

NANOPARTICULATE DRUG DELIVERY SYSTEM: A NOVEL APPROACH

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REVIEW ARTICLE

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ABSTRACT:

As because of several advantages over to the conventional drug delivery Nanoparticulate drug delivery prepared in several means by several ways of methods have several applications in different discipline of Pharmaceutical science. There are various parameters for Evaluation of Nanoparticles as Drug Delivery system so we can justified as nanoparticulate drug delivery system: a novel approach.

Key words: Nanoparticles, NPDDSs, nanocrystals, CNT, SCF, SAS, DSC

Introduction: Nanoparticles are solid colloidal particles consisting of macromolecular substances that vary in size from 10nm to 1,000 nm. The drug of interest is dissolved, entrapped, adsorbed attached or encapsulated into the Nanoparticle matrix. Depending upon the

method of preparation, Nanoparticles, nanospheres or nanocapsules can be obtained with different properties and release characteristics for the encapsulated therapeutic agent [1, 2].

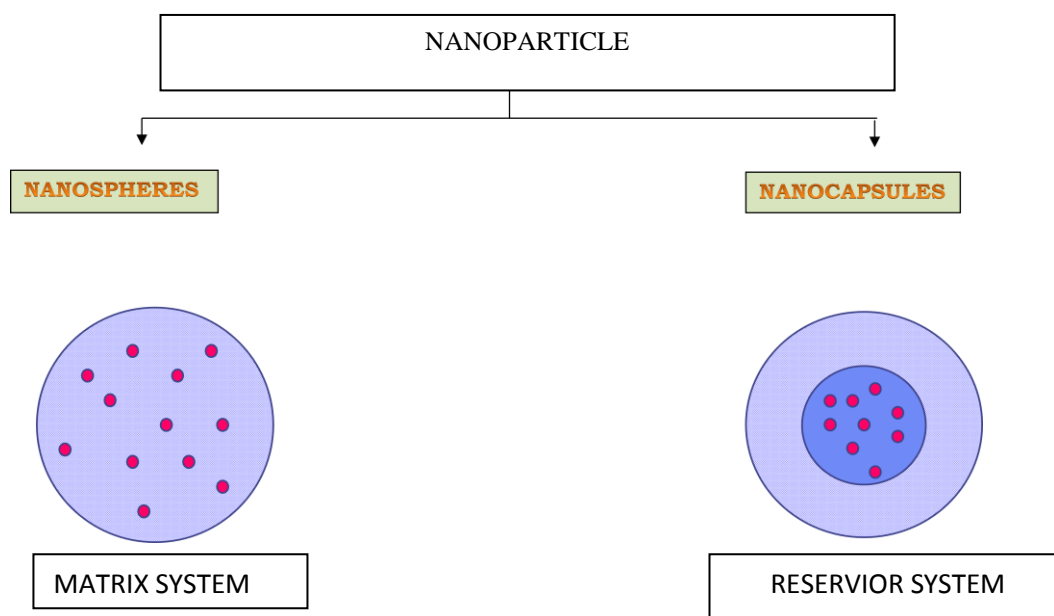


Figure 1: Nanoparticle system [3].

Nanoparticulate Drug-Delivery Systems: Nanoparticulate drug-delivery systems (NPDDSs) are being explored for the purpose of solving the challenges of drug delivery. Coming in many shapes and sizes, most carriers are less than 100 nm in diameter. NPDDSs provide methods for targeting and releasing

therapeutic compounds in much defined regions. These vehicles have the potential to eliminate or at least ameliorate many problems associated with drug distribution. As many drugs have a hydrophobic component, they often suffer from problems of precipitation in high concentration, and there are many

examples of toxicity issues with excipients designed to prevent drug aggregation. [4]

To combat these issues, many NPDDSs provide both hydrophobic and hydrophilic environments, which facilitate drug solubility. Alternatively, many drugs suffer from rapid breakdown and/or clearance in vivo. Encapsulating the drugs in a protective environment, NPDDSs increase their bioavailability, thereby allowing the clinicians to prescribe lower doses. With recent advances in polymer and surface conjugation techniques as well as microfabrication methods, perhaps the greatest focus in drug-delivery technology is in the design and applications of NPDDSs. Ranging from simple metal–ceramic core structure to complex lipid–polymer matrices, these submicron formulations are being functionalized in numerous ways to act as therapeutic vehicles for a variety of conditions. PDDSs can be defined as the DDSs where nanotechnology is used to deliver the drug at nanoscale. Below 100 nm, materials exhibit different, more desirable physical, chemical, and biological properties. Given the enormity and immediacy of the unmet needs of therapeutic areas such as CNS disorders, this can lead to drugs that can extend life and save untimely deaths. [5, 6]

