility. Moreover, the hydrophilic blocks can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core.

As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation. In addition, the corona may prevent recognition by the reticuloendothelial system and therefore preliminary elimination of the micelles from the bloodstream.

A final feature that makes amphiphilic block copolymers attractive for drug delivery applications is the fact that their chemical composition, total molecular weight and block length ratios can be easily changed, which allows control of the size and morphology of the micelles.

Functionalization of block copolymers with cross linkable groups can increase the stability of the corresponding micelles and improve their temporal control. Substitution of block
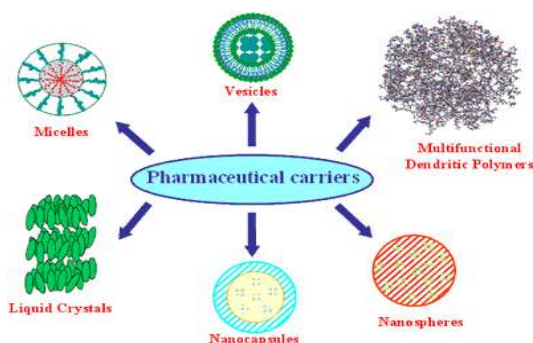
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copolymer micelles with specific ligands is a very promising strategy to a broader range of sites of activity with a much higher selectivity.(Torchilin V.P,2001) An example is the recently published study on nanoshells with beclomethazone dipropionate, (N.N.Gaber ,2006) Which showed improved pharmaceutical and DNA delivery to tumours and the central nervous system (CNS) due to an enhanced permeability and retention(EPR).
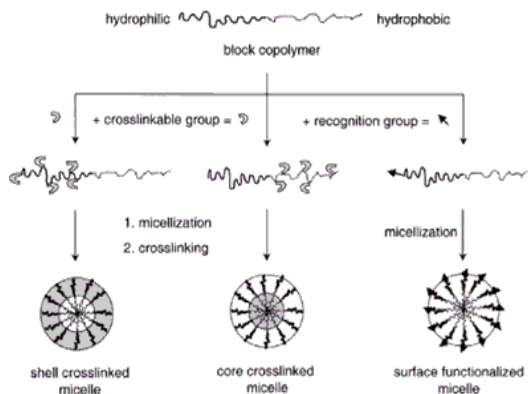

Figure 2. Block copolymer micelles (Costas Kaparissides,2006)

Dendrimers

Dendrimers are hyper branched, tree-like structures and have compartmentalized chemical polymer. Dendrimers contain three different regions: core, branches, and surface (Fig. 3). The macromolecule constituents radiate in branching form from the central core, creating an internal cavity as well as a sphere of end groups that can be tailored according to requirements. They can be tailored or modified into biocompatible compounds with low cytotoxicity and high bio permeability. They bear promising properties for delivery of bioactive ranging from drugs, vaccines, metal, and genes to desired sites. Their hollow interior provides space to incorporate drugs and other bioactive physically or by various interactions to act as drug delivery vehicles.

Most important applications of dendrimers are solubilisation, gene therapy, dendrimer based drug delivery, immunoassay and MRI contrast agent. Dendrimers is ideal carrier for drug delivery due to advantages like very low size (1-5 nm), feasibility to develop with defined molecular weight, very low polydispersity index (ratio of weight average molecular weight (Mw) to number average molecular weight (Mn) of polymer), good entrapment efficiency and offering surface for functionalization. They can be modulated for target-specific drug delivery but their toxicity profile renders them not very popular system for use as delivery means.
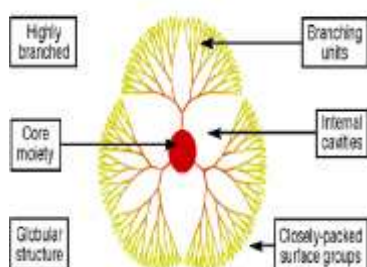
Fig. 3: Schematic representation of a dendrimers showing core, branches, and surface.(Jain, K.K,2005)

