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NANO-SIZED DRUG DELIVERY SYSTEMS FOR HERBAL THERAPEUTICS

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ABSTRACT

Herbal active constituents are used by the human race since times immemorial for different ailments. But, these phytochemicals suffer limitations, such as stability issues, poor lipid or aqueous solubility and absorption problems. To overcome these problems, novel drug delivery systems are being developed for phytochemicals. Nanotechnology is a multidisciplinary field, used to formulate nano-sized drug delivery systems. Many herbal drugs have been incorporated into these systems for improvement of stability, bioavailability, patient compliance and reduction of toxicity and to minimize frequent dosing. The present review highlights the different forms of nanoparticulate systems and their applications in therapy.

KEYWORDS: Novel drug delivery systems, Nanotechnology, Phytochemicals.

INTRODUCTION

Herbal remedies and natural products are being used for an ancient time to cure the diseases. Natural products (NPs) that are isolated from the plants are known as 'herbal remedies' herbal remedies and NPs have been the roots of these medicines and will be the main source of the medicines and therapeutics in the future.[1] The activity of herbal medicines depends on overall functions of a variety of active constituents, each active constituent plays important role and they are all related to each other.[2] Certain limitations of herbal medicines and phytochemicals such as instability in highly acidic pH, pre systemic metabolism in liver,

solubility and absorption problems, can lead to drug levels below therapeutic concentration in the plasma, resulting in less or no therapeutic effects. Also, most of the plant actives such as glycosides, tannins, flavonoids, etc. are polar molecules and are poorly absorbed due to large molecular size – which limits the absorption via passive diffusion, and poor lipid solubility which severely limits their ability to cross the lipid-rich biological membranes. These limitations lead to reduced bioavailability and hence, low therapeutic index of plant actives. Incorporation of novel drug delivery technology to plant actives minimizes the presystemic metabolism, degradation of drug in the gastrointestinal tract, distribution/ accumulation of drug in the non targeted tissues and organs, and hence, reduces the side effects and improves the therapeutic efficacy and ultimately, the patient compliance.[3]

NOVEL DRUG DELIVERY SYSTEM FOR HERBAL DRUGS

Phytochemicals need a scientific approach to deliver the components in a sustained manner to increase patient compliance and avoid repeated administration; this can be achieved by designing novel drug delivery systems (NDDS's) for herbal constituents. NDDS's helps to increase the therapeutic value by reducing toxicity and increasing the bioavailability, and so on.[2]

Various NDDS that have been used with herbal drugs and phytochemicals may be broadly classified into the following groups[3]

1. Vesicular delivery systems :- liposomes, ethosomes, phytosomes, transferosomes
2. Particulate delivery systems :- microspheres, nanoparticles, micropellets
3. Biphasic systems : - micro / nano emulsions.

NANOTECHNOLOGY AS A NOVEL DRUG DELIVERY SYSTEM:

Nanotechnology is a field of applied science and technology which aims to develop devices and dosage forms in the range of 1-100nm. The applications of nanotechnology for treatment, diagnosis, monitoring and control of biological systems which have recently been referred as nanomedicine.[2] Nanomedicine is a large area of application, where devices such as nanoparticles, nanomachines, nanofibers and optical and mechanical nanosensors, could bring fundamental benefits.[4]

Definition

Nanotechnology is a multidisciplinary field that uses principles from chemistry, biology, physics, and engineering to design and fabricate nanoscale devices. The term

'nanotechnology' was derived by Greek word "nanos" that means "dwarf". Nano device and nano strategy are one billionth of a meter or 10^{-9}m. To formulate a novel nanoparticle drug delivery system, the following physiochemical parameters are essential i.e. temperature, pH, monomer concentration, ionic strength as well as surface charge, particle size and molecular weight.[1] The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.[5]

Table 1: Advantages and disadvantages of nanoparticulate drug delivery systems

Sr. No.	Advantages	Disadvantages
1.	Very long-term stability.	Nanoparticles have low encapsulation efficiency.
2.	Good control over release kinetics of encapsulated compound.	It may involve use of harsh toxic solvents in the preparation process.
3.	Nanoparticles can enhance the bioavailability of entrapped bioactive.	Small particles size and large surface area readily result in limited drug loading and burst release.
4.	Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.	Their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.
5.	Both hydrophobic and hydrophilic drug can be incorporated.	They may cause immune response and allergic reactions in body.
6.	Nanoparticles have longer clearance time.	Loss of drug during storage.
7.	Different routes of administration can be possible.	Water- soluble drugs can be rapidly leaked out in the presence of blood components.
8.	Large scale production is possible.	If any damage occurs at the molecular level then it is not possible to revert it.
9.	Lyophilization is also possible.	High water content of the dispersions (70-99.9%).
10.	Dose accuracy and thus decreased toxicity.	The high manufacturing costs of nanoparticle leads in overall product cost.
11.	Suitable for combination therapy with two or more drugs.	

