



Nanoparticulate targeted drug delivery systems- a review

Sindhuja Devaraj, Ganesh GNK*

Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Tamil Nadu, India

Article History:

Received on: 26.08.2019

Revised on: 17.11.2019

Accepted on: 27.11.2019

Keywords:

Nanoparticles,
Site-specific drug
delivery,
Bioavailability,
Therapeutic index,
Advantages

ABSTRACT

Nanoparticulate drug delivery system are the rapidly developing system, and nanoparticles are present in the size range of 1-100nm. Nanoparticles composed of various thermal, electrical, and optical property. Nanoparticles offers the potential advantages over the traditional dosage forms it is ascribable to the properties of nanoparticles. Nanoparticulate drug delivery system ensures the site-specific delivery of a drug (Targeting drug delivery) and aids in improving the efficacy of the new as well as old drugs and has the potential in crossing the various physiological barriers and also improves the therapeutic index of the drugs and increases the patient compliance. The objectives of this review is to classify the nanoparticles based on the different groups, surface properties of nanoparticles, describe the strategies of drug targeting, the necessity of nanoparticles their general method of preparation, different methods used in characterization, self- assembly and mechanism of drug release in a systemic manner. The potential advantages and limitations of various nanoparticulate drug delivery systems are also discussed elaborately.



*Corresponding Author

Name: Ganesh GNK

Phone: 919442191918

Email: gnk@jssuni.edu.in

ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v11i2.2246>

Production and Hosted by

IJRPS | www.ijrps.com

© 2020 | All rights reserved.

INTRODUCTION

The Nanoparticles are particulate dispersions with a size range of 1-100nm, and they exist in at least one dimension. It is enveloped by the interfacial layer and composed of ions, organic, and inorganic molecules. The interfacial layer plays an essential role in the properties of nanoparticles (Horikoshi and Serpone, 2013; Velavan *et al.*, 2015). It exhibits various optical, thermal, and electrical property. The term Nanoparticles is a combination of Nanospheres and Nanocapsules, as shown

in Figure 1.

In the 1960s, the polymeric micelles and liposomes were synthesized and are not referred to as nanoparticles, and in the 1970s, the nanoparticles and dendrimers are synthesized without the proper understanding about the nanotechnological application. In 1980s, the fundamental studies of nanoparticles and the development of micelles as drug delivery systems had tremendous growth. Then later in 2000, the USA established the national nanotechnology initiative (NNI), and soon abundant of projects in nanotechnology taken place, and about 20 research centres were funded by National Science Foundation (NSF) (Wanigasekara and Witharana, 2016). Nanoparticles are effectively taken up by cells than micro molecules, and awareness about nanoparticles had lead their way to the targeted drug delivery systems (Mishra *et al.*, 2016). Targeted drug delivery system is a science of specifying the drug to the desired site. The concept of targeting delivery is dated from 1902. Paul Ehrlich was the first to postulate it as a "Magic Bullet." He postulated that the optimal quantity of therapeutic molecules like drugs, vaccines, etc., can be delivered to the

desired therapeutic site in a successful rate using the targeting delivery. The therapeutic response of the drug depends on the interaction between the drug molecules and the cell that are associated with biological events at the receptor site in a concentration-dependent manner. To achieve this, the optimal quantity of the drug at the desired site it has to be delivered with control of the drug input rate. Whenever the drugs are coupled with targeting ligands, they fulfill the attributes of "Magic Bullet" (Fahmy *et al.*, 2005).

Potential advantages and disadvantages of nanoparticles

Singh *et al.* (2011), Nanoparticles have the potential advantages and few Disadvantages as they are in Table 1.

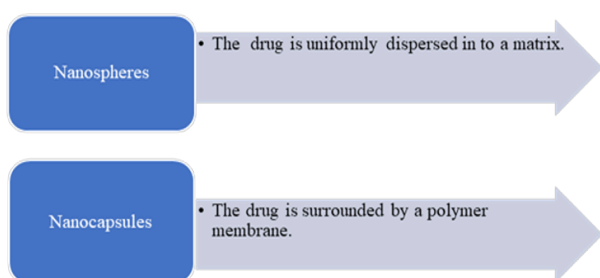


Figure 1: Definition of Nanocapsule and Nanosphere

Classification of nanoparticulate drug delivery system

Nanoparticulate drug delivery system is classified in to various systems like the Lipid system, Polymeric system, a combination of polymeric and lipid system as shown in Figure 2.