Nanoparticles

Including nanospheres and nanocapsules can be amorphous or crystalline. They are able to absorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation. In nanocapsules, the drug is confined to a cavity surrounded by a polymer membrane, while nanospheres are matrix systems within which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention in the controlled release of drugs in targeting particular organs/tissues, as carriers of DNA in gene therapy and in their ability to deliver proteins, peptides and genes by the oral route.
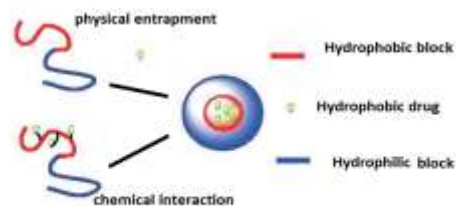
Polymeric nanoparticles

Generally, polymers that are used for preparation of nanoparticles fall into two major categories: natural polymers and synthetic polymers.

A number of natural polymers such as heparin, dextran, albumin, gelatine, alginate, collagen, and chitosan have been intensively investigated. Synthetic polymers including polyethylene glycol (PEG), polyglutamic acid (PGA), polylactic acid (PLA), polycarprolactone (PCL) and N-(2 hydroxypropyl) methacrylamide copolymer (HPMA) have been exploited as well. General requirements for those polymers are biocompatibility, biodegradability, and their capacity to be functionalized (Tong R, 2007).The formation of polymeric nanoparticles has been summarized by several review articles (Cho K,2008; Zhang GZ,2001).

In most cases, the polymeric nanoparticle consists of two parts, a hydrophobic core which serves as the container for anticancer agents and a hydrophilic shell which stabilizes the nanoparticle in aqueous environments. The drug can be loaded into polymeric nanoparticles through two methods: by physical entrapment or by chemical conjugation.

A hydrophobic interaction between the core of the polymeric nanoparticle and the drug molecule allow the drug to be entrapped in the nanoparticle core. For instance, deoxychilic acid-modified heparin can self-assemble into 100~200 nm nanoparticles (Park K,2004) and its hydrophobic core can be used to entrap 4~12% of the total weight of doxorubicin (Park K,2006)

When the drug molecule is covalently conjugated onto the polymer, the chemical properties of the linker between the drug and polymer are critical. If the linker is too stable, drug release may be delayed, while if the linker is too unstable, drug may be released before the nanoparticle reaches the tumor. Therefore, a proper linker is very important to the drug-polymer conjugate. A variety of pH-sensitive linkers have been developed such as hydrozone and cis-aconityl (Kratz F,1999 ; Ulbrich K,2004). These chemical bonds are stable in the blood circulation system (pH=7), but quickly decompose and release drug molecules inside the tumor where pH values typically drop below 5.5.

Fig.4; Plymeric nanoparticle.

Liposomal nanoparticles (Solid lipid Nanoparticles)

SLN consist of a solid lipid matrix at room and body temperature, where the drug is normally incorporated in the submicron size range (below 1µm) (S.A.Wissing ,2004) SLN

are composed of physiological lipids and the surfactants that have an accepted GRAS (Generally Recognized as Safe) status.SLN can be produced in large scales by high-pressure homogenization without using organic solvents and have been used in parenteral ,pulmonary ,and dermal applications SLN with cationic lipids have also been considered as new transfection agents.

For example, SLN prepared with a cationic lipid (DOTAP) had the same transfection efficiency as the liposomes from the same cationic lipid, but with SLN the range of strong non-viral transfection agents that can be produced in large scale is widened.

A study of methotrexate-loaded solid lipid nanoparticle (MTx-SLN) for topical treatment of psoriasis, and its formulation and clinical implication was recently published. (K.Tabatt ,2004) .

The formulation and preparation of MTx-SLN gel were optimized for the cetyl alcohol lipid, Tween 80, as surfactant and sodium tauroglycocholate as co-surfactant. Theoptimized SLN particle size was 123 nm and an entrapment efficiency of 52% was obtained.