Advantages:

1. Particle size and surface characteristics of Nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration. [7]
2. 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. [8]
3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. 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.
4. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
5. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc. [9]

Types of Nanoparticulate system:

Table 1: Types of Nanoparticle System [10]

Sr. No.	Types of Nanoparticles	Material Used	Applications
1.	Polymeric Nanoparticles [11].	Biodegradable polymers	Controlled and targeted drug delivery
2.	Solid lipid Nanoparticles	Melted lipid dispersed in an aqueous surfactant	Least toxic and more stable colloidal carrier systems as alternative to polymers
3.	Nanocrystals & nanosuspensions	Drug powder is dispersed in a surfactant solution	Stable systems for controlled delivery of poorly water soluble drugs
4.	Polymeric micelles	Amphiphilic block copolymers	Systemic and controlled delivery of water insoluble drugs
5.	Liposomes [12].	Phospholipid vesicles	Controlled and targeted drug delivery
6.	Dendrimers	Tree like molecules with defined cavities	Drug targeting

7.	Magnetic NPs	An inorganic core of iron oxide (magnetite) coated with polymer such as dextran	Drug targeting, Diagnostic tool in biology and medicine
8.	Gold nanoshells	Dielectric (typically gold sulfide or silica) core and a metal (gold) shell	Tumor targeting
9.	Nanowires or Carbon nanotubes	Metals, semiconductors or carbon	Gene and DNA delivery
10.	Ferofluids	Iron oxide magnetic NPs surrounded by a polymeric layer	For capturing cells and other biological targets from blood or other fluids and tissue samples
11.	Nanopowder	two or more different cations (positively charged elements) in their chemical formula	for targeted applications like infrared windows, catalysts, fuel cells, and even cosmetics