Lipid system

The lipid-based Nanoparticulate drug delivery system contains lipid moieties and surfactants. The lipid system possesses a solid core made of lipid and a matrix that contains soluble lipophilic molecules. The lipid system is further classified in to non- Vesicular and Vesicular types.

Non- Vesicular systems

The non-vesicular Nanoparticle system is classified in to two types, which includes, Particulate systems and the emulsifying systems.

Particulate system

The particulate Non-vesicular Nanoparticle system is further divided in to Solid lipid Nanoparticles, Nanostructured lipid carriers, Lipid- drug Nanoconjugates.

Solid lipid nanoparticles(SLN'S)

SLN's are drug carriers which are colloids and are composed of lipids which are solid at room temperature and the surfactants. SLN's size range from 50-1000nm for colloid drug delivery application. They combine the advantages of liposomes, polymeric nanoparticles, and emulsions while minimizing some of their individual disadvantages. They typically contain a hydrophobic solid matrix core with a phospholipid coating. The hydrophobic tail regions of the phospholipid are embedded into the core matrix, and that is why the core exclusively possesses a hydrophobic nature. So it is to be expected that the solid lipid nanoparticles have a higher entrapment efficiency for hydrophobic drugs in the core compared with conventional liposomes (Gohla, 2000).

Advantages

1. Improved bioavailability
2. Biodegradable
3. Controlled and targeted release.
4. Stable than liposomes.

Disadvantages

1. Poor entrapment efficiency.
2. May cause allergic reaction and immune response in the body.
3. Difficult to handle because of small size and large surface area.
4. cost of production is high

Nanostructured lipid carriers(NLC'S)

Nanostructured lipid carriers composed of solid and liquid lipids in their structure. NLC's are developed to Increase the drug loading capacity than SLN'S.NLC'S are prepared by hot homogenization, Cold homogenization, and Microemulsion techniques. The drug release of the NLC'S takes place by diffusion and the degradation of lipids in the body. It has the High drug loading capacity due to highly unordered lipid structures. The NLC's are classified into three types, Type-1, in which the solid lipids and liquid lipids are blended together. Type-2, in which drugs are accommodated into the solid, but increased solubility in the parts of lipid matrix.type-3, the lipids are mixed in the manner preventing from crystallizing (Fang *et al.*, 2012; Li *et al.*, 2017).

Advantages of Nanostructured lipid carriers

1. It possess increased solubility and enhanced storage stability.
2. It has increased permeability and Bioavailability.
3. Site-specific delivery.
4. It has reduced Toxicity.
5. Increased drug Loading capacity.

Lipid and drug nanoconjugates

The lipid drug nanoconjugates are the system in which the drug molecules are covalently attached with the lipids, and thus the conjugate of lipids and the drug molecules improves the lipophilicity of the drugs, and it also changes other properties, and covalent conjugation of the hydrophilic drugs to hydrophobic molecules increases the balance between the permeability and solubility. The linkers are used in the preparation of the Lipid drug nanoconjugates (Li *et al.*, 2017; Banerjee and Kundu, 2018).

Advantages

1. Lipid and drug nanoconjugates are biocompatible and possess less toxicity.
2. It promotes the bioavailability and stability of the drugs.
3. It prolongs the duration of the action of the drug.
4. It Protects drugs from enzyme degradation and aids in site-specific targeting.

Emulsifying system

The Emulsifying system of the Non-vesicular lipid system is further classified in to Self-emulsifying, Self-nano emulsifying and Nanoemulsions systems.

Self-emulsifying systems

Self-emulsifying system are the systems composed of the Lipophilic phase, and the surfactants along with drug and size ranges from 5-200 nm. The self-emulsifying system contains the mixture of triglyceride oils, surfactants, and the co-solvents, and these will emulsify under the condition of gentle agitation like GIT. In peroral administration, the hydrophobic drugs are encapsulated as a unit dosage form and can be released in the lumen of the gut as a fine emulsion (Singh *et al.*, 2015). The self-emulsifying system also has certain Advantages and Disadvantages as they are discussed in Table 2.