The use of MTx- SLN improved the therapeutic response and the MTx-SLN base gel was observed to reduce adverse effects of therapy, promoting better patient compliance. It is therefore possible to consider it as a supplementary to oral therapy, particularly in the final stage of psoriasis treatment.
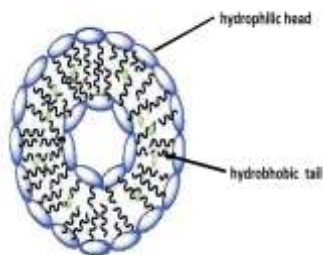

Fig.5- Solid lipid nanoparticle

Nanocrystals

Nanocrystals are single crystalline nanoparticles consisting of aggregates of hundreds of molecules combined in a single crystal with a thin coating as a surfactant. They are produced according to a technique called nanonization using dispersion in an aqueous surfactant solution (E.Merisk ,2003) nanocrystals are being developed to improve the bioavailability of poorly soluble drugs.

The production of nanocrystals and nano suspensions is called nanonization There are several techniques to obtain this kind of nanomaterials, such high pressure homogenization wet milling and by nanocrystallization from supersaturated solution state or spray drying Nanonization increases surface area and drug solubility, thus enhancing oral bioavailability, and enabling administration by injection or infusion as intravenous aqueous solution of drugs that are poorly soluble in water.

Nanocrystals are taken up by the mononuclear phagocytic system to allow regional specific delivery. It is known from the literature that these nanoparticles act very quickly when pathogens persist intracellularly, e.g., targeting antimycobacterial, fungal or leishmanicidal active macrophages (O.Kayser ,2005) the industry Nano Crystal (King of Prussia, Pennsylvania, USA) prepares pharmaceuticals in Nano crystalline form for a greater efficiency in their absorption. These new particles are surface coated to enhance clinical efficiency and consistency of the less soluble pharmaceuticals.

But nanocrystallization is more than a general method to improve bioavailability of poorly soluble drugs.

Liquid crystals

Liquid Crystals combine the properties of both liquid and solid states. They can be made to form different geometries, with alternative polar and non-polar layers (i.e., a lamellar phase) where aqueous drug solutions can be included.

Hydrogels

Hydrogel are three-dimensional polymer networks that swell but do not dissolve in aqueous media. They are used to regulate drug release in reservoir-based systems or as carriers in swelling-controlled release devices.

On the forefront of controlled drug delivery, hydrogels, as en viro-intelligent and stimuli-sensitive gel systems, can modulate drug release in response to pH, temperature, ionic strength, electric field, or specific analyte concentration differences.

Release can be designed to occur within specific areas of the body. Hydrogels as drug delivery systems are very promising if combined with the technique of molecular imprinting (Byrne M. E ,2002).
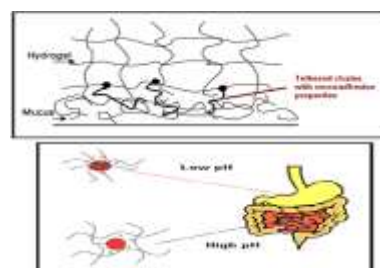

Fig.6;- Mucoadhesive and pH sensitive Hydrogel or Nanogel.

