A comprehensive review on nanoparticle drug delivery system

Shakywar Yogesh[1], Dwivedi Sumeet[2*], Gupta Shailesh[1], Jain Alpa[3] and Kharia Anil[1]
1, Modern Institute of Pharmaceutical Sciences, Indore, M.P.-India
2, Ujjain Institute of Pharmaceutical Sciences, Ujjain, M.P.-India
3, School of Pharmacy, DAVV, Indore, M.P.-India

Abstract

Nanoparticles (NP) are defined as particles with a diameter smaller than 100 nm, are increasingly used in different applications, including drug carrier systems and to pass organ barriers such as the blood-brain barrier. Because of their unique properties Nanocrystals (quantum dots) and other nanoparticles (gold colloids, nanobars, dendrimers and nanoshells) have been receiving a lot of attention for potential use in Therapeutics, Bioengineering and therapeutics drug discovery. The use of nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. Currently many substances are under investigation for drug delivery and more specifically for cancer therapy. Interestingly pharmaceutical sciences are using nanoparticles to reduce toxicity and side effects of drugs and up to recently did not realize that carrier systems themselves may impose risks to the patient. The present paper deals with all these aspects of NP.

Key-words: Nanoparticles, Types, Drug delivery system
*Corresponding Author
E.mail: herbal0914@rediffmail.com, Mob: +919893478497

Introduction

In nanotechnology, a particle is defined as a small object that behaves as a whole unit in terms of its transport and properties. It is further classified according to size: in terms of diameter, fine particles cover a range between 100 and 2500 nanometers, while ultrafine particles, on the other hand, are sized between 1 and 100 nanometers. Similar to ultrafine particles, nanoparticles are sized between 1 and 100 nanometers. Nanoparticles may or may not exhibit size-related properties that differ significantly from those observed in fine particles or bulk materials. Nanoclusters have at least one dimension between 1 and 10 nanometers and a narrow size distribution. Nanopowders are agglomerates of ultrafine particles, nanoparticles, or nanoclusters. Nanometer-sized single crystals, or single-domain ultrafine particles, are often referred to as nanocrystals. Nanoparticle research is currently an area of intense scientific interest due to a wide variety of potential applications in biomedical, optical and electronic fields. Nanoparticles play an important role in a number of these applications. “NPs,” which in general terms are defined as engineered structures with diameters of < 100 nm, are devices and systems produced by chemical and/or physical processes having specific properties. The reason why nanoparticles (NP) are attractive for such purposes is based on their important and unique features, such as their surface to mass ratio, which is much larger than that of other particles and materials, allowing for catalytic promotion of reactions, as well as their ability to adsorb and carry other compounds. [1]

The composition of the engineered nanoparticles may vary. Source materials may be of biological origin like phospholipids, lipids, lactic acid, dextran, chitosan, or have more “chemical” characteristics like various polymers, carbon, silica, and metals. The interaction with cells for some of the biological components like phospholipids will be quite different compared to the non biological components such as metals like iron or cadmium. Especially in the area of

engineered nanoparticles of polymer origin there is a vast area of possibilities for the chemical composition. Although solid NPs may be used for drug targeting, when reaching the intended diseased site in the body the drug carried needs to be released. So, for drug delivery biodegradable nanoparticle formulations are needed as it is the intention to transport and release the drug in order to be effective. However, model studies to the behavior of nanoparticles have largely been conducted with non-degradable particles. Most data concerning the biological behavior and toxicity of particles comes from studies on inhaled nanoparticles as part of the unintended release of ultrafine or nanoparticles by combustion derived processes such as diesel exhaust particles. [1-5]

Types of nanoparticles

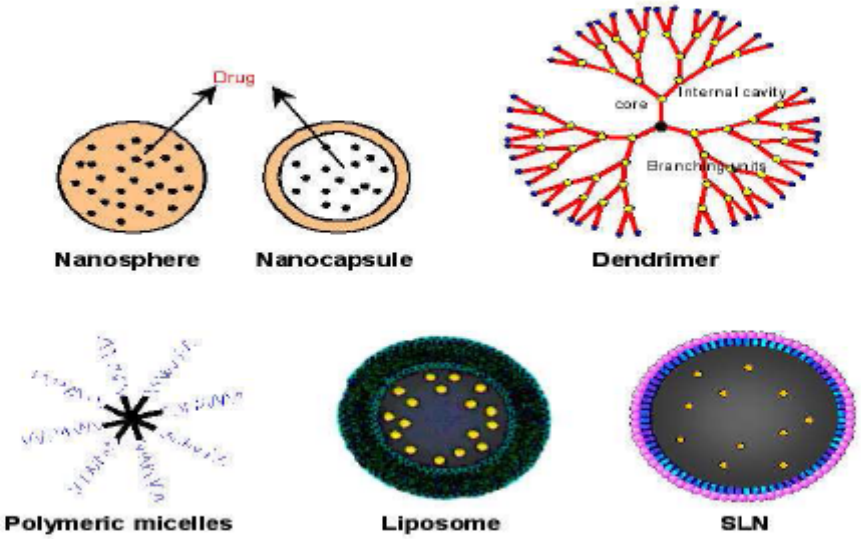


Figure 1: Types of nanoparticles

Liposomes

Liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Liposomes are characterized in terms of size, surface charge and number of bilayers. It exhibits number of advantages in terms of amphiphilic character, biocompatibility, and ease of surface modification rendering it a suitable candidate delivery system for biotech drugs. Liposomes have been used successfully in the field of biology, biochemistry and medicine since its origin. These alter the pharmacokinetic profile of loaded drug to a great extent especially in case of proteins and peptides and can be easily modified by surface attachment of polyethylene glycol-units (PEG) making it as stealth liposomes and thus increase its circulation half-life. [5-7]