Self-Nanoemulsifying systems

Self-nano emulsifying systems are composed of synthetic or natural oils, Surfactants, co-Surfactants, and it forms emulsions on mild agitation in an aqueous media. Self-nano emulsifying systems are thermodynamically stable, and it provides the large interfacial area for the partitioning of the drug between the aqueous and oil phase. It enhances the oral bioavailability and improves the solubility of poorly soluble drugs. They are also referred to as ultrafine, microemulsion, etc., (Savale, 2015).

Advantages

1. They improve bioavailability.
2. It improves the solubility of poorly soluble drugs.
3. It dissolves the large quantities of lipophilic drugs and provides low-interfacial tension.
4. It protects the drugs from enzymatic degradation and hydrolysis reactions.

Nanoemulsion

Nanoemulsion is the nanosized colloidal dispersion system, and they are a combination of two immiscible systems with stabilizers to form a single stable phase. Nanoemulsions are referred to as submicron, ultrafine, and microemulsions. The various types of surfactants, such as Non-ionic, cationic, anionic, and zwitter ion surfactants, are used in the preparation of nanoemulsions. They are classified in to three types as oil in water(O/W), Water in oil(W/O) type, and the bi-continuous system (Gurpret and Singh, 2018).

Advantages

1. Improved bioavailability and enhanced the therapeutic efficacy of drugs.
2. Reduced toxic and side-effects.
3. Increased rate of permeation into the skin.
4. It protects the drug from the oxidation and hydrolysis process.

Vesicular systems

The vesicular systems contains one or more concentric bilayers and are highly assembled; these are formed as a result of self-Assembling of Nanoparticles. The vesicular system is essential for targeting the delivery of drugs since they have the potential to restrict the activity of drug at the desired site. In the vesicular system, both hydrophilic and hydrophobic drugs can be easily encapsulated (Jain *et al.*, 2014a).

Liposomes

Liposomes were first explained by Bangham in 1965, while the study of the cell membrane. Liposomes are artificial vesicles are small and spherical in shape and made up of cholesterol and natural Phospholipids. The size, Hydrophobic, and hydrophilic character of liposomes made them as a Promising system for drug delivery (Verma, 2015). The bilayer components of the liposomes determines the 'fluidity' or 'rigidity' and their charge. The liposomes can entrap both hydrophilic and hydrophobic compounds it avoids the degradation of the compounds entrapped within the vesicles and release it to the desired site (Bozzuto and Moli-nari, 2015). They are also capable of entrapping the unstable compounds includes antimicrobials, antioxidants, and bioactive elements. The mechanism by which the liposomes act within and outside the body includes (Patra *et al.*, 2018).

1. The liposomes attaches to the surface of the cell and unite with them and releases their content into the cell.
2. The liposomes containing phospholipids are incorporated into the cell membrane and are taken by the cell by which the entrapped drug is released.

Based on the size and Number of Lamellae, liposomes are divided as Multi lamellar vesicles (MLV), Large unilamellar Vesicles(LUV), small unilamellar Vesicles(SUV) (Akbarzadeh *et al.*, 2013). The Advantages and Disadvantages of Liposomes are discussed in Table 3.

Niosomes

The Niosomes are Non- ionic surfactants of multilamellar vesicle structure and are comparable to liposomes instead of phospholipids. They include Non- ionic surfactants. Niosomes are studied as an alternate to the liposomes. They mainly accommodate two types of components are Non- ionic surfactant and the additives. The niosomes can entrap both hydrophilic and hydrophobic components. The presence steroidal system in the formulation of niosomes improves the rigidity of the bilayers and increases permeability. This protects the premature degradation and inactivation of a drug due to immunological and pharmacological effects. The niosomes are considered as a better carrier than liposomes upon factors such as cost, stability, entrapment efficiency, and bioavailability. Niosomes are used as a potential carrier for the delivery of drugs, antigen, hormones, and bioactive agents (Usman *et al.*, 2017; Rajera *et al.*, 2011). The Figure 3 represents the generalized figure for the Lipid-based vesicular system. Table 4 represents the

advantages and disadvantages of Niosomes.