TYPES OF NANOPARTICLES

Table 2: Classification of nanoparticulate drug delivery systems

Sr. No.	Nanotechnology system	Type of nanoparticle	Particle size distribution (nm)	Reference
1.	Polymeric systems	1.1.Dendrimers	1-10	6
		1.2.Polymeric nanoparticle	10-1000	7
		1.3.Polymeric micelles	10-100	8
		1.4.Nanocapsules/Nanospheres	100-300	9
		1.5. Nanogels	200-800	8
		1.6.Polymer-drug nano-conjugates	1-15	9
		1.7. Chitosan nanoparticles	100-800	10, 11
		1.8.Nanofibers/Nanowires	10-100	12
2.	Lipid systems	2.1. Solid lipid nanoparticles	50-400	13
		2.2. Nanostructured lipid carriers	200-800	14
		2.3. Liposomes	10-1000	15
		2.4. Polymerosomes	100-300	16
3.	Metal nanostructures or inorganic nanoparticles	3.1. Carbon nanotubes	1-50	17
		3.2. Gold nanoparticles	100-200	16, 18
		3.3. Magnetic nanoparticles	100-600	19
		3.4. Quantum dots	2-10	12, 20
		3.5. Iron oxide nanoparticles	1-250	21
		3.6. Silver nanoparticles	1-100	22
4.	Surfactant based nanosystem	4.1.Niosomes	10-150	8
		4.2.Nanoemulsion/microemulsions	Droplet size 50-100	23
		4.3.Nanocrystals	10-100	24

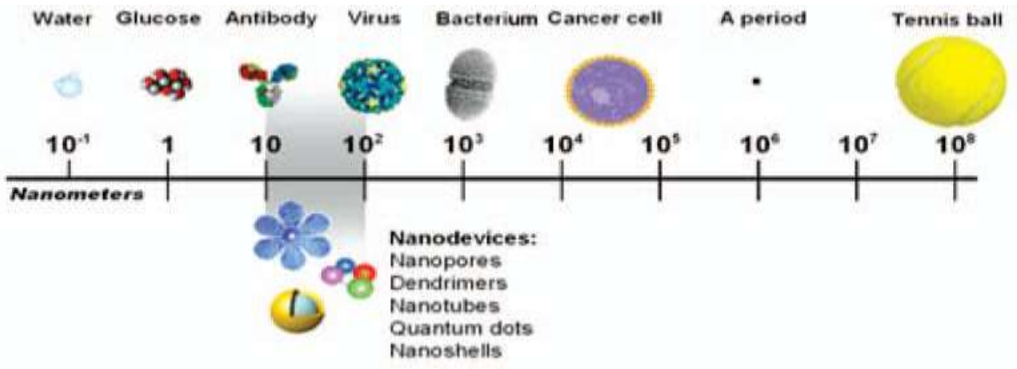

Fig. 1: The scale of nanotechnology. Nanotechnology devices are characterized by dimensions in the sub-cellular (or macromolecular) range.[4]

There are numerous engineered constructs, assemblies, architectures and particulate systems, whose unifying feature is the nanometer scale size range (from a few to 250 nm).

1. Polymeric systems

1.1. Dendrimers

The word dendrimer comes from a Greek word which means to "tree" (dendrimer). Dendrimers are nanometer-sized, highly branched, monodisperse, supramolecular complexes with symmetrical architecture.[25] They are composed of three functional units: the inner core, the internal shell containing the repetitive units, and the terminal functional groups.[26]

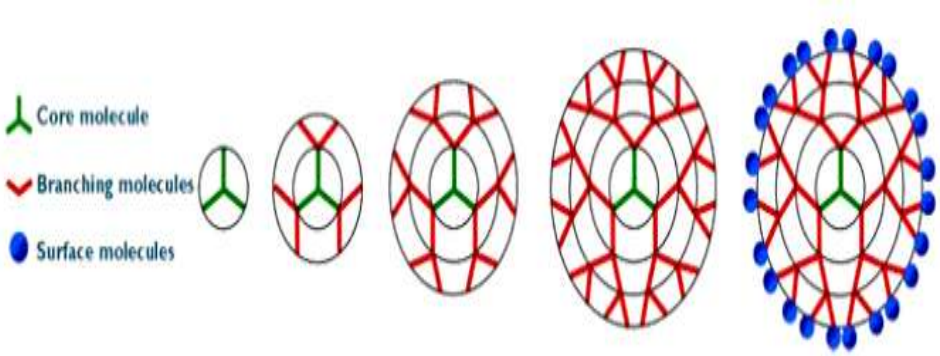

Fig. 2: Growth of dendrimer nanoparticle[27]

It is a highly branched synthetic polymer and consists of a monomer unit attached core, leading to a monodisperse, treelike, star-shaped or generational structure with precise molecular weights, diameters in the 2 to 10 nm range size, its unique architectural design, high degree of branching, multivalency, globular structure and representative of a new segment of polymer science, often been referred to as the "Polymers of the 21st century". Poor solubility, bioavailability, permeability, biocompatibility and toxicity can be overcome by dendrimers.[6] Different types of dendrimers includes - Radially layered poly (amidoamineorganosilicon) Dendrimers (PAMAMOS), Poly (amidoamine) dendrimers (PAMAM), Poly (Propylene Imine) dendrimers (PPI), Chiral dendrimers, Liquid crystalline dendrimers, Tecto dendrimer, Hybrid dendrimers, Multilingual Dendrimers, Micellar Dendrimer.[6]

1.2. Polymeric nanoparticles:

Polymeric nanoparticles are polymeric colloidal spheres that are very small in size ranging from 10-1000nm and have ability to entrap the drug within the matrix or adsorb or conjugate at their surface. The release of the drug from the nanoparticles occurs through the diffusion and erosion from the matrix.[7] Polymers that are being used in the pattern are categorized in biodegradable (eg. Poly lactic acid, poly glycolic acid, polycaprolactone, etc.) and non-

biodegradable polymers (eg. Ethyl cellulose, poly urethane, polyethylene, etc.). Biodegradable polymers have persuaded the attention of the scientists because they degrade in the body and do not have any further toxicity. Nanosizing led to increased solubility of components, reduction in the dose via improved absorption of active ingredient. Because of polymeric nature, nanoparticles they can be used for controlled release as well as for targeting the drug to particular tissue or organ. The surface of the polymeric nanoparticles can be covalently conjugated to folic acid, monoclonal antibodies, and aptamers to achieve targeted delivery and cell-specific uptake.[9]