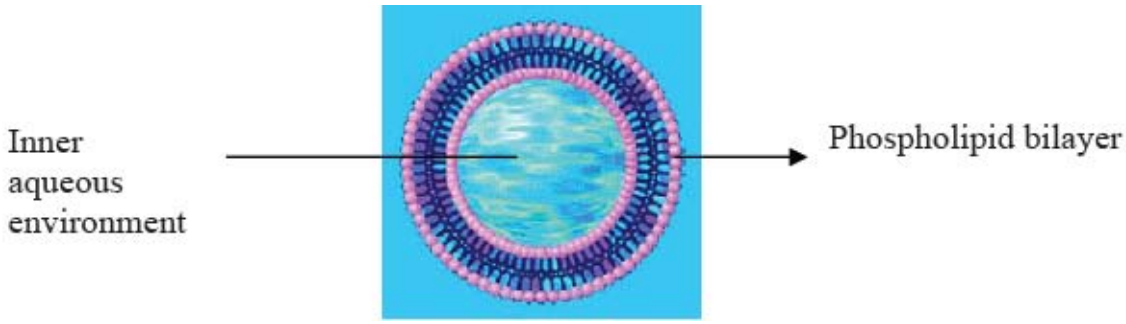


Figure 2: Structure of Liposomes

Table: 1 Liposomal formulation in market

Product	**Status**	**Payload**	**Indication**
Daunoxome®	Market	Daunorubicin	Cancer
Doxil®/caelyx®	Market	Doxorubicin	Cancer
Moet®	Market	Doxorubicin	Cancer
Ambisome®	Market	Amphotericin B	Fungal infections

Nanocrystals and nanosuspension

Nanocrystals are aggregates of around hundreds or thousands of molecules that combine in a crystalline form, composed of pure drug with only a thin coating comprised of surfactant or combination of surfactants. Problems typical of poorly soluble drugs like reduced bioavailability, improper absorption pattern and problems of preparing the parenteral dosage form may be resolved by formulation as nanocrystals. Only a minimum quantity of surfactants needs to be added in nanocrystals for steric and electrostatic surface stabilization. The size of nanocrystals allows for safe and effective passage through capillaries. Potential of nanocrystals can be inferred by the FDA approval of Rapamune®, containing sirolimus which is an immunosuppressant drug to prevent graft rejection in children after liver transplantation and Emend®, which contains aprepitant, MK 869, is used in the treatment of emesis associated with the cancer chemotherapy.[7-10]

Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) were developed at the beginning of the 1990s as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles as a colloidal carrier system for controlled drug delivery. Main reason for their development is the combination of advantages from different carriers systems like liposomes and polymeric nanoparticles. SLN have been developed and investigated for parenteral , pulmonal and dermal application routes. Solid Lipid Nanoparticles consist of a solid lipid matrix, where the drug is normally incorporated, with an average diameter below 1 μm. To avoid aggregation and to stabilize the dispersion, different surfactants are used that have an accepted GRAS (Generally Recognized as Safe) status. SLN have been considered as new transfection agents using cationic lipids for the matrix lipid composition. Cationic solid lipid nanoparticles (SLN) for gene transfer can be formulated using the same cationic lipids as for liposomal transfection agents.[11-16]

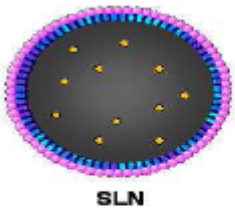


Figure 3: structure of solid lipid nanoparticle.

Polymeric nanoparticles

In comparison to SLN or nanosuspensions polymeric nanoparticles (PNPs) consists of a biodegradable polymer. The advantages of using PNPs in drug delivery are many, being the most important that they generally increase the stability of any volatile pharmaceutical agents and that they are easily and cheaply fabricated in large quantities by a multitude of methods. Also, polymeric nanoparticles may have engineered specificity, allowing them to deliver a higher concentration of pharmaceutical agent to a desired location.[11-16]

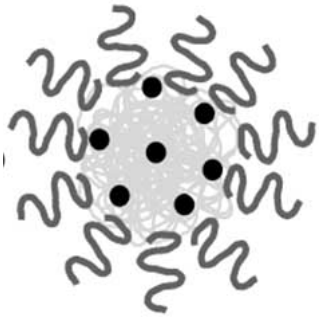


Figure 4: Polymeric nanoparticles

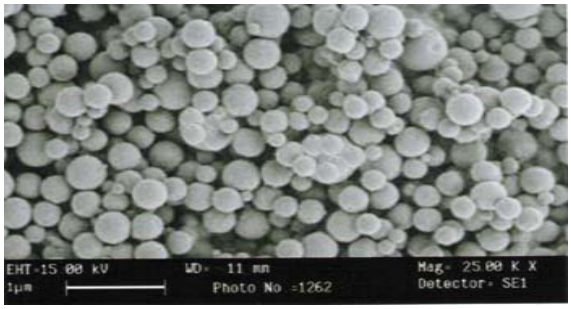


Figure 5: SEM image of polymer nanoparticles

Polymeric nanoparticles are a broad class comprised of both vesicular systems (nanocapsules) and matrix systems (nanospheres).

<u>Nanocapsules</u>

Nanocapsules are systems in which the drug is confined to a cavity surrounded by unique polymeric membrane whereas nanospheres are systems in which the drug is dispersed through out the polymer matrix. The various natural polymers like gelatin, albumin and alginate are used to prepare the nanoparticles; however they have some inherent disadvantages like poor batch-to-batch reproducibility, prone to degradation and potential antigenicity. Synthetic polymers used for nanoparticles preparation may be in the form of preformed polymer e.g. polyesters like polycaprolactone (PCL), poly lactic acid (PLA) or monomers that can be polymerized *in situ* e.g. polyalkyl cyanoacrylate. The candidate drug is dissolved, entrapped, attached or encapsulated throughout or within the polymeric shell/matrix. Depending on the method of preparation, the release characteristic of the incorporated drug can be controlled. Polymeric nanoparticulate systems are attractive modules for intracellular and site specific delivery. Nanoparticles can be made to reach a target site by virtue of their size and surface modification with a specific recognition ligand. Their surface can be easily modified and functionalized. [11-16]