Bioconjugates

Conjugation of biological (peptides/proteins) and synthetic polymers is an efficient means to improve control over nanoscaled structure formation of synthetic polymeric materials that can be used as drug delivery systems. Conjugation of suitable biocompatible polymers to bioactive peptides or proteins can reduce toxicity, prevent immunogenic or antigenic side reactions, enhance blood circulation times and improve solubility. Modification of synthetic polymers or polymer therapeutics with suitable oligopeptide sequences, on the other hand, can prevent random distribution of drugs throughout a patient's body and allow active targeting. Functionalization of synthetic polymers or polymer surfaces with peptide sequences derived from extracellular matrix proteins is an efficient way to mediate cell adhesion. The ability of cationic peptide sequences to complex and condense DNA and oligonucleotides offers prospects for the development of non- viral vectors for gene-delivery based on synthetic polymeric hybrid materials. (Alvarez-Lorenzo C ,2004).
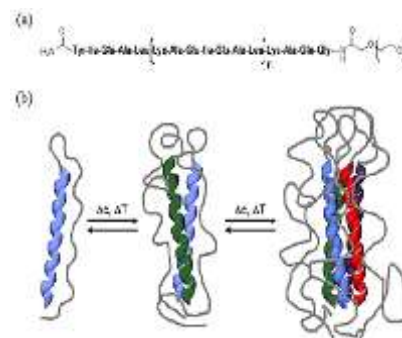

Fig.7-Bioconjugates

Liposomes

Liposomes are defined, spherical, self-closed structures formed by one or more concentric lipid bilayers containing an aqueous phase inside and between the bilayers (S.P.Vyas ,2005) (see in fig.8).The lipids used in the formation of liposomes are usually comprised of a hydrophilic head group and two hydrophobic fatty acyl chains. These amphiphilic molecules spontaneously assemble into aggregates in an aqueous environment. Water-soluble molecules occupy the aqueous compartment, whereas molecules of a more lipophilic character occupy the lipid bilayers. Liposomes can vary substantially in size and lamellarity. They are subdivided into multilamellar vesicles (MLV) consisting of several concentric bilayers, large unilamellar vesicles (LUV) and small unilamellar vesicles (SUV) that are less than 150 nm in diameter. Liposomes can be formed by a variety of methods. When they are prepared by hydration of the dried lipid mixture, they spontaneously form MLVs. Other procedures, such as prolonged exposure to ultrasound or pressure-driven filtration through small-pore filters, cause MLVs to form SUVs. Other procedures lead to the formation of LUVs (W.W. Sulkowski ,2005). For instance, large vesicles are prepared from an initial phosphatidylserine aqueous solution, which, when sonicated and subjected to ultrasound, produces small unilamellar vesicles (SUV) with diameter of 200–500 Å. After adding 1 to 10mM (threshold 1–2 mM) calcium ion (Ca2+) and incubating for 30–60 min at a room temperature above   10°C (preferably 37 °C), intermediate cochleate (spiral-shaped) lipid cylinders form. Finally, addition of a calcium-chelating agent such as EDTA or EGTA to these cochleate cylinders produces the desired large closed spherical unilamellar vesicles (LUV) by fusion (United States Patent 4078052). Liposomes (LUVs) with a large internal aqueous space and high capture capacity are produced by reverse-phase evaporation (REV). The procedure is based on the formation of 'inverted micelles' small water droplets which are stabilized by a phospholipid monolayer and dispersed in excess of organic solvent. Slow removal of the organic solvent leads to the transformation of these inverted micelles into a viscous gel-like state. At a critical point in this procedure, the gel state collapses and some of the inverted micelles disintegrate. The resulting excess of phospholipid contributes to the formation of a complete bilayer around the remaining micelles, leading to the formation of LUVs
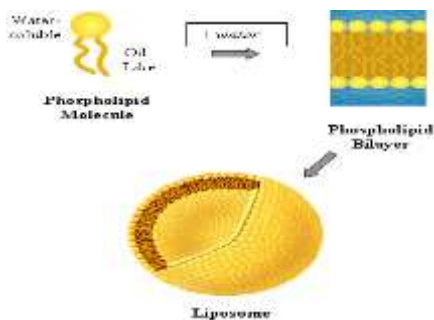

Fig.8: The formation of liposomes, from phospholipid molecules to a unilamellar   vesicle.

Advances in Liposomes (STEALTH Liposomes).