Transfersomes

Transfersomes are complex vesicular aggregates are optimized to attain extremely flexible, and self- regulating membrane and vesicles are ultra-deformable. It can Cross the microporous barriers efficiently even when the passages are smaller than average aggregates. Similar to liposomes, it is composed of a lipid bilayer that surrounds the aqueous core, and it also composed of one natural amphiphilic lipid (Phosphatidylcholine) and are supplemented by a bilayer softener (Jain *et al.*, 2014b).

The transfersomes are developed due to the disadvantage associated with liposomes and Niosomes poor skin permeability, their aggregation, and fusion in skin tissues and are not suitable for transdermal delivery. The Presence of an amphiphilic surfactant allows transfersomes to alter the membrane composition so it can penetrate the skin pores (Sachan *et al.*, 2013).

Advantages

1. Easily penetrate through the narrow pores of the skin.
2. They can sustain drug release and protect the drug from enzyme degradation.
3. It can be utilized for both topical as well as systemic delivery of drugs.

Disadvantages

1. Chemically unstable
2. Highly expensive
3. The purity of phospholipids also plays a major role.

Virosomes

Virosomes are the spherical unilamellar phospholipid bilayer vesicles, and they are the most widely investigated biological carriers. Virosomes hold the potential progressive application in the field of vaccines and gene delivery. Virosomes are developed to improve the efficiency of interaction between the cellular target for the introduction of molecules directly to the cells. The virosomes mainly composed of immune-stimulating regenerate influenza virosomes (IRIVS), consist of naturally occurring Phosphatidylcholine and phospholipids. Virosomes are capable of entrap even the antisense molecules (Singh *et al.*, 2017; Inamdar *et al.*, 2015)

Advantages

Table 1: Advantages and Disadvantages of Nanoparticles

Advantages	Disadvantages
Improved bioavailability and efficacy. Increased solubility. Increased biosafety and Biocompatibility. Sustained and controlled release of drugs.	Poor oral bioavailability Insufficient tissue distribution. Instability in circulation time particle-particle aggregation due to large surface area
Site-specific targeting and protection of fragile drugs	Difficulty in the physical handling of liquid forms
Easier transport across the physiological barriers, and increased resident time in the body.	Limited drug loading

Table 2: Advantages and Disadvantages of Self-emulsifying systems

Advantages of Self-emulsifying systems	Disadvantages of Self-emulsifying systems
It possess increased oral bioavailability. It avoids the enzymatic degradation. Improved drug loading capacity and faster onset of action.	Instability of drugs. A higher concentration of surfactants. IVIVC associated problems.

Table 3: Advantages and Disadvantages of Liposomes

Advantages of liposomes	Disadvantages of liposomes
Increased therapeutic efficacy of the drug Increased stability via encapsulation They are non- toxic, biocompatible, biodegradable, and non- immunogenic. Flexible to couple with ligands and achieve active targeting. Provides the sustained release of drugs Improved stabilization of protein molecules	Low solubility Short half-life Phospholipids sometimes may undergo oxidation and hydrolysis. Leakage and fusion of encapsulated molecules. High cost involved in the production Only fewer stables

Table 4: Advantages and Disadvantages of Niosomes

Advantages of Niosomes	Disadvantages of Niosomes
Osmotically active and are stable than liposomes. Increased Bioavailability and permeation. Absence of tissue Irritation and damage and reduced toxicity. It provides sustained release. Handling, transportation, and storage is easier.	Physically unstable Leakage and fusion of entrapped drug Aggregation of the molecules High Production cost Hydrolysis of the entrapped drug that limits the shelf- life.

- | | |
|---------------------------------------------------|---------------------------------------------------------------------|
| 1. Virosomes are biodegradable and biocompatible. | 1. Shorter shelf- life |
| 2. It can sustain the release of drugs. | 2. The raw materials poor quality |
| 3. It protects the drug from enzyme degradation. | 3. Problems associated with Manufacturing |
| 4. It is non- immunogenic. | 4. Non availability of data related to the chronic use of virosome. |

Disadvantages**Bilosomes**

Bilosomes are the vesicular drug delivery vehicle that protects the vaccines from the enzyme degradation. Bilosomes are the formulations in which the Bile salts are incorporated into the membrane of Niosomes. Bile salts are used to increase the oral bioavailability and as penetration enhancers. The Bilosomes differ from the liposomes and Niosomes by their composition, chemical stability, and storage condition. Bilosomes are developed to prevent the antigen from degradation, enhanced mucosal penetration, and avoid problems during the GI transit ([Chilkwar et al., 2015](#)).