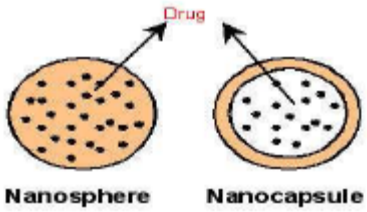


Figure 5: Nanospheres and Nanocapsules

Nanospheres

From its definition nanospheres are considered as a matrix system in which the matrix in uniformly dispersed. These are spheric vesicular systems.[17-19]

Dendrimers

Dendrimers, a unique class of polymers, are highly branched macromolecules whose size and shape can be precisely controlled. Dendrimers are fabricated from monomers using either convergent or divergent stepgrowth polymerization. The well defined structure, monodispersity of size, surface functionalization capability, and stability are properties of dendrimers that make them attractive drug carrier candidates. Drug molecules can be incorporated into dendrimers via either complexation or encapsulation. Dendrimers are being investigated for both drug and gene delivery, as carriers for penicillin, and for use in anticancer therapy. Dendrimers used in drug delivery studies typically incorporate one or more of the following polymers: polyamidoamine (PAMAM), melamine, poly(L-glutamic acid) (PG) , polyethyleneimine (PEI) , poly(propyleneimine), and poly(ethylene glycol) (PEG) ,Chitin.[19-20]

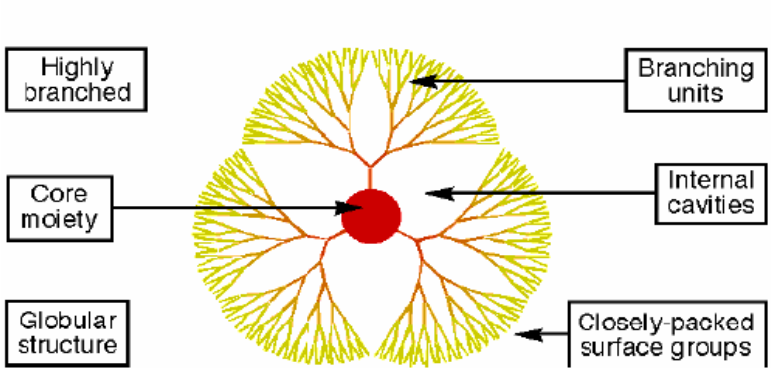


Figure 6: Dendrimers

Silicon-based structures

Silicon-based structures can be fabricated by photolithography, etching, and deposition techniques commonly used in the manufacture of semiconductors and microelectromechanical systems (MEMS). The most commonly investigated silicon-based materials for drug delivery are porous silicon and silica, or silicon dioxide. Architectures include calcified nanopores, platinum-containing nanopores, porous nanoparticles, and nanoneedles.

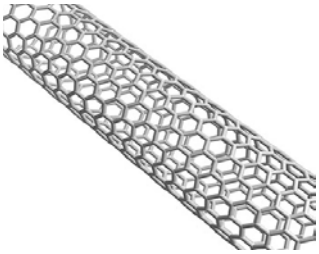
Porous hollow silica nanoparticles (PHSNP) are fabricated in a suspension containing sacrificial nanoscale templates such as calcium carbonate. Silica precursors, such as sodium silicate, are added into the suspension, which is then dried and calcinated creating a core of the template material coated with a porous silica shell. The template material is then dissolved in a wet etch bath, leaving behind the porous silica shell. Creation of drug carriers involves the mixing of the PHSNPs with the drug molecule and subsequently drying the mixture to coalesce the drug

molecules to the surface of the silica nanoparticles. As shown, the porous hollow nanoparticles exhibit a much more desirable gradual release. Examples of therapies being investigated for use with silicon-based delivery systems include porous silicon embedded with platinum as an antitumor agent , calcified porous silicon designed as an artificial growth factor , silicon nanopores for antibody delivery , and porous silica nanoparticles containing antibiotics , enzymes , and DNA. [21-27]

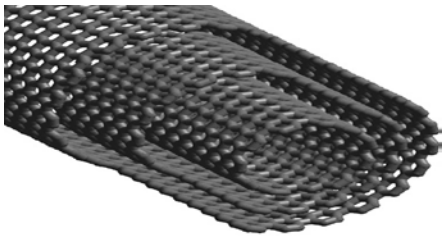
Carbon structures

Two nanostructures,that have received much attention in recent years are hollow, carbon-based, cage-like architectures: nanotubes and fullerenes, also known as buckyballs. Single-wall nanotubes (SWNTs), multiwall nanotubes (MWNTs), and C60 fullerenes are common configurations. The size, geometry, and surface characteristics of these structures make them appealing for drug carrier usage. SWNTs and C60 fullerenes have diameters on the order of 1nm, about half the diameter of the average DNA helix.

MWNTs have diameters ranging from several nanometers to tens of nanometers depending on the number of walls in the structure. Fullerenes and carbon nanotubes are typically fabricated using electric arc discharge (EAD), laser ablation (LA), chemical vapor deposition (CVD), or combustion processes. Surface-functionalized carbon nanotubes (CNTs) can be internalized within mammalian cells, and when linked to peptides may be used as vaccine delivery structures. It is used as small molecule transporter and also involved in transport of DNA, indicating potential use as a gene delivery tool. For example, temperature-stabilized hydrogels for drug delivery applications incorporate CNTs. Tissue-selective targeting and intracellular targeting of mitochondria have been shown with use of fullerene structures. Furthermore, experiments with fullerenes have also shown that they exhibit antioxidant and antimicrobial behavior.[21-27]



(a) single walled (SWNTs)



(b) multi walled (MWNTs)

Metal structures

Metallic nanoparticles are emerging as good delivery carrier for drug and biosensor. Although nanoparticles of various metals have been made yet silver and gold nanoparticles are of prime importance for biomedical use. Their surface functionalization is very easy and various ligands have been decorated onto the surface. A large numbers of ligands have been linked to nanoparticles including sugars, peptide, protein and DNA. They have been used for active delivery of bioactive, drug discovery, bioassays, detection, imaging and many other applications due to surface functionalization ability, as an alternative to quantum-dots.[21-27]