1.3. Polymeric Micelles

Micelles exhibit easily controllable and good pharmacological properties so they can be used to carry a 62-63 number of drugs. Micelles are colloidal particles with a size usually within a range of 5–100 nm. Micelles consist of amphiphiles or surface-active agents (surfactants), which exist of two distinct regions: mostly a hydrophilic head-group and a hydrophobic tail.[29] Micelles consists of an inner hydrophobic core capable of solubilizing lipophilic substances and an outer hydrophilic corona which serves as the stabilizing interface between the internal hydrophobic core and external aqueous environment.[30] Polymeric micelles have been reported for the delivery of the poorly soluble, hydrophobic herbal drugs.[23]

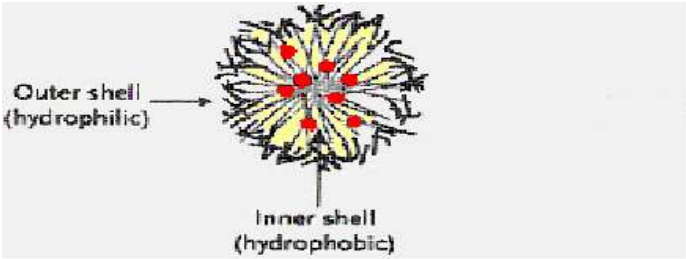

Fig. 3: Cross Section of polymeric micelles. [29]

1.4. Nanospheres / Nanocapsules

Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. These are solid-state nanoparticles, ranging from 10 to 200 nm in size, and can be either crystalline or amorphous. The drug is dissolved or encapsulated or attached to the nanoparticles and, depending on the methods used for preparation; one can get nanospheres, nanocapsules, or aquasomes.

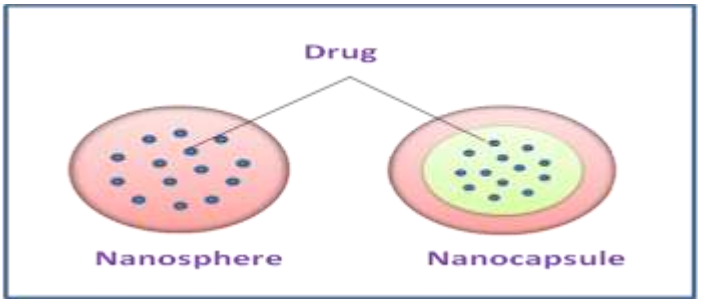

Fig. 4: Difference between nanosphere and nanocapsule

Table 3: Key Difference between Nanosphere, Nanocapsule and Aquasomes

Nanosphere	Nanocapsule	Aquasomes
Spherical particles composed of natural polymers such as gum, chitosan, gelatin, albumin, or collagen and the drug or gene is uniformly dispersed in it.	Vesicular materials in which the drug or gene is encased in a cavity surrounded by a polymeric material.	Spherical particles composed of calcium phosphate or ceramic diamond covered with a polyhydroxyl oligomeric film.

1.5. Nanogels

Nanogel refers to a nanoparticle composed of a crosslinked hydrophilic polymer network (hydrogel). Nanogels are most often composed of synthetic polymers or biopolymers which are chemically or physically crosslinked. Nanogels are usually in the 10-100nm in diameter. Like hydrogels, the pores in nanogels can be filled with small molecules or macromolecules and their properties, such as swelling, degradation, and chemical functionality, can be controlled. Nanogels represent miniature hydrogel particles that were formulated by using an emulsification/solvent evaporation technique by chemically crosslinking polyethyleneimine with double-end–activated poly (ethylene oxide). [9]

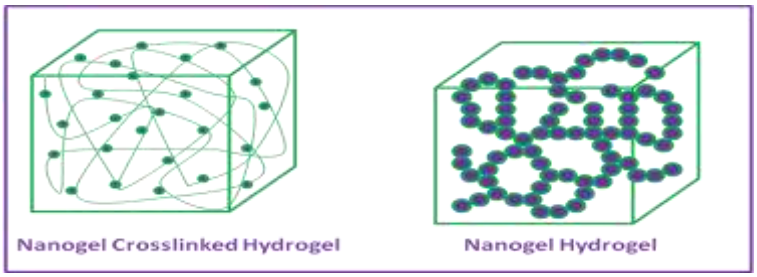

Fig. 5: Nanogel

1.6. Polymer–Drug Nanoconjugates

Polymer–drug conjugates are formed through side-chain grafting of drugs to polymer chains, allowing them to deliver high doses of chemotherapeutic drugs. The size of polymer–drug

conjugates is generally below 20 nm.[32] The polymer–drug conjugates are composed of a water-soluble polymer that is chemically conjugated to a drug via a biodegradable spacer. The spacer is usually stable in the bloodstream but cleaved at the target site by hydrolysis or enzymatic degradation. Such drug conjugates can be selectively accumulated at the tumor site by the EPR effects, followed by release of the drug by cleavage of the spacer. For example, N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-based drug conjugates such as HPMA copolymer –doxorubicin conjugate (PK1) and HPMA copolymer–doxorubicin conjugate containing galactosamine as a targeting moiety (PK2), developed for the treatment of primary or secondary liver cancer.[33]

1.7. Chitosan Nanoparticles

Chitosan is a modified natural carbohydrate polymer prepared by the partial N-deacetylation of chitin, a natural biopolymer derived from crustacean shells such as crabs, shrimps and lobsters. Chitosan is also found in some microorganisms, yeast and fungi. The primary unit in the chitin polymer is 2-deoxy-2-acetylamino glucose. These units combined by glycosidic linkages, forming a long chain linear polymer. Chitosan is available in a wide range of molecular weight and degree of deacetylation. Molecular weight and degree of deacetylation are the main factors affecting the particle size, particles formation and aggregation.[34] Chitosan and its derivatives can be covalently cross-linked to prepare nano-sized particles as the drug carriers.[35] For the preparation of chitosan particles, several techniques are available such as emulsion, ionotropic gelation, reverse micellar, solvent evaporation, spray drying, coacervation, and sieving methods.