In general, larger liposomes are eliminated from the blood circulation more rapidly than smaller ones (J. Senior ,1982) . Binding of opsonins to liposomes depends on liposome size; consequently, the reticuloendothelial (RES) uptake of liposomes by the liver is size-dependent (H. Harashima ,1994). The action of the reticuloendothelial system results in rapid removal from the blood and accumulation in tissues such as liver and spleen. *In vivo* behaviour of liposomes is also determined by their constituent parts, viz., phospholipids and other amphiphilic molecules, cholesterol and molecules bound to the liposome surface. The circulatory half-life of liposomes can be significantly increased through use of sterically shielded lipids in their construction. 'Steric stabilization' refers to the colloidal stability resulting from the attachment of hydrophilic polymers or glycolipids on to the liposome surface (see Fig. 9). These liposomes are less reactive toward serum proteins and less susceptible to RES uptake than non-stabilized liposomes (T.M. Allen, 1995).Hence, such liposomes show prolonged life-times in the circulation. The putative mechanism by which sterically stabilized liposomes are thought to decrease RES-mediated places the stabilizer in the space immediately adjacent to the liposomal surface effectively excluding other macromolecules from this space. Consequently, access to and binding of blood plasma opsonins to the liposome surface are hindered, preventing interactions with RES macrophages. Polyethylene glycol (PEG) is the most widely used polymeric steric stabilizer. PEG is a linear in structure with many useful properties. It is highly soluble in aqueous and organic media and possesses very low immunogenicity and antigenicity (S. Dreborg ,1990) and is non-toxic. It can be attached to the liposome surface in various ways, but the most widely used method is to anchor the polymer in the liposome membrane via a cross-linked lipid (PEG-DSPE) . The grafted polymer moiety extends about 50 Å from the lipid surface and exerts a strong intermembrane repulsive force (D. Needham ,1992). It was shown that Steric stabilisation of liposomes with PEG increases their longevity in the circulation (D.C.Drummond ,1999).
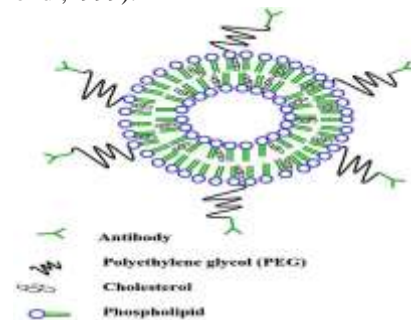
Fig.9- PEGylated liposomes

Stealth liposomes for Tumour therapy.

Stealth liposomes is highly overcomes problem associated with RES clearance of conventional liposomes due to modification of surface properties by PEG. Stealth liposome is responsible for Enhanced permeability & retention effect (EPR). (Dorota Kozlowska,2009).
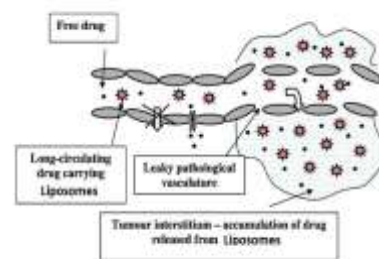
Fig.10-Long circulatory liposomes targeting tumours cells.

Carbon nanotubes

Carbon nanotubes are hexagonal networks of carbon atoms, 1 nm in diameter and 1–100 nm in length, as a layer of graphite rolled up into a cylinder. There are two types of nanotubes:

single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs), which differ in the arrangement of their graphene cylinders (Fig.11). (Baba R,2007).
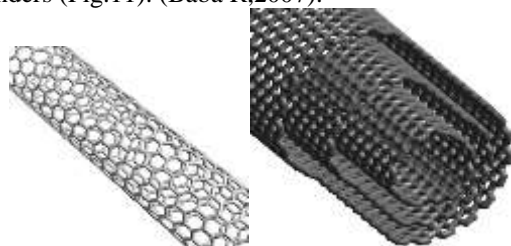
Single walled (SWNTs)   **Multi walled (MWNTs)**
Fig.11.Carbon Nanotubes

These are small macromolecules that are unique for their size, shape, and have remarkable physical properties.