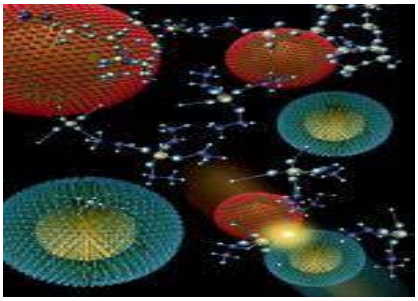
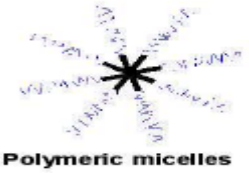


Figure 7: Surface functionalized gold nanoparticles

Polymeric micelles

Amphiphilic block copolymers assemble into nanoscopic supramolecular core-shell structures known as 'polymeric micelles'. Polymeric micelles are usually of <100 nm and their hydrophilic surface protects their nonspecific uptake by reticuloendothelial system. Micelles are formed in solution as aggregates in which the component molecules (e.g., amphiphilic AB-type or ABA-type block copolymers, where A and B are hydrophobic and hydrophilic components, respectively) are generally arranged in a spheroidal structure with hydrophobic cores shielded from water by a mantle of hydrophilic groups.



Polymeric micelles have proved an excellent novel drug delivery system due to high and versatile loading capacity, stability in physiological conditions, slower rate of dissolution, high accumulation of drug at target site and possibility of functionalization of end group for conjugation of targeting ligands.[21-27]

Nanoparticle production processes

Nanoparticles can be produced by either Dispersion-based processes (which involves breaking larger micrometer-sized particles into nanoparticles) or precipitation-based processes. [22-29]

Dispersion-based processes

a) Wet milling

Wet milling is an attrition-based process in which the drug is dispersed first in an aqueous-based surfactant solution. The resulting suspension is subjected to wet milling using a pearl mill in the presence of milling media.

b) High-pressure Homogenization

High-pressure homogenization is based on the principle of cavitation (*i.e.*, the formation, growth, and implosive collapse of vapor bubbles in a liquid. In this process, a drug presuspension (containing drug in the micrometer range) is prepared by subjecting the drug to air jet milling in the presence of an aqueous surfactant solution.

The main advantage of high-pressure homogenization is that it is suitable for both large- and laboratory-scale production because high-pressure homogenizers are available in various sizes. In addition, homogenization creates negligible nanoparticle contamination, which is one of the most important objectives of a nanoparticle production process.

A limitation of this process is that the pressure used is so high that in some cases, the crystal structure changed.

c) Emulsification Technology

Emulsification also can be used to prepare nanoparticle suspensions. In this method, the drug solution in an organic solvent is dispersed in the aqueous phase containing surfactant. This step is followed by the evaporation of organic solvent under reduced pressure, which results in the precipitation of drug particles to form a nanoparticle suspension which is stabilized by the added surfactant. The use of microemulsion as templates for producing drug nanosuspensions.

Precipitation-based processes

a) Spray freezing into liquid (SFL)

In this process, developed at the University of Texas at Austin (Austin, TX) and commercialized by Dow Chemical Company (Midland, MI), an aqueous, organic, or aqueous–organic cosolvent solution; aqueous–organic emulsion; or drug suspension is atomized into a cryogenic liquid such as liquid nitrogen to produce frozen nanoparticles which are subsequently lyophilized to obtain free flowing powder.

b) Evaporative precipitation into aqueous solution (EPAS).

The EPAS process also was developed by the University of Texas at Austin and commercialized by Dow Chemical Company. In this process, the drug solution in a low boiling liquid organic solvent is heated under pressure to a temperature above the solvent's normal boiling point and then atomized into a heated aqueous solution containing stabilizing surfactant.

c) Rapid expansion from a liquefied-gas solution (RESS)

In an RESS process, a solution or dispersion of phospholipids or other suitable surfactant in the supercritical fluid is formed. Then, rapid nucleation of drug is induced in the supercritical fluid containing surfactant. This process allows rapid, intimate contact of the drug dissolved in supercritical fluid and the surfactant which inhibits the growth of the newly formed particles.

d) Precipitation with a Compressed Fluid Antisolvent (PCA)

In the PCA process (patented by RTP Pharmaceuticals and licensed to SkyePharma Plc [London, UK]), supercritical carbon dioxide is mixed with organic solvents containing drug compounds. The solvent expands into supercritical carbon dioxide, thus increasing the concentration of the solute in the solution, making it supersaturated, and causing the solute to precipitate or crystallize out of solution.