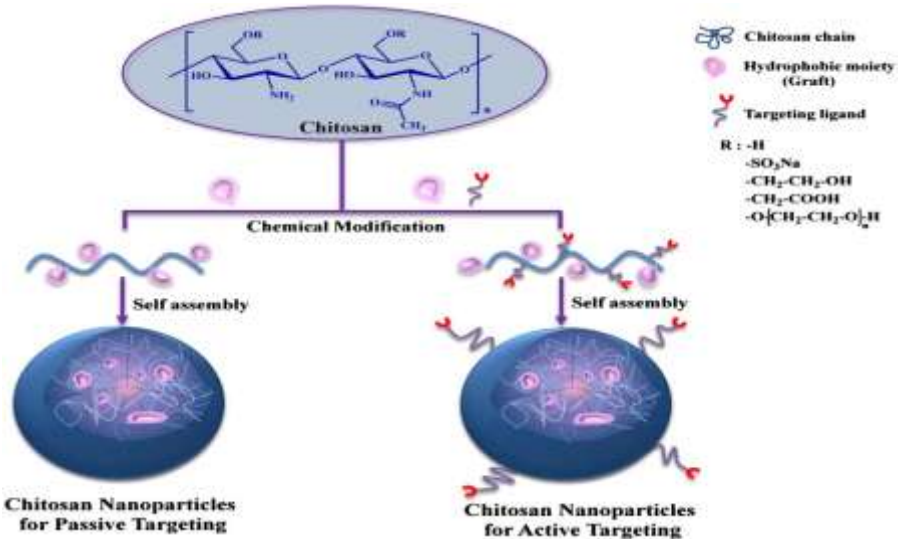

Fig. 6: Self-assembled chitosan nanoparticles[33]

A variety of hydrophilic and hydrophobic drugs can be loaded into the chitosan nanoparticles during the preparation of the nanoparticles, in which the loading efficiency of the drug may depend on its physicochemical characteristics and the preparation method.

1.8. Nanofibers/Nanowires

A nanowire is a nanoparticle whose diameter is much smaller than its length. Nanowires typically have diameters of 10-100nm or less and lengths of 100 nm - 10µm. As a fibrous scaffold, nanofibers are able to entrap drugs with a high loading capacity and high encapsulation efficiency because of their low weight and inherent high surface-to-volume ratio.[12] Electro-spinning is a very simple and versatile method for creating polymer-based high functional and high performance nanofibers. Functional nanofibers or the nanofibers with multi-compositions can be prepared by electrospinning of polymers blended with additional compounds like nanoparticles, carbon nanotubes, catalysis, and enzymes, ceramics and so on.[36]

2. Lipid systems

2.1. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN) introduced in 1991, are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their ability to improve performance of pharmaceuticals, nutraceuticals and other materials.[37] In general, they are more stable than liposomes in biological systems due to their relatively rigid core consisting of hydrophobic lipids that are solid at room and body temperatures, surrounded by a monolayer of phospholipids.

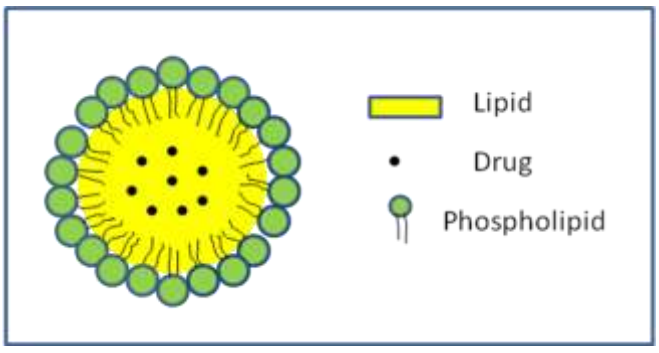

Fig. 7: Structure of solid lipid nanoparticle (SLN)[37]

SLN possess a solid lipid core matrix that can solubilize lipophilic molecules. The lipid core is stabilized by surfactants (emulsifiers). To achieve and maintain a solid lipid particle upon administration, the lipid nanoparticles melting point must exceed body temperature (37 °C). High melting point lipids investigated include triacylglycerols (triglycerides), acylglycerols, fatty acids, steroids, waxes, and combinations thereof. Surfactants that are investigated include bile salts such as sodium taurocholate, biological membrane lipids such as lecithin, biocompatible nonionics such as ethylene oxide/propylene oxide copolymers, sorbitan esters, fatty acid ethoxylates, and mixtures thereof. Because of their ease of biodegradation, they are less toxic than polymer or ceramic nanoparticles.[38] SLN have been developed and investigated for parenteral, pulmonal and dermal application routes.[24]

2.2. Nanostructured Lipid Carriers (NLC):

NLC's are made of combination of solid and liquid lipids. NLC were introduced to overcome the potential difficulties with SLNs such as Payload for a number of drugs too low, drug expulsion during storage of formulations, high water content of formulated SLN dispersions. The goal to develop NLC was to increase the drug loading and to prevent drug expulsion.[38] The inclusion of liquid lipids in NLCs provides flexibility in modulating drug encapsulation and drug release. High encapsulation has been achieved for lipophilic drugs (90–98%), whereas the encapsulation efficiency for hydrophilic molecules is relatively low (20–30%). The location of the drug in the core or inside the shell of lipid nanoparticles depends on the nature of the lipid, drug properties, the solubility of the drug in the lipid, and the preparation method.[40] NLC's may find extensive application in topical drug delivery, brain targeting, oral and parenteral administration of cosmetic and pharmaceutical actives.