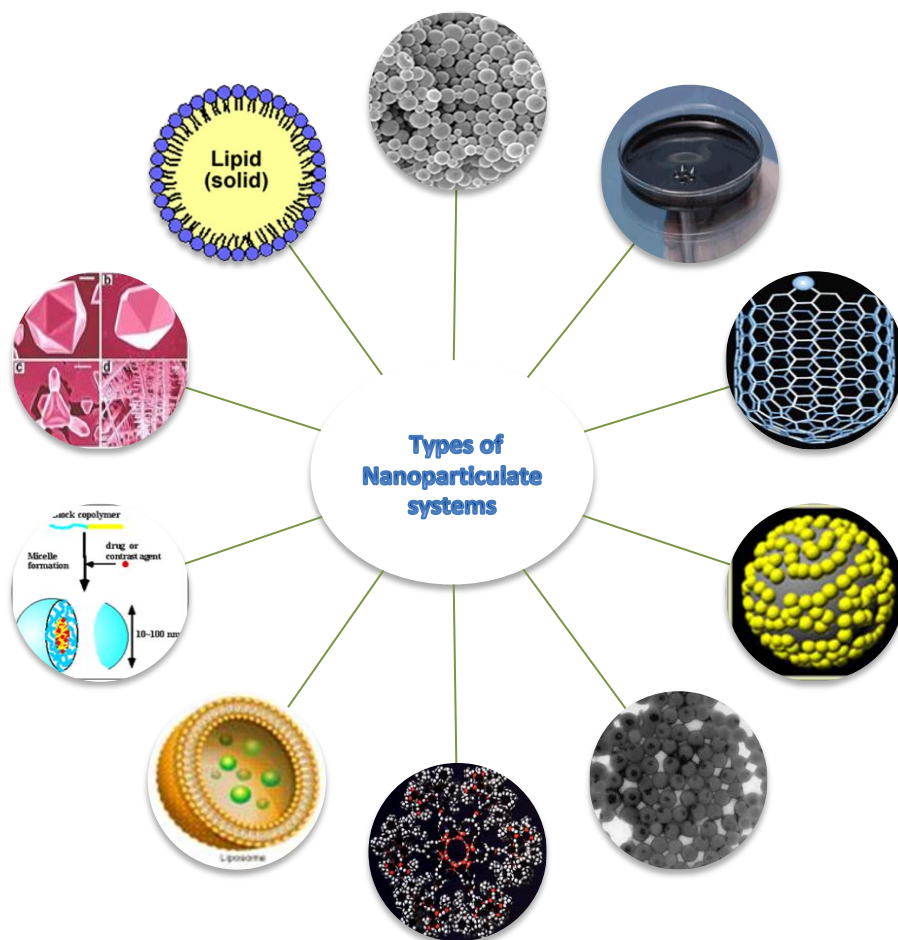


Figure 2: Types of Nanoparticle System

Nanoparticulate Formulation:

1. Materials
2. Preparation of Nanoparticles
3. Surface Modification of Nanoparticles

4. Drug Loading into Nanoparticles

1. Materials:

Polymer Based Nanoparticulate Drug-Delivery System [11]. In materials mainly used are

Alinates, Chitosen, Gelatin, Pullulan, Gliadin, Lipid-Based Colloidal Nanodrug-Delivery Systems etc.

Nanoparticulate Polymeric Micelles as Drug Carriers:

Polymeric micelles are self-assemblies of block copolymers in aqueous media. Many advantages have been demonstrated with their unique core shell architecture. Hydrophilic shells from the aqueous exterior segregate the hydrophobic cores. Hydrophobic drugs can be solubilized into the hydrophobic core structures of polymeric micelles at concentrations much higher than their intrinsic water solubility. Polymeric micelles are known to have high drug-loading capacity, high water solubility, and appropriate size for long circulation in the blood. The hydrophilic shell surrounding the micellar core can protect undesirable phenomena such as intermicellar aggregation, or precipitation, protein adsorption, and cell adhesion. The chemical composition of the polymeric micelles can be tailor-made to have desirable physicochemical properties for drug solubilization. The hydrophobic drug is incorporated into the hydrophobic core by interactions such as metal–ligand coordination bonding and electrostatic interaction. The extent of drug solubility depends on the compatibility between the drug and the micelle core. One of the limitations of drug-loaded polymeric micelles is low stability in aqueous solution, and the stability becomes even lower as the drug-loading content increases. Various types of drugs can be loaded into the hydrophobic core of polymeric micelles by chemical conjugation or physical entrapolymeric micelles sent utilizing various interactions such as hydrophobic interactions, or ionic interactions, or hydrogen bonding. Furthermore, the hydrophobic core serves as a reservoir from

which the drug is released slowly over an extended period of time. The hydrophobic inner core is solubilized by the hydrophilic shell, which prevents the inactivation of the core-encapsulated drug molecules by decreasing the contact with the inactivating species in the aqueous (blood) phase. As the outer hydrophilic part of the polymeric micelles interacts with biocomponents such as cells and proteins, it affects their pharmacokinetics and disposition, as well as their surface properties. [13]

Dendrimer-Based Drug-Delivery Systems

Three-dimensional tree-like branched macromolecules possess some fascinating characteristics: a well-defined structure, a very narrow molecular weight distribution, a three-dimensional structure tuned by dendrimer generation and dendron structure, and flexibility for tailored functional groups with high density on the periphery. Studies of biomedical application of dendrimers are becoming more and more attractive especially in the field of nonviral gene vector and NPDDS. [14]

Drug Nanocrystals

Drug nanocrystals are pure solid drug particles with a mean diameter below 1000 nm. A nanosuspension consists of drug nanocrystals, stabilizing agents such as surfactants and/or polymeric stabilizers, and a liquid dispersion medium. The dispersion media can be water, aqueous solutions, or nonaqueous media. The term “drug nanocrystals” implies a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous. Drug nanocrystals have to be distinguished from polymeric nanoparticles, which consist of a polymeric matrix and an incorporated drug. Drug nanocrystals do not consist of any matrix material.