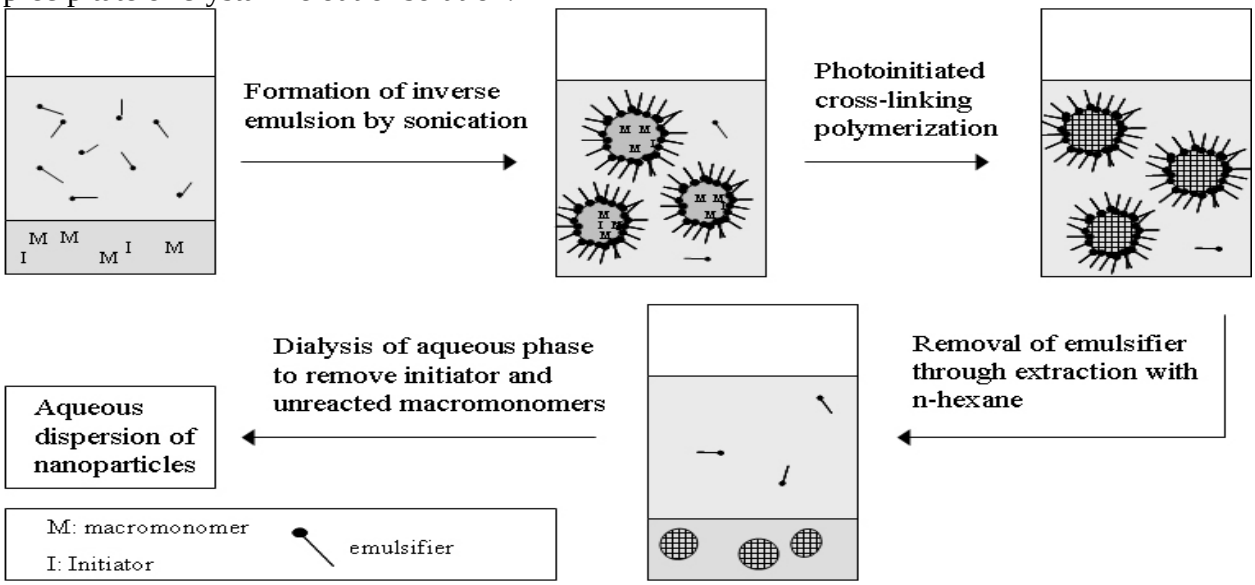


Figure 8: Nanoparticle preparation via inverse emulsion photopolymerization

Drug Loading

A successful NP system may be one which has a high loading capacity to reduce the quantity of the carrier required for administration. Drug loading into NPs is achieved by two methods: one, by incorporating the drug at the time of NP production or secondly, by adsorbing the drug after the formation of NPs by incubating them in the drug solution. A larger amount of drug can be entrapped by the incorporation method than by adsorption.

Mechanism of action of drug release[29-31]

There are three primary mechanisms by which active agents can be released from a delivery system:

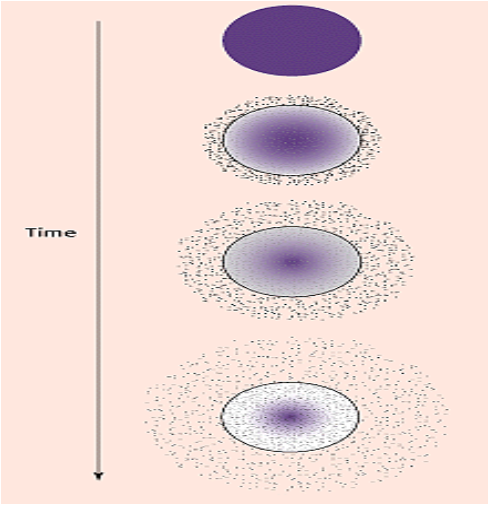
Diffusion

Degradation

Swelling followed by diffusion

Diffusion

Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale—as through pores in the polymer matrix—or on a molecular level, by passing between polymer chains.



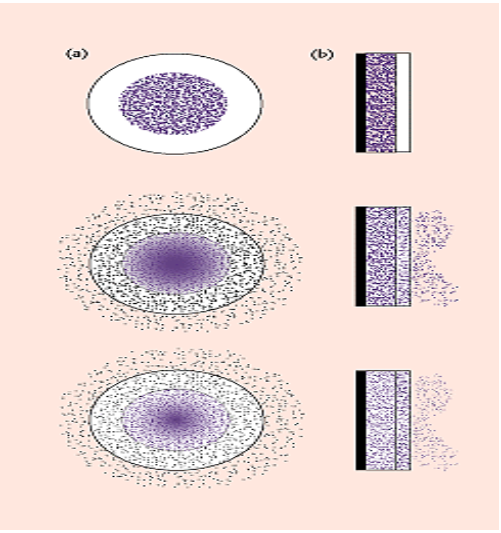


Figure 9: represent the rate of release of the drug

Figure 10: (a) an implantable or oral reservoir delivery system, (b) a transdermal drug delivery system, in which only one side of the device will actually be delivering the drug.

Swelling

Swelling-controlled release systems are initially dry and, when placed in the body, will absorb water or other body fluids and swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment. Examples of these types of devices are shown in Figures for reservoir and matrix systems, respectively.

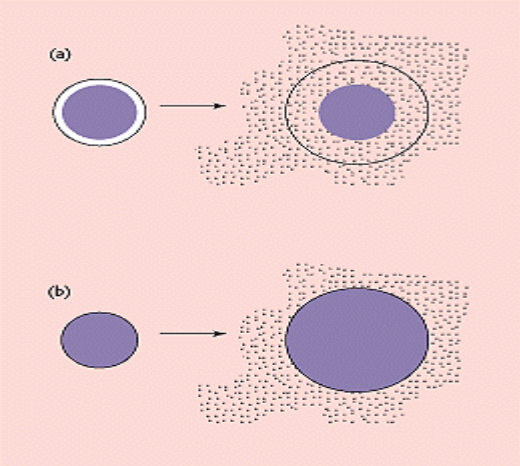


Figure11: Drug delivery from (a) reservoir and (b) matrix swelling-controlled release systems.

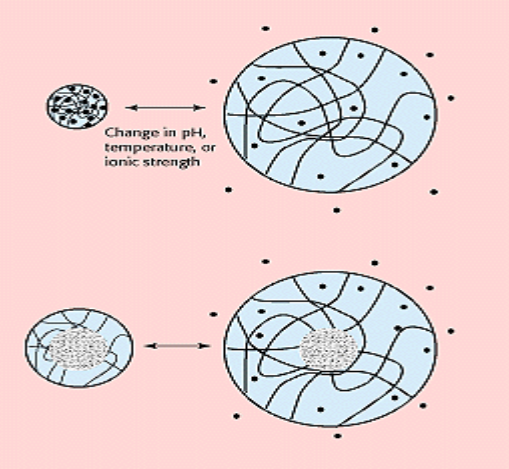


Figure 12: Drug delivery from environmentally sensitive release systems

Degradation

It take place in two ways

(a) bulk-eroding and (b) surface-eroding :

In surface eroding systems, polymer degradation is much faster than the water imbibition into the polymer bulk. Thus, degradation occurs predominantly within the outermost polymer layers. Consequently, erosion affects only the surface and not the inner parts of the system (heterogeneous process). In contrast, bulk eroding polymers degrade more slowly and the imbibition of water into the system is much faster than the degradation of the polymer. Hence, these polymers are rapidly wetted and polymer chain cleavage occurs throughout the system. Consequently, erosion is not restricted to the polymer surface only (homogeneous process). As a basic rule, polymers containing very reactive functional groups tend to degrade fast and tend to be surface eroding, whereas polymers with less reactive functional groups tend to be bulk eroding. PLGA-based microparticles can generally be regarded as bulk eroding dosage forms.