Nanotubes offer some distinct advantages over other drug delivery and diagnostic systems due to very interesting physicochemical properties such as ordered structure with high aspect ratio, ultra-light weight, high mechanical strength, high electrical conductivity, high thermal conductivity, metallic or semi-metallic behaviour and high surface area. (Muller-Goymann C.C ,2004)

Future Opportunities and Challenges

Development of Nanocarriers based delivery systems for therapeutic agents of increased complexity, able to tackle challenging diseases.Nanoformulations have already been applied as drug delivery systems with great success, including anti-tumour therapy, gene therapy,

AIDS therapy, radiotherapy, in the delivery of proteins, antibiotics, virostatics, vaccines and as vesicles to pass the blood-brain barrier.

There are many technological challenges to be met, in developing the following techniques:

Targeted delivery schemes that accumulate the therapeutic agent specifically on the diseased cells for cancer treatment.
➢Targeted agents able to deliver a drug that stabilizes the atheromatic plaque and prevents rupturing.
➢Delivery of drug that selectively attaches to stem cell niches and release local stimulating factors for the treatment of musculoskeletal disorders.
➢Nano carriers with special surface properties able to cross the blood brain-barrier (BBB) for the treatment of neurodegenerative diseases.
➢Non-parenteral formulations of Nano carriers containing insulin.
➢Nano carriers based system for tissue engineering.e.g.for delivery of cytokines to control cellular growth and differentiation and stimulate regeneration.
➢Advanced polymeric carriers for the delivery of therapeutic peptide & proteins.
➢Development of Nano carriers for cell and gene targeting system.
➢Universal formulation schemes that can be used as intravenous, intramuscular or per oral drug.
➢Nano carriers for intracellular targeting.
➢Combined therapy and medical imaging, for example, nanoparticles for diagnosis and manipulation during surgery (e.g. thermotherapy with magnetic particles)
➢Functions (active drug targeting, on-command delivery, intelligent drug release devices, bio responsive triggered systems, self-regulated delivery systems, systems interacting with the body, smart delivery)

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Table 1. Micellar nanoparticles commercialized and in progress by industries for biological and medical applications. (Salata. O.V, 2004)

Drug	Industry	Market	Technology
Estradiol	Novavax	YES	Micellar Nanoparticle
Testosterone for FSD	Novavax	PHASE II	Micellar Nanoparticle

Table 2. Example of dendrimers approved by FDA in clinical phase II and III (Nanotech Rx, 2006; W.V ine,2006)

Drug	Clinical phase	Indication
Vivagel (dendrimers)	Phase II	HIV/AIDS
NB-001	Phase III	Anti-Herpes

Table 3.Examples of polymeric nanoparticles approved by FDA (Nanotech Rx,2006 ;R.Duncan ,2003;infosho,2006)

Drug	Industries	Indication
TrivCor	Abbot Lab.	Drug to treat high cholesterol
Abraxane(Paclitaxel-taxol)	Amer.BioScience	Mamary cancer (Metastitic)
Risperdal Consta. Albumin nanoparticle	Johnson &Johnson	Schizophrenia treatment

Table 4.Example of Nanocrystals approved by FDA (D.Myshko ,2004)

Drug	Industries	Indication
Rapamune nanocrystal	Wyeth	Reduction prevention in Rim transplantation.
Tricor (Fenofibrate)	--------	Lipid lowering agent.

Table 5. Liposomal drug delivery system in market approved by FDA. (Nelson A Ochekpe,2009)

Drug	Industry	Indication
Doxorubicin	Ortho Biotech, Bridgewater, NJ,USA	**Ovarian cancer and** Kaposi's sarcoma
Amphotericn B	Gilead Sciences Inc	Fungal infections
Morphine	EKR Therapeutics, Bedminster	Analgesia
Estradiol	Novavax,	Menopausal – Hot flushes