Polymers:

Table 2: Various polymers used in various methods of Nanoparticles preparations:

Methods of Nanoparticles preparation	Polymers
Monomers polymerization	Poly(alkyl cyanoacrylate), Poly(alkyl methacrylate), Poly(styrene), Poly(vinylpyridine)
Nanoprecipitation	Poly(ϵ -caprolactone), Poly(lactic acid), Poly(lactic-co-glycolic acid), Poly(methacrylate)

Solvent evaporation	Poly(ϵ -caprolactone), Poly(lactic acid), Poly(lactic-co-glycolic acid), Poly(β -hydroxybutyrate), Ethyl cellulose
Salting out	Cellulose acetate phthalate, Poly(alkyl methacrylate), Ethyl cellulose, Poly(lactic acid), Poly(lactic-co-glycolic acid)
Desolvation, denaturation, ionic gelation	Albumin, Casein, Gelatin, Alginate, Chitosan, Ethyl cellulose

Stabilizer: Generally surfactants are used as stabilizers to reduce high surface free energy of nanosized particles. Generally used stabilizers are Cellulosic, Poloxamers 184, 188, 338, 407, Poloxamine 908, Polysorbates 20, 40, 60, 80, Lecithin, Cremophor EZ and RS 40, Polyoxyethylene lauryl ether, Povidone, Lecithin is stabilizer of choice for parenteral preparations.

Organic Solvents:

Water immiscible organic solvent: Methylene chloride, Chloroform, DCM

Partially water miscible solvent: Ethyl acetate, Ethyl formate, Butyl lactate, Triacetin, Propylene carbonate, Benzyl alcohol

Water miscible solvent: Ethanol, Isopropanol

Co-surfactants: Bile salts Dipotassium Glycerrhizinate, Transcutol, Glycofurol, Ethanol, and Isopropylalcohol.

Other Additives: Includes Buffers, Salts, Polyols, Osmogents, and Cryoprotectants.

Metallic Nanoparticle Drug - Delivery Systems: It includes Gold Nanoparticles, Iron Nanoparticles

Nanotubes:

Carbon nanotubes (CNT) have shown substantial potential in a variety of biological applications including use as DNA and protein biosensors, ion channel blockers, bioseparators, and biocatalysts (Bianco et al. 2005a). This potential stems from their specific surface or adaptable size-dependent properties in combination with their anisotropic character. Their anisotropy is of consequence since it influences their electronic, photonic, mechanical, and chemical properties.

The chemical composition of a nanotube can have significant impact on its structure. Polymeric nanotubes are hollow, molecular scale versions of nanowires. [15] Carbon nanotubes are cylindrical macromolecules with

variable radii starting at a few nanometers with maximum lengths up to 20 cm (Martin Steinhart et al. 2003).

Drug Nanocrystals: Drug Nanocrystals are pure solid drug particles with a mean diameter below 1000 nm. A nanosuspension consists of drug nanocrystals, stabilizing agents such as surfactants and/or polymeric stabilizers, and a liquid dispersion medium. The dispersion media can be water, aqueous solutions, or nonaqueous media. The term "drug nanocrystals" implies a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous. Drug nanocrystals have to be distinguished from polymeric nano particles, which consist of a polymeric matrix and an incorporated drug. Drug nanocrystals do not consist of any matrix material.

2. Preparations of Nanoparticles:

Solvent Evaporation:

- Polymer is dissolved in organic solvent like acetone, chloroform etc.
- The drug is dissolved or dispersed into the preformed polymer solution.
- Then the mixture is emulsified with aqueous phase to prepare o/w emulsion by using a surfactant.
- After formation of a stable emulsion, the organic solvent is evaporated either by increasing temperature/under reduced pressure or by continuous stirring.
- The w/o/w method is also applied to prepare water soluble drug loaded NPs.
- Both the above method uses a high speed homogenization or Sonication.

Spontaneous emulsification/Solvent diffusion method:

- It is a modified version of solvent evaporation method.

- Here water soluble solvent like acetone along with water insoluble solvent like chloroform are used as an oil phase.
- Due to spontaneous diffusion of water soluble solvent, an interfacial turbulence is created between two phases that leads to formation of smaller particles.
- As the concentration of water soluble solvent increases, a considerable decrease in particle size can be achieved [16].

Salting out: Drug and polymer are first dissolved in solvent and then they are subjected to homogenization with aqueous solvent having salting out agent and at last salts are removed by cross-flow filtration.