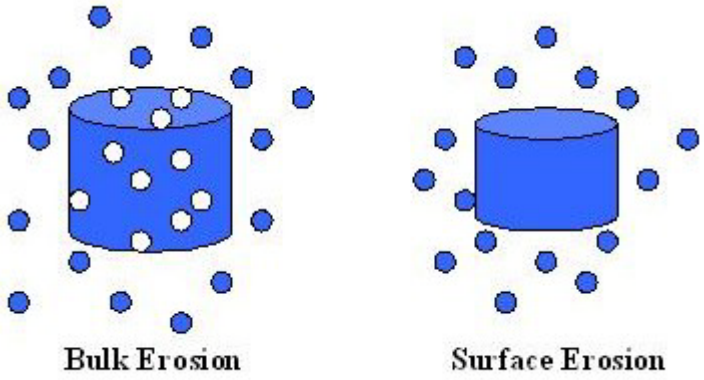


Figure 13: Comparison of bulk and surface erosion mechanisms.

Methods of determination of drug release [30-33]

The following methods for the determination of the in vitro release have been used:

1. Side by side diffusion cells with artificial or biological membranes
2. Dialysis bag diffusion technique
3. Reverse dialysis sac technique
4. Ultracentrifugation
5. Ultra filtration (Centrifugal) technique

Characterization of Nanoparticles [30-32]

Table no. 2: Different parameters & characterization methods for nanoparticles

Parameters	**Characterization methods**
Particle size & size distribution	photon correlation spectroscopy, Scanning electron microscopy (SEM), Transmission electron microscopy (TEM), Atomic force microscopy (AFM), Mercury porositometry, Laser defractrometry
Charge determination	Laser droplet anemometry, Zeta potentiometer
Surface hydrophobicity	Water contact angle measurements, rose bangle (dye) binding, hydrophobic interaction chromatography, X-ray photoelectron spectroscopy
Chemical analysis of surface	Static secondary ion mass spectrometry, sorptometer
Carrier drug interaction	Differential scanning calorimetry
Nanoparticle dispersion stability	Critical flocculation temperature(CFT)
Release profile	In-vitro release characteristic under physiologic & sink condition
Drug stability	Bioassay of drug extracted from nanoparticle, chemical analysis of drug

Application of nanoparticles

Health implications of Nanoparticles [30-36]

Nanoparticles can enter the human body in several ways; (i) via the lungs where a rapid translocation through the blood stream to vital organs is possible, including crossing the BBB, and absorption by (ii) the intestinal tract, or (iii) the skin.

a) Skin

Particles 500–1000 nm in size, theoretically beyond the realms of nanotechnology, can penetrate and reach the lower levels of human skin, 128 and smaller particles are likely to move deeper into the skin. TiO2 particles are often used in sunscreens to absorb UV light and therefore to protect skin against sunburn or genetic damage. It has been reported that micrometer-sized particles of TiO2 get through the human stratum corneum and even into some hair follicles – including their deeper parts.

b) Intestinal tract

The kinetics of particle translocation in the intestine depends on diffusion and accessibility through mucus, initial contact with enterocyte or M-cell, cellular trafficking, and post-translocation events. Charged particles, such as carboxylated polystyrene nanoparticles or those composed of positively charged polymers exhibit poor oral bioavailability through electrostatic repulsion and mucus entrapment. The smaller the particle diameter the faster they could permutate the mucus to reach the colonic enterocytes; 14 nm diameter permeated within 2 min, 415 nm particles took 30 min, while 1000-nm particles were unable to translocate this barrier.

c) Lung

Based on three particle-types titanium dioxide (TiO2), carbon black, and diesel particles, hazard studies in rats demonstrate that ultrafine or nanoparticles administered to the lung produce more potent adverse effects in the form of inflammation and subsequent tumors compared with larger sized particles of identical chemical composition at equivalent mass concentrations or intratracheally-instilled doses. Surface properties, such as surface chemistry and area, may play a significant role in nanoparticle particle toxicity.

Clinical aspects

Several nanoparticle technologies are currently in clinical trials and a few have progressed to clinical use. There are some FDA approved drug products employing nanotechnology. *Rapamune* (Wyeth-Ayerst Laboratories), an oral tablet dosage form containing nanoparticles of the immu-nosuppressant drug Rapamycin, was approved by the U.S. FDA. Some of the pharmaceutical products based on nanotechnologies are summarized in Table.

Table no. 3 : Examples of pharmaceuticals products based on nanotechnologies

Brand name	Description	Advantages
Emend (Merck & Co. Inc.)	Nanocrystal aprepiant (antiemetic) in a capsule	Enhanced dissolution rate & bioavailability
Rapamune (Wyeth-Ayerst Laboratories)	Nanocrystallied Rapamycin (immunosuppressant) in a tablet	Enhanced dissolution rate& bioavailability
Abraxane (American Biosciences, Inc.)	Paclitaxel (anticancer drug) bound albumin particles	Enhance dose tolerance and hence effect elimination of solvent associated toxicity
Rexin-G (Epeius Biotechnology corporation)	A retroviral vector carrying cytotoxic gene	Effective in pancreatic cancer treatment
Olay Moisturizers (Proctor and Gamble)	Contains added transparent, better protecting nano zinc oxide particles	Offer better UV protection
Trimetaspheres (Luna Nanoworks)	MRI images	enhanced MRI images at least 25 times better than current contrast agents
SILCRYST (Nucryst Pharmaceuticals)	Enhance the solubility and sustained release of silver nanocrystals	Better protection from infection

Nano-balls (Univ. of South Florida)	Nano-sized plastic spheres with drugs (active against methicillin-resistant staph (MRSA) bacteria) chemically bonded to their surface that allow the drug to be dissolved in water.	More powerful antibiotics