Advantages

1. Bilosomes doesn't required to use the live pathogens, that makes them safe and effective.
2. It removes the cold-chain process required for the preparation of vaccines.
3. It is less toxic.
4. It improves the patient compliance.

Aquasomes

Aquasomes are the three-layered self- assembled vesicular nanocarrier system. These are like "Bodies of water," and their water like properties preserve and protect fragile biological molecules. Aquasomes are composed of solid-phase nanocrystalline core coated with an oligomeric film on which the biological molecules get adsorbed with or without the modification. Aquasomes maintain conformational integrity and a high degree of surface exposure in the targeting of bioactive molecules like enzymes, antigens, and genes to specific-sites ([Patel et al., 2018](#); [Gulati et al., 2015](#)).

Advantages of Aquasomes

1. Aquasomes preserves the structural integrity of the biological molecules.
2. Aquasomes composed of large surface areas so that the drugs can be loaded efficiently.
3. Aquasomes avoids the reticuloendothelial clearance because of their size and stability.
4. It can sustain the release of the drug.
5. It is biodegradable.

Ethosomes

Ethosomes are the non- invasive ethanolic liposomes and composed of malleable vesicles. Ethosomes contains the cholesterol, phospholipids, and

alcohol in it that enables drugs to penetrate deep into the skin layers and in the systemic circulation. Ethosomes permeate easily and rapidly through the layers of the skin and have increased higher transdermal flux ([Aggarwal and Nautiyal, 2016](#)).

Advantages

1. It is a non- invasive technique.
2. The larger molecules can be delivered.
3. It can sustain the drug release.
4. Increases the permeation of the drugs.

Disadvantages

1. Skin irritation may occur.
2. The yield of a drug is poor.
3. Loss of the product occur on transportation.
4. The drug should be soluble in both lipophilic and hydrophilic environment.

Herbosomes

Herbosomes are vesicular structures composed of Phospholipids and the herbal extracts. Herbosomes improves the permeability and bioavailability and easily crosses the lipid-rich biomembranes. Herbosomes protect the phytoconstituents from the digestive secretions ([Dewan et al., 2016](#)).

Advantages

1. Herbosomes shows enhanced permeation and aids in the delivery of larger molecules.
2. They are non-invasive and shows better stability.
3. Prolonged duration of action.
4. It is biodegradable.

Disadvantages

1. It has very short- half-life.
2. Difficulty in targeting.
3. Hydrolysis and fusion takes place due to the presence of phospholipids.



Figure 2: Classification of Nanoparticulate drug delivery system

Polymeric system

The polymer-based nanoparticles are the system in which the drugs are encapsulated, dissolved, and entrapped in the matrix of the polymer. The polymeric system based nanoparticles are further classified into Nano micelles and Nanospheres. The polymeric system increases the safety, efficacy, and bioavailability of the drugs (Ochekpe *et al.*, 2009; Mirza and Siddiqui, 2014).

Nanomicelles

Micelles are self-assembled structure composed of both hydrophobic and hydrophilic segments. Micelles are in a size range of 5-100 nm. They are arranged in different morphologies that includes spheres, rods, and tubes, etc., They are formed with

lipids of low critical micellar concentration and also formed as a result of interaction between the polar groups and the surrounding water molecules they are separated as a hydrophobic and hydrophilic segments (Hanafy *et al.*, 2018).

Advantages

1. It protects the drug from elimination by (MPS) system.
2. Improves the solubility of the drugs.
3. Both hydrophobic and hydrophilic drugs can be loaded.

Disadvantages

1. Stability in the bloodstream is reduced due to reduced critical micellar concentration.
2. Leakage and fusion of the polymer assembly.
3. Reduced circulation Half-life.