Monomer polymerization: Here we will see NPs formation using poly (alkyl cyano acrylate).

- The cyanoacrylic polymer is added to an aqueous acidic solution of surface active agent (polymerization medium) under vigorous mechanical stirring.
- Drug is dissolved in the polymerization media either before the addition of monomer or at the end of polymerization reaction.
- The NP suspension is then purified by ultracentrifugation or by resuspending the particles in an isotonic surfactant free medium.
- Particle size and molecular mass of NP depend upon the type & conc. of surfactant, pH of the medium, conc. of monomer and stirring speed.

Nanoparticles prepared by hydrophilic polymers:

i) Denaturation: It involves emulsification of an aqueous solution containing a natural polymer and the drug to be entrapped in an oil emulsion.

- The particles are hardened by heat Denaturation, cooling below the gelation point or by cross-linking with suitable agent.

ii) Desolvation: Commonly known as coacervation (similar to microspheres)

iii) Ionic gelation: Ion induced gelation results into formation of NPs.

Supercritical fluid technology:

i) Rapid expansion of super critical solution (RESS)

- The solute of interest is first dissolved in SCF.
- Then the solution is expanded through a nozzle.
- Thus the solvent power of SCF decreases and so the solute precipitates.
- This technique is clean because the precipitated solute is completely solvent free.
- Unfortunately, most polymers exhibit little or no solubility in SCF, thus making the technique less of practical interest.

ii) Supercritical anti-solvent (SAS)

- Both the solution of solute in a suitable solvent and SCF are charged in the precipitation vessel.
- Because of high pressure, enough antisolvent will enter into the liquid phase, so the solvent power will be reduced and solute precipitates.

iii) Gas anti-solvent technique (GAS)

- It is a modified version of SAS method.
- The solution of solute is rapidly introduced into the SCF through a narrow nozzle.
- The SCF completely extracts the solvent, causing precipitation of solute. [17]

Particle Size Reduction Techniques

Nanoparticles Produced by Media Milling Processes: The use of media mills for the production of ultrafine particles is very common [18]

Nanosuspensions: The need for nanosuspensions as a dosage form was recognized as a means to administer therapeutic quantities of water-insoluble dosage forms. It is prepared by precipitation, High pressure homonization or both combined techniques.

Magnetic Nanoparticles: The penetration of magnetic fields through human tissue and the ability to remotely detect or manipulate magnetic materials have been investigated for use in medicine for centuries.

Surface coatings and functionalization for biological Applications [19]:

3. Surface Modification of Nanoparticles:

Following two methods are useful for surface modification:

- i) Surface coating with hydrophilic polymers/surfactants: PEG, PEO, Poloxamer, Poloxamine, Polysorbate, Lauryl ethers (Brij-35)
- ii) Development of biodegradable co-polymers with hydrophilic segments (PLA-PEG, PLGA-PEG)

These modification lead to change in zeta potential and hydrophobicity of NPs that ultimately affects following properties:

- Stability
- Mucoadhesive properties
- Oral absorption
- Protein adsorption at surface

4. Drug loading in Nanoparticles: Following methods are used for drug loading into NPs:

- i) Entrapment method
 - It involves the incorporation of the drug at the time of NP production.
 - It depends on the concentration of monomers.
 - Large amount of drug can be entrapped by this method as compared to adsorption method.
- ii) Adsorption method
 - Here, the drug is loaded by incubating the pre-formed NPs in the drug solution.
 - The capacity of adsorption depends on the hydrophobicity of the polymer and the specific surface area of NPs.
- iii) Chemical conjugation
 - New method for drug loading of water soluble drugs.
 - In one article, they have utilized this method to prepare conjugated doxorubicin-PLGA NPs. These NPs showed higher loading capacity as compared to unconjugated doxorubicin-PLGA NPs.