Table 4: Key Difference between SLN and LNC's:

Sr. No	Parameters	SLN	NLC's
1.	Composition	Solid lipid.	Mixture of solid and liquid lipid.
2.	Core	Solid lipid core	Liquid lipid core
3.	Lipids used	Several highly purified lipids, such as tristearin used.	Mixtures of mono-, di-, and triacylglycerols including monoacids and poly(acid acyl) glycerols are used.
4.	Size range	100-400nm	200-800nm
5.	Methods of preparation	Hot or cold high-pressure homogenization, solvent emulsification–evaporation, emulsification–diffusion technique, and phase inversion.	Hot or cold high-pressure homogenization.

2.3. Liposomes

Liposomes are biodegradable, colloidal, spherical, and bilayered vesicles of 0.05-5.0µm diameter, composed of a lipid bilayer membrane entrapping an aqueous core[41]. The lipid bilayer membrane is normally composed of natural and synthetic phospholipids. Liposomes, first prepared by Bangham *et. Al.*[42] Hydrophilic molecules can be encapsulated in the inner aqueous phase while hydrophobic molecules can be carried in the hydrophobic domains of the lipid bilayer.[32]

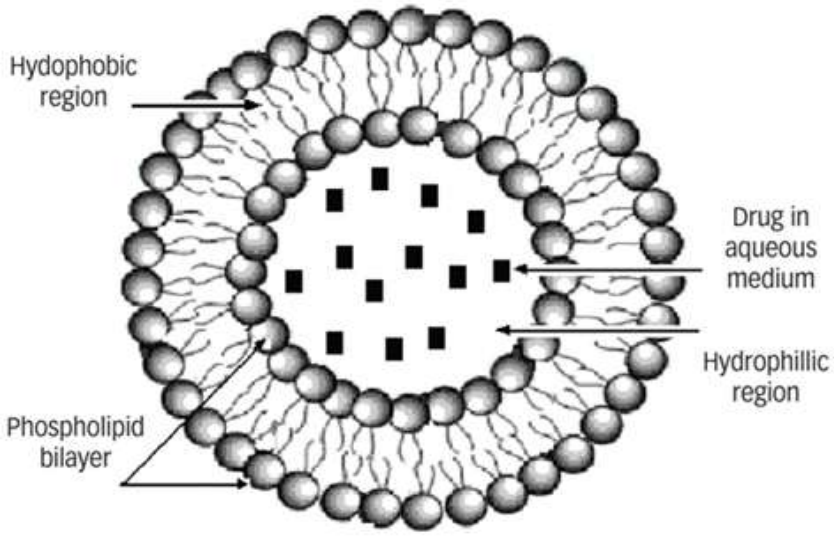

Fig. 8: Structure of liposome.

The fate of liposomes *in vivo* after intravenous administration is dependent on several factors namely, lipid composition, surface charge, steric effect, fluidity of the lipid bilayer, and mean size of liposome.[9]

2.4. Polymerosomes

Polymerosomes have a structure similar to liposomes, but are composed of synthetic polymer/polypeptide amphiphiles and self-assemble to form polymer shell vesicles (~100 nm) when hydrated and extruded. The hydrophilicity/hydrophobicity ratio is used to control the morphology of the nanoparticle, which can range from spherical to cylindrical. The membrane core thickness can be controlled by the molecular weight of the diblock copolymer. Polymerosomes show higher stability and lateral fluidity than liposomes and the drug release is triggered by the degradation of the polymer chain and destabilization of the shell layer.[32]

3. Metal Nanostructures / Inorganic Nanoparticles

3.1. Carbon Nanotubes

Carbon nanotubes were discovered in 1991 by 'Sumio Iijima' of NEC and are effectively long, thin cylinders of graphite. Graphite is made up of layers of carbon atoms arranged in a hexagonal lattice. CNT's are hollow, ellipsoid cylinders or tube of carbon atoms bonded to each other via sp2 bonds which are stronger than sp and sp3 as well as excellent mechanical strength and high electrical and thermal conductivity. Depending upon the structure, CNT's are classified in Table 5.

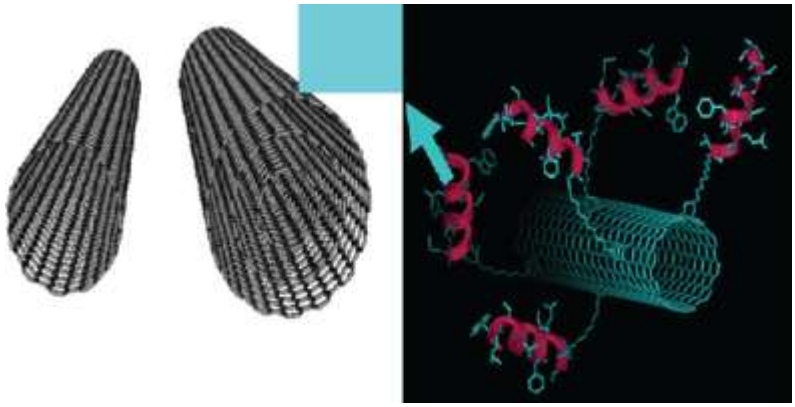

Fig. 9: Structure of single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs), as well as drug loaded carbon nanotubes.[12]