Nanospheres

Nanospheres are the spherical nanoparticles size ranges from 10-200nm and a matrix system in which the drug is dispersed uniformly in the matrix. Nanospheres are biodegradable and biocompatible, and some of them are modified, such as starch, gelatine, and polylactic acid nanospheres. They can be amorphous or crystalline. The nanospheres can be injected or ingested (Ibrahim *et al.*, 2018).

Advantages

1. Site-specific targeting.
2. Reduced toxicity.
3. It can sustain the release of the drug.

Disadvantages

1. Difficulty in handling nanospheres in dry and liquid forms.
2. Larger surface area and leads to particle aggregation.
3. Due to the smaller size limited release of the drug.

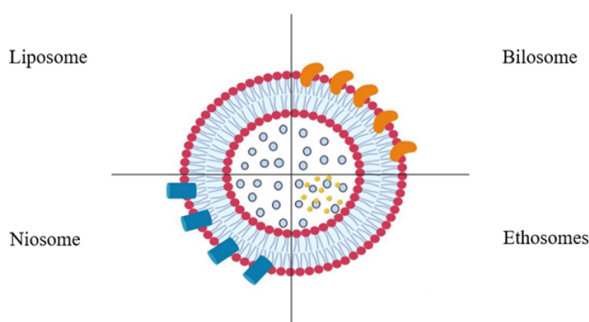


Figure 3: Lipid-based Vesicular system

Lipid and polymeric system

Core/shell Nanoparticles

Core-shell nanoparticles are composed of a core, and it is covered with another material on top the size ranges from 1-20nm. Core-shell materials can be prepared from the semiconductors, insulators,



Figure 4: Strategies of Drug Targeting

and metals. They possess highly favourable chemical and optical properties. In the core-shell nanosystem, the drug can be either adsorbed and encapsulated. Higher surface area and increased drug loading capacity. The surface modifications are done to nanocarriers such that they release their drug at the desired site (Chatterjee *et al.*, 2014).

Advantages

1. Decreased cytotoxicity.
2. It possesses increased dispersibility and biocompatibility.
3. Increased chemical and thermal stability.
4. Possesses better conjugation with the biomolecules.

Others

This includes the various other types of nanoparticulate system that are made up of carbon and semiconductor types that includes, Fullerenes, Dendrimers, and Quantum-dots.

Fullerenes

Gokhale and Somani (2015), Fullerenes are a fourth allotropic form of carbon. A fullerene is any molecule composed entirely of carbon, in the form of a hollow sphere, ellipsoid, or tube. A fullerene is a carbon cage structure having a fused ring system which consists of pentagons and hexagons. C60 and C70 are the most accessible members of this family.

Types

Buckyball clusters

It is spherical, and the most common is C60 atoms can be entrapped within it.

Nanotubes

Hollow tubes of very small dimensions with single or multiple walls used in the electrical industry.

Megatubes

Varying in dimensions than nanotubes as larger in diameter with walls of different thickness, which is potentially used for the transport of a variety of molecules of different sizes.

Polymers

Chain, two or three dimensional, formed under high pressure and temperature conditions.

Nano"onions"

Spherical particles having multiple layers which surrounds buckyball core. Typical diameter is 3-5 nm; proposed for lubricants.

Linked "ball-and-chain" dimers

Two buckyballs linked by a carbon chain.

Advantages

1. The fullerenes are the most powerful radical scavenging, and so its used as a neuroprotective agent.
2. These are hydrophobic and can become water-soluble are capable of carrying drugs to the genes.
3. Fullerenes possess antimicrobial activity.
4. They are stable when the number of carbon atom decreases.
5. Due to their size, they are also used as lubricants and glidants.

Dendrimers

Dendrimers are monodisperse, unimolecular, Nano-sized structures in a range of 20 nm. It is composed of tree-like arms and branches. It was first discovered by Fritz Vogtle in 1978. The structure of dendrimer begins with a central atom or group of atoms said as core then from centre atom the other branches arises called 'dendrons' it grows through the various chemical reactions and the outer layer is made up of repeated units. They are robust and are covalently fixed. Dendrimers are generally prepared by the divergent or convergent method. Dendrimer vectors are commonly used as parenteral injections, directly into the tumour tissue or intravenously for systemic delivery. Dendrimers are used in diagnostic imaging, gene transfection, and also in detection of therapeutic treatment of tumour (Pandita *et al.*, 2014; Lombardo *et al.*, 2019).