Nanoparticles as drug carrier vehicle

1. It helps in improving solubility and bioavailability, reducing toxicity, enhancing release and providing better formulation opportunities for drugs.70
2. Major advantages of nano-sizing include (i) increased surface area, (ii) enhanced solubility, (iii) increased rate of dissolution, (iv) increased oral bioavailability, (v) more rapid onset of therapeutic action, (vi) less amount of dose required, (vii) decreased fed/fasted variability, and (viii) decreased patient-to-patient variability.[67-75,79]
3. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.[79,80,82,83]
4. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.
5. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
6. Generally nanoparticles have relatively higher intracellular uptake compared to microparticles and are available to a much wider range of biological targets due to their small size and relative mobility. 100 nm nanoparticles had a 2.5 fold greater uptake than 1 μm microparticles, and 6 fold greater uptake than 10 μm microparticles.
7. Nanotechnology offered numerous smart materials that are used for tissue repair and replacement, implant coatings, tissue regeneration scaffolds, structural implant materials, bone repair, bioresorbable materials, some implantable devices (sensory aids, retina implants etc.), surgical aids, operating tools, and smart instruments. [67-72]

Cancer therapy: Nanotechnology can have a revolutionary impact on cancer diagnosis and therapy. Available therapies commonly employed in cancer treatment include surgery, chemotherapy, immunotherapy, and radiotherapy. Nanotechnology offers tremendous opportunities to aid and improve these conventional therapies by virtue of its nanotools. Some nanotools that have played key role in cancer therapy are listed below.

Table no 4: Applications of various nanosystems in cancer therapy

Nanosystem	**Applications in cancer therapeutics**
Carbon nanotubes	DNA mutation detection, disease protein biomarker detection
Dendrimers	Controlled release drug delivery, image contrast agents
Nanocrystals	Improved formulation for poorly-soluble drugs
Nanoparticles	MRI and ultrasound image contrast agents, targeted drug delivery, permeation enhancers, reporters of apoptosis, angiogenesis, etc.
Nanoshells	Tumor-specific imaging, deep tissue thermal ablation
Nanowires	Disease protein biomarker detection, DNA mutation detection, gene expression detection
Quantum dots	Optical detection of genes and proteins in animal models and cell

	assays, tumor and lymph node visualization.

Photodynamic cancer therapy is based on the destruction of the cancer cells by laser generated atomic oxygen, which is cytotoxic. A greater quantity of a special dye that is used to generate the atomic oxygen is taken in by the cancer cells when compared with a healthy tissue. Hence, only the cancer cells are destroyed then exposed to a laser radiation. Unfortunately, the remaining dye molecules migrate to the skin and the eyes and make the patient very sensitive to the daylight exposure. This effect can last for up to six weeks.

To avoid this side effect, the hydrophobic version of the dye molecule was enclosed inside a porous nanoparticle. The dye stayed trapped inside the Ormosil nanoparticle and did not spread to the other parts of the body. At the same time, its oxygen generating ability has not been affected and the pore size of about 1 nm freely allowed for the oxygen to diffuse out.

Multicolour optical coding for biological assays

Single quantum dots of compound semiconductors were successfully used as a replacement of organic dyes in various bio-tagging applications. This idea has been taken one step further by combining differently sized and hence having different fluorescent colours quantum dots, and combining them in polymeric microbeads. A precise control of quantum dot ratios has been achieved. The selection of nanoparticles used in those experiments had 6 different colours as well as 10 intensities. It is enough to encode over 1 million combinations. The uniformity and reproducibility of beads was high letting for the bead identification accuracies of 99.99%.

Manipulation of cells and biomolecules

Functionalised magnetic nanoparticles have found many applications including cell separation and probing. Most of the magnetic particles studied are spherical, which somewhat limits the possibilities to make these nanoparticles multifunctional. Alternative cylindrically shaped nanoparticles can be created by employing metal electrodeposition into nanoporous alumina template. Depending on the properties of the template, nanocylinder radius can be selected in the range of 5 to 500 nm while their length can be as big as 60 μm. By sequentially depositing various thicknesses of different metals, the structure and the magnetic properties of individual cylinders can be tuned widely.

Protein detection

Proteins are the important part of the cell's language, machinery and structure, and understanding their functionalities is extremely important for further progress in human well being. Gold nanoparticles are widely used in immunohistochemistry to identify protein-protein interaction. However, the multiple simultaneous detection capabilities of this technique are fairly limited. Surface-enhanced Raman scattering spectroscopy is a well-established technique for detection and identification of single dye molecules. By combining both methods in a single nanoparticle probe one can drastically improve the multiplexing capabilities of protein probes.

Conclusions

The Nanocomposites 2000 conference has revealed clearly the property advantages that nanomaterial additives can provide in comparison to both their conventional filler counterparts and base polymer. Properties which have been shown to undergo substantial improvements include:

- Mechanical properties e.g. strength, modulus and dimensional stability
- Decreased permeability to gases, water and hydrocarbons

- Thermal stability and heat distortion temperature
- Flame retardancy and reduced smoke emissions
- Chemical resistance
- Surface appearance
- Electrical conductivity
- Optical clarity in comparison to conventionally filled polymers
- Increased bioavailability
- Dose proportionality
- Decreased toxicity
- Smaller dosage form (i.e., smaller tablet)
- Stable dosage forms of drugs which are either unstable or have unacceptably low bioavailability in non-nanoparticulate dosage forms.
- Increased active agent surface area results in a faster dissolution of the active agent in an aqueous environment, such as the human body. Faster dissolution generally equates with greater bioavailability, smaller drug doses, less toxicity.
- Reduction in fed/fasted variability.

To date one of the few disadvantages associated with nanoparticle incorporation has concerned toughness and impact performance. Some of the data presented has suggested that nanoclay modification of polymers such as polyamides, could reduce impact performance. Clearly this is an issue which would require consideration for applications where impact loading events are likely. In addition, further research will be necessary to, for example, develop a better understanding of formulation/structure/property relationships, better routes to platelet exfoliation and dispersion etc.