Table 5: Types of carbon nanotubes and their description

Sr. no.	Type	Description
	Single walled nanotube	SWNT prepared by wrapping a one atom thick layer of graphite called grapheme into a seamless cylinder.
	Multi walled nanotube	MWNT consists of multiple layers of graphite rolled in on them to form a tube shape.
	Double walled nanotube	DWNT are a synthetic blend of both SWNT & MWNR, they exhibit the electrical & thermal stability of the latter & the flexhibility of the former.
	Nanotorus	It is a theoretically described carbon nanotube having large magnetic moments and thermal stability.
	Nanobud	It is a hybrid of carbon nanotube and fullerene. In this fullerene like buds are covalently bonded to the outer sidewalls of carbon nanotube and has useful properties of both fullerenes and carbon nanotubes.
	Fullerene	Fullerenes are spherical cages containing 28 to more than 100 carbon atoms[25]. The discovery of a spherical crystal form of carbon, bound by single and double bonds that form a three-dimensional spheroidal crystal, named fullerenes[44].
	Functionalized CNT	Contain additional groups on their surface like -COOH, -OH, etc.

3.2. Gold Nanoparticles

Colloidal gold, also known as gold nanoparticles, is a suspension (or colloid) of nanometer-sized particles of gold.[45] A common synthesis involves the reduction of a gold salt in the presence of capping agent molecules such as thiols, citrates or phosphines.[46]

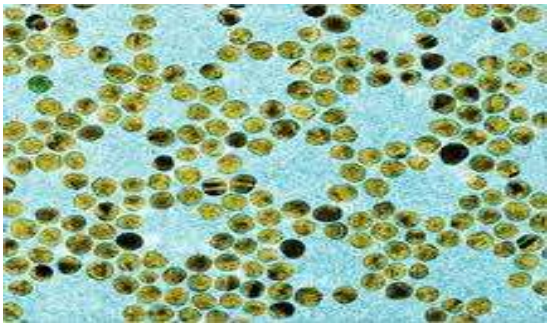

Fig. 10: Schematic representation of gold nanoparticles[48]

Gold nanoparticles exhibit unique physicochemical properties including surface plasmon resonance (SPR) and the ability to bind amine and thiol groups, allowing surface modification and use in biomedical applications[47]

3.3. Magnetic Nanoparticles

Magnetic nanoparticles play very important role in magnetic fluids; the first ferrofluids were primary used as a means to study magnetic domain structure in solids. The most commonly used ferrofluid contains spherical magnetic particles with typical size of 10 nm, dispersed in an apolar solvent. The behavior of such ferrofluids is mainly determined by their magnetic properties. An important property of concentrated ferrofluids is that they are strongly attracted by permanent magnets, while their liquid character is preserved.

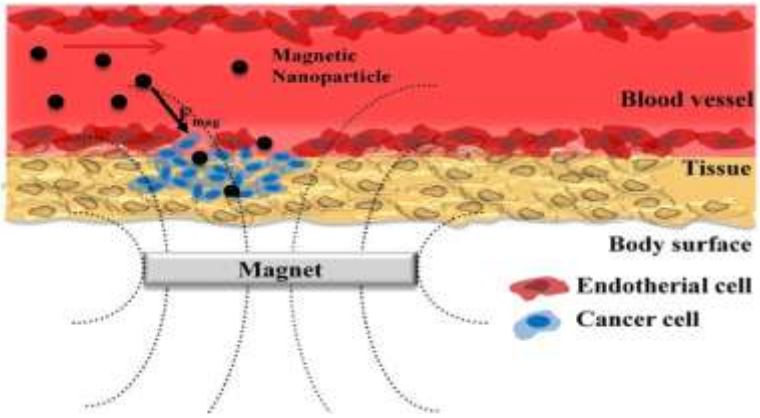

Fig. 11: Schematic representation of magnetic nanoparticle-based drug delivery system[49]

Magnetic nanoparticles offer some attractive possibilities in biomedicine as they have controllable sizes ranging from a few nanometers up to tens of nanometers[50]

3.4. Quantum Dots

Quantum dots are inorganic fluorescent semiconductor nanoparticles composed of 10–50 atoms with a diameter ranging from 2 to 10 nm. Their sizes and shapes which determine their absorption and emission properties can be controlled precisely. They are widely studied for optical image application in living systems and are stable for months without degradation and alteration.[20, 12] Quantum dots are closely related to atoms than a bulk material because of their discrete, quantized energy level. They have been nicknamed Artificial Atoms.

3.5. Iron Oxide Nanoparticles

Iron (III) oxide (Fe_2O_3) is a reddish brown, inorganic compound which is paramagnetic in nature and also one of the three main oxides of iron, while other two being FeO and Fe_3O_4. The Fe_3O_4, which also occurs naturally as the mineral magnetite, is also super-paramagnetic in nature. Due to their ultrafine size, magnetic properties, and biocompatibility, super-paramagnetic iron oxide nanoparticles (SPION) have emerged as promising candidates for various biomedical applications, such as enhanced resolution contrast agents for MRI, targeted drug delivery and imaging, hyperthermia, gene therapy, stem cell tracking, molecular/cellular tracking, magnetic separation technologies (e.g., rapid DNA sequencing) early detection of inflammatory, cancer, diabetes, and atherosclerosis.[21]