Characterization & Evaluation of Nanoparticles [20, 21]:

Physicochemical Characterization:

Table 3: Physicochemical characterization of Nanoparticles [22]:

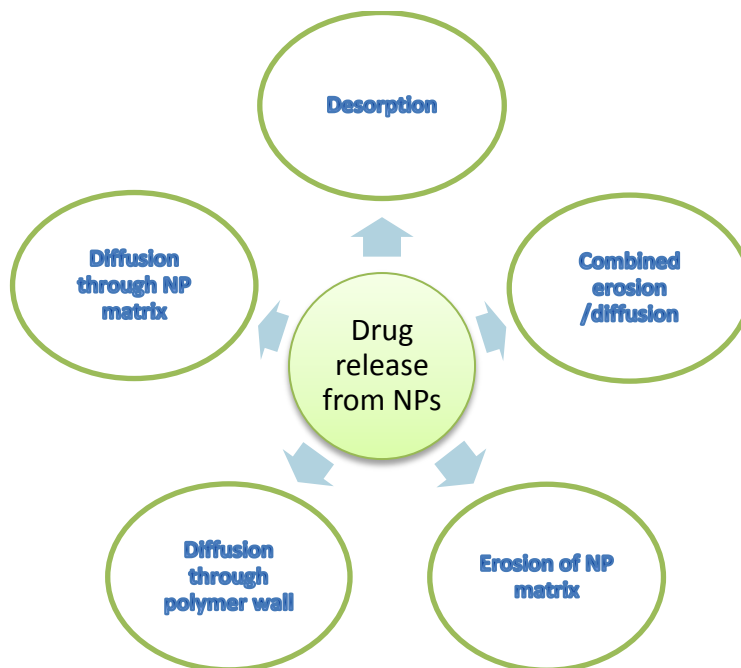
Parameter	Methods
Particle size	Photon correlation spectroscopy, Transmission electron microscopy, Scanning electron microscopy, Scanned-probe microscopy, Fraunhofer diffraction LASER diffractometry, Coulter counter
Molecular Weight	Gel permeation chromatography
Density	Helium compression pycnometry
Crystallinity	X-ray diffraction, DSC, DTA
Surface charge	Electrophoresis Laser Doppler anemometry Amplitude-weighted phase structure determination
Hydrophobicity	Hydrophobic interaction chromatography Contact angle measurement
Surface properties	Static secondary-ion mass spectrometry
Surface element analysis	X-ray photoelectron spectroscopy for chemical analysis

Drug Release from Nanoparticles [23]: Methods to study in vitro release are as follow:

1. Side- by- side diffusion cells with artificial or biological membrane

2. Dialysis bag diffusion technique
 3. Reverse dialysis sac technique
 4. Ultracentrifugation
 5. Ultrafiltration
 6. Centrifugal ultrafiltration
- ✓ Mechanisms of drug release from NPs are as follow:

Table 4: Mechanism of drug release from Nanoparticles [24]:



Application: Nanotechnology in Chemotherapy, Nanotechnology in Cancer, Nanotechnology in Diabetes, Nanotechnology in CVS Disorders, Nanotechnology in CNS Disorders, Nanotechnology in Tissue Repair & Regeneration, Nanotechnology in Surgery, Nanotechnology in Organ Transplantation, Nanotechnology to Deliver Nutrition

Supplements, Nanotechnology in Cosmetics [25], Nanoparticulate Drug-Delivery Systems for Proteins and Peptides [26], Ocular Applications of Nanoparticulate Drug-Delivery System [27], Nanoparticulate Drug-Delivery Systems for Pulmonary Treatment [28], Nanoparticulate Drug-Delivery Systems for Central Nervous System [29]

Nanoparticle Company Directory [30]

COMPANY	PRODUCTS
CytImmune [31]	Gold Nanoparticles for targeted delivery of drugs to tumors
Invitrogen [32]	Qdots for medical imaging
Evident [33]	Quantum Dots
American Elements[34]	Nanoparticles and Quantum Dots
Applied Nanotech [35]	Nanoparticles, carbon nanotube composites and Nanoparticle based sensors.
Antaria [36]	Zinc oxide Nanoparticles used in coatings to reduce UV exposure
Nanoledge [30]	Epoxy resins strengthened with Nanoparticles
Ap Nano materials[37]	Lubricants enhanced with Nanoparticles
BASF [38]	Fabric Enhanced with Nanoparticles
Nanocs	Gold & silver Nanoparticles

Conclusion: Now a day's Nanoparticles are used very much because of more bioavailability of drug as compare to conventional formulations almost 3 to 4 folds increment of bioavailability as compare to original so Nanoparticles are used very much in pharmaceutical sciences & various faculties of sciences as well

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