Advantages

1. Dendrimers are highly water-soluble.
2. They are biocompatible.

3. It releases the drug at the specific site.

4. It improves the solubility and bioavailability of drugs.

Quantum-dots(QD)

Quantum dots are referred to as semiconductor nanosized crystals. The QD size ranges from 2-20nm. QD have unique, fascinating optical properties and become an indispensable tool in biomedical research, fluorescence imaging, and detection. This may behave as a targeting delivery that will not only also identify it binds to diseased cells and treats it. The QD in their In Vivo application, they cause the cytotoxicity. When QD are coated with the peptides can reduce the toxic effects since the surface functionalization plays the main role in nanoparticle toxicity. QD also serves as a structural scaffold and image contrasting agent (Lombardo *et al.*, 2019; Drbohlavova *et al.*, 2009).

Advantages

1. The prevention of nanoparticle aggregation in a biological environment.
2. It suppresses the non-specific adsorption of biomolecules at the nanoparticles surface.
3. The colloidal stability can be increased.

Strategies of drug targeting

(Mishra *et al.*, 2016), Drug targeting to a specific site increases the therapeutic efficacy of the drug and also decreases the toxicity that arises. Drug targeting mainly follows two strategies, as mentioned in Figure 4.

Passive targeting

Passive targeting is based on the accumulation of the drug or drug carrier system at a particulate site due to Pharmacological or physicochemical factors. Passive targeting do not requires any carriers for drug delivery. The passive targeting occurs in almost all types of drug delivery carriers, and it cannot be described as a form of selective targeting. Nanoparticles tend to accumulate other organs than the desired sites such as in the liver, lungs, and spleen. It is because of the distribution of the drug in a body takes place by blood circulation. The nanoparticles are targeted in a better manner to a particular tissue or cell by refining their physicochemical properties (Wakaskar, 2017).

Active targeting

Active targeting involves the modification of drug or drug carrier Nanosystems with active agents

such as Ligands that are having the ability to interact with the specific cell, tissue, or organ in the body. The ligand molecules includes antibodies, Proteins, peptides, nucleic acids, and sugars. The target molecules includes proteins, lipids, and sugars. The interaction between the target and the ligand molecules is enhanced by the multivalent nature of the nanoparticles, and thus more the number of the ligand in the nanoparticles increases the affinity for the target. Active targeting increases the accommodation of nanoparticles in target cells and increases the efficacy of the loaded drugs (Rajkumar *et al.*, 2017). The active targeting is further classified in to three levels, which includes

First-order targeting

First-order targeting is a distribution of drug and drug carriers system to the capillary bed of a target site, tissue, and organ. It includes targeting in a plural cavity, cerebral ventricles, lymphatics, joints, eyes, etc...

Second-order targeting

Second-order targeting is a delivery of drugs to specific cell types like tumour cells. E.g., targeting to Kupffer cells in the liver.

Third-order targeting

Third-order targeting is a delivery of drugs specifically to the intracellular site of the targeted cell. E.g., intracellular localized target through endocytosis.

Mechanism of drug release

To design the effective nanoparticulate drug delivery system, both drug release and polymer degradation are taken in to a consideration. The rate release of the drugs mainly depends on,

1. Drug solubility
2. Desorption of the adsorbed drug/surface bound drug
3. Diffusion of the drug through the matrix
4. Nanoparticulate matrix degradation/erosion
5. The combined process of diffusion/erosion

Since the nanoparticles are coated by a polymer that releases the drug by either controlled diffusion or erosion from the core across the matrix. There is evidence that the method of incorporation The coating acts as a barrier for the release of the drug, so the solubility and diffusivity of drug in the polymer matrix becomes the important factors to be considered. Further, the rate of drug release is also affected

by the interaction between the drug and the excipients (Mudshinge *et al.*, 2011).

General method of preparation of nanoparticulate system

Generally, there are two methods exist for the preparation of the nanoparticles, it includes "Top-down"(breaking the larger particles) and "Bottom-up"(building up process) Approach. The most convenient method for the manufacturing