3.6. Silver Nanoparticles

Silver nanoparticles are the particles of silver, with particle size between 1-100 nm in size. While frequently described as being “silver” some are composed of a large percentage of silver oxide due to their large ratio of surface to bulk silver atoms. Typically, they are synthesized by the reduction of a silver salt with a reducing agent like sodium borohydride in the presence of a colloidal stabilizer. The most common colloidal stabilizers used are polyvinyl alcohol, poly (vinylpyrrolidone), bovine serum albumin (BSA), citrate, and cellulose. Newer novel methods include the use of β-d-glucose as a reducing sugar and a starch as the stabilizer to develop silver nanoparticles ion implantation used to create silver nanoparticles.[22]

- **Dissolution and release of toxic ions from inorganic nanoparticle[54]**

The interfacial properties of inorganic nanoparticles in solution, including the rates of reactions mediated on the surface, adsorption capacity and change of redox state, are likely to affect the fate of nanoparticles in the environment and possibly toxicity in organisms. Hence, a size-dependent change in crystallinity related to the decrease in the excess of surface free energy for nanoparticles smaller than 20 nm can enhance the interfacial reactivity and modify their reactivity in the biological environment. Electric and magnetic properties are known to be related to the size and the crystallinity. The driving force for dissolution depends on the crystal solubility within a given environment, the concentration gradient between the particle and the solution, the specific surface area (SSA) and the aggregation state. Chemically unstable nanoparticles can be oxidized, reduced and dissolved in biological media, leading to the release of toxic ions. Nanoparticles that show a higher solubility in cellular growth media (such as ZnO nanoparticles) show a stronger toxicity to mammalian cells than do nanoparticles with a low solubility (such as TiO_2). Solubility is highly dependent on solvent properties (for example pH, ionic strength and the presence of adsorbing species) and on the particles properties (for example SSA, surface morphology, surface energy and reactivity, and aggregation states). It has been found that the bactericidal effect of silver nanoparticles between 1 and 100 nm in diameter was highest in the 1–10-nm range, where there are more highly reactive surfaces. These particles penetrate bacteria, strongly interact with sulphur- and phosphorus-containing compounds and release toxic silver ions.

The presence of active sites on nanoparticles that are able to generate reactive oxygen species (ROS) and arise from size-dependent differences in atomic and electronic structure suggests one possible origin of size dependence in toxicity. Figure 12 represents The potential relationship between the size dependence of the crystalline structure of nanoparticles (typically <30 nm), their interfacial properties (for example dissolution, oxidation, adsorption/desorption, electron transfer, redox cycles, Fenton reactions and surface acido-basicity) and potential mechanisms of toxicity (for example, the generation of ROS, the release of toxic ions, the oxidation of proteins and the adsorption of pollutants). $OH^{\cdot}$, hydroxyl radical; $O_2^{\cdot -}$, anion superoxide.

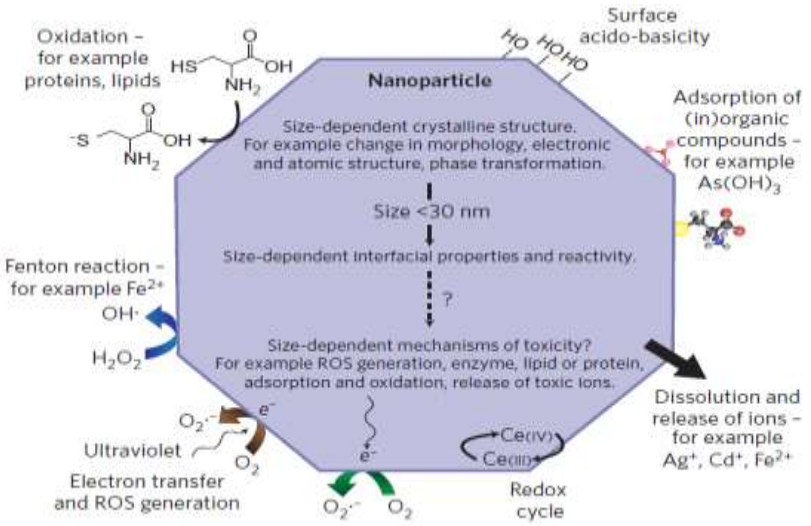

Fig. 12: A number of physicochemical mechanisms can occur at the surface of an inorganic nanoparticle. [54]

4. Surfactant based systems

4.1. Niosomes

Niosomes are self-assembled, submicron vesicles of nonionic surfactants with closed bilayer structures similar to liposomes. However, they are much more stable and less expensive than liposomes. The hydrophobic parts of the surfactant face toward the core, whereas the hydrophilic groups interface with the surrounding aqueous medium. Niosomes can be constructed by using a variety of amphiphiles, which possess a hydrophilic head group and a hydrophobic tail.

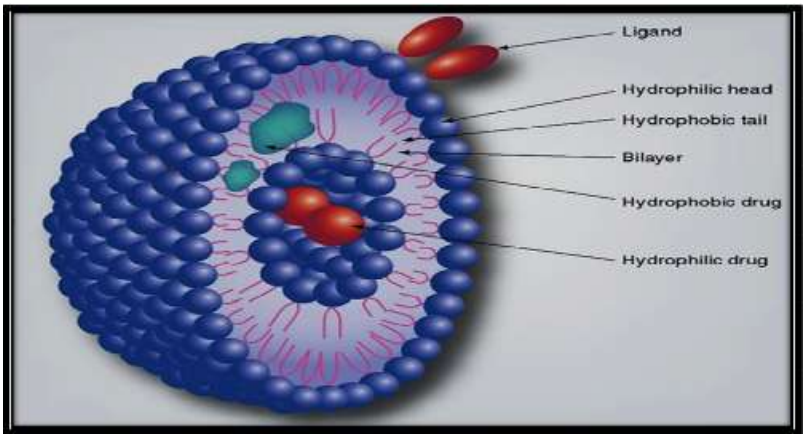

Fig. 13: Structure of Niosome[55]