References:

1. Kreuter, J. (1994). “Nanoparticles, in Encyclopaedia of Pharmaceutical Technology”, Swarbrick J, Editor. Marcel Dekker Inc.: New York, USA., 165-90.
2. Barratt, G., M. (2000). “Therapeutic applications of colloidal drug carriers”. Pharm. Sci. Technol., 3:163-171.
3. Couvreur, P., Dubernet, C., Puisieux, F. (1995), “Controlled drug delivery with nanoparticles: current possibilities and future trends. Eur. J. Pharm. Biopharm., 41: 2-13.
4. Vauthier-Holtzscherer, C., Benabbou, S., Spenlehauer, G., Veillard, M., Couvreur, P. (1991), “Methodology for the preparation of ultra-dispersed polymer system”. STP Pharma Sciences.1: 109-116.
5. Redhead, H. (1997). “Drug loading of biodegradable nanoparticles for site specific drug delivery”. University of Nottingham Nottingham.
6. http://www.nano.irS
7. http://www.nanotechnologydevelopment.com/products/introduction-to-nanoparticles.html
8. http://www.clubofamsterdam.com
9. http://www.rsc.org/deliver
10. http://ajrccm.atsjournals.org/cgi/content/full/172/12/1487#BIB2#BIB2
11. http://www.nanotechproject.org/inventories/medicine/
12. http://www.yashnanotech.com/nano-application.php
13. http://www.understandingnano.com/medicine.html

14. Jain S., Jain N.K. Liposomes as drug carrier, In: Jain NK, editor. Controlled and novel drug delivery. 2nded. CBS publisher, New Delhi, 2002,.304-52.
15. Baba R .Patent and Nanomedicine. Nanomedicine (2007) 2(3), 351-374.
16. Khopde AJ, Jain, NK. Dendrimer as potential delivery system for bioactive In: Jain NK, editor. Advances in controlled and novel drug delivery. CBS publisher, New Delhi, 2001, 361-80.
17. http://www.nano.ir/news/attach/t1406.pdf
18. http://en.wikipedia.org/wiki/Nanoshell
19. http://www.research.ibm.com/nanoscience/nanotubes.html
20. http://www.springerlink.com/index/df9dlf4d944jexgh.pdf
21. www.iop.org/EJ/article/1742-6596/.../jpconf9_187_012047.pdf
22. www.pdfgeni.com/book/coacervation-method-pdf.html - United States
23. Scholes, P., D., Coombes, A.,G., Illum, L., Davis, S., S., Watts, J., F., Ustariz, C., Vert, M., Davies, M., C., Detection and determination of surface levels of poloxamer and PVA surfactant on biodegradable nanospheres using SSIMS and XPS. J. Controlled Release, 1999. 59(3):261-78.
24. Vauthier-Holtzscherer, C., Benabbou, S., Spenlehauer, G., Veillard, M., Couvreur, P. (1991) "Methodology for the preparation of ultra-dispersed polymer systems", STP Pharma Sciences, 1: 109-116.
25. Vauthier, C., Dubernet, C., Chauvierre, C., Brigger, I., Couvreur, P. (2003). "Drug delivery to resistant tumors: the potential of poly(alkyl cyanoacrylate) nanoparticles", J. Controlled Release. 93(2): 151-60.
26. Panyam, J., Sahoo, S., K., Prabha, S., Bargar, T., Labhasetwar, V. (2003). "Fluroescence and electron microscopy probes for cellular and tissue uptake of poly (DL-co-glycolide) nanoparticle", Int. J. Pharm, 262: 1-11.
27. Panyam, J., Labhasetwar, V. (2003). "Biodegradable nanoparticles for drug and gene delivery to cells and tissue". Adv. Drug Delivery Rev. 55(329- 47)
28. Moghimi, S., M., Hunter, A., C., Murray, J., C. (2001). "Long-circulating and target-specific nanoparticles: theory to practice". Pharmacol. Rev., 53(2): 283-318.
29. Kreuter, J. (1994). "Nanoparticles, in Colloidal Drug Delivery Systems", J.Kreuter, Editor., Marcel Dekker: New York. 219- 342.
30. Haixiong, G., Yong, H., Jiang, X., Cheng, D., Yuan, Y., Bi,H., Yang, C.(2002). "Preparation, characterization, and drug release behaviors of drug nimodipine-loaded poly(ϵ-caprolactone)-poly(ethylene oxide)- poly(ϵ-caprolactone) amphiphilic triblock copolymer micelles. J.Pharm. Sci. 91(6): 1463-73.
31. Desai, M., P., Labhasetwar, V., Walter, E., Levy, R., J., and Amidon, G., L. (1997). "The mechanism of uptake of biodegradable microparticles in caco- 2 cells is size dependant". Pharm. Res., 14: 1568-73.
32. Linhardt, R., J. (1989). "Biodegradable polymers for controlled release of drugs, in Controlled Release of Drugs", M. Rosoff, Editor., VCH Publishers: New York 53–95.
33. Redhead, H., M., Davis, S., S.,Illum, L.(2001), "Drug delivery in poly(lactide-coglycolide) nanoparticles surface modified with poloxamer 407 and poloxamine 908: in vitro characterisation and in vivo evaluation". J. Controlled Release, 70(3): 353-63.
34. Barrera, D., A., Zylstra, E., Lansbury, P., T., Langer, R. (1993). "Synthesis and RGD peptide modification of a new biodegradable co polymer; poly(lactic acid-co-lysine)". J Am Chem Soc, 115: 11010-11.

35. Davda, J., Labhasetwar, V. (2002). “Characterisation of nanoparticle uptake by endothelial cells”. Int J Pharm. 223: 51-59.
36. Woodward, S., C., Brewer, P., S., Montarned, F., Schindler, A., Pitt, C. (1985). The intracellular degradation of p polycaprolactone”. J. Biomedical Mater. Res., 19: 437– 44.