The majority of the methods involve hydration of a mixture of surfactant/lipid at elevated temperature, followed by size reduction using sonication, extrusion, or high-pressure

homogenization. Finally, the unentrapped drug is removed by dialysis, centrifugation, or gel filtration. The smaller niosomes are relatively more unstable than larger ones and, therefore, require stabilizers to prevent aggregation. The stability of the niosomes can be further improved by the addition of charged molecules such as dicetyl phosphate, which prevents aggregation by charge repulsion.[51] Generally, an increase in surfactant/lipid level increases the drug encapsulation efficiency in niosomes.[52] The rate of drug release from the niosome is dependent on the surfactant type and its phase-transition temperature.

4.2. Nanoemulsion / microemulsions:

Nanoemulsions and Microemulsions are the emulsions of O/W type having the size range of several microns. They are prepared by using the surfactants which are considered safe for the human use and approved by the FDA. These types of emulsions have higher surface area and hence can easily penetrate through the skin. They are also non toxic and non irritant in nature. Nanoemulsions can be prepared by the high pressure homogenization and microfluidisation technique.[23] Nanoemulsion is thermodynamically stable, transparent, stable, and spontaneously formed with a high proportion of surfactants, whereas as macroemulsion is milky and non-stable that requires some energy to form and usually stabilized by a surfactant and a cosurfactant. Generally, the droplet size of these systems is less than 100 nm and they flow easily. The formation of nanoemulsion is dependent on a narrow range of oil, water, surfactant, and cosurfactant concentration ratios. A cosurfactant is commonly used to lower the interfacial tension and fluidize the interfacial surfactant. Nonionic and zwitterionic surfactants are the first line of choice for emulsion-based systems. As these systems have water and oil phases, both hydrophilic and lipophilic drugs can be delivered using nanoemulsions. Drug release from the nanoemulsions depends on whether the drug is in the internal or external phase.[9]

4.3. Nanocrystals

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. Only a minimum quantity of surfactants needs to be added in nanocrystals for steric and electrostatic surface stabilization. Nanocrystal technology can be utilized for many dosage forms. The size of nanocrystals allows for safe and effective passage through capillaries.[24]

APPLICATIONS

❖ Nanoparticle as therapeutic agents

Nanoparticle are selected as therapeutic agents for their properties such as biodegradability, biocompatibility, conjugation, complexation, or encapsulation and their ability to be functionalized.

❖ Diagnostics

i. Magnetic nanoparticles, bound to a suitable antibody, are used to label specific molecules, structures or microorganisms.
ii. Gold nanoparticles, tagged with short segments of DNA can be used for detection of genetic sequence in a sample.
iii. Multicolor optical coding for biological assays has been achieved by embedding different-sized quantum dots, into polymeric microbeads.
iv. Nanopore technology for analysis of nucleic acids converts strings of nucleotides directly into electronic signatures.

❖ Targeted drug delivery

Drug targeting systems should be able to control the fate of a drug entering the body. Nanotechnology offers here another challenge to come to this goal a bit closer, to deliver the drug in the right place at the right time. Targeting is the ability to direct the drug-loaded system to the site of interest.

Two most important aspects of nanoparticle drug delivery must be.

- The specific targeting of the diseased tissue with nanoparticles (appropriate size and functionalization with antibodies or other means of selective binding provides means of enhanced delivery of drugs and reduced nonspecific toxicity);
- The timed release of the drug (to prevent nonspecific toxicity the drug must not diffuse out of the particle while it is still in the circulatory system, and must remain encapsulated until the particle binds to the target).

Targeted encapsulated drug delivery using NPs is more effective for improved bioavailability, minimal side effects, decreased toxicity to other organs, and is less costly.[24]

Table 6: Some examples of herbal nanoparticulate drug delivery systems:

Sr. No.	Plant name, family	Phytochemical	Nanoparticulate system	Application	Reference
1.	*Argemone mexicana* Linn., *Papaveraceae*	isoquinoline alkaloids	Silver nanoparticles	Treatment of cervical cancer cell line SiHa	56
2.	*Plectranthus amboinicus, Lamiaceae. Hemigraphis colorata,* Acanthaceae.	Saponins and tannins	Solid lipid nanoparticles	Anti-inflammatory, Antimicrobial, antioxidant	57
3.	*Embelia ribes* Myrsinaceae	Embelin	Chitosan nanoparticles	Antibacterial	58
4.	*Bacopa monniera* Scrophulariacae	triterpenoids, steroids, saponins	Gold nanoparticles	Antibacterial	59
5.	*Bauhinia tomentosa Linn* Caesalpiniaceae	terpenoids, sterols flavonoids, tannins, carbohydrates, cardiac glycosides, saponins, proteins and amino acids.	Gold nanoparticles	Anticancer	60
6.	*Nigella sativa* Linn Ranunculaceae	fixed oils, proteins, alkaloids, saponins and essential oil.	NIPAAm-VP co-polymeric micelles	Antibacterial	61
7.	*Curcuma longa Zinziberaceae*	Curcumin	Nanosphere	Anticancer	62
8.	Tripterygium wilfordii Hook	Celastrol	Liposomes	Antitumor	63
9.	*Azadirachta indica*	Neem seed oil	Nanoemulsion	Antibacterial	64
10.	*Hibiscus rosa sinensis*	Extract	Microemulsion	Alopecia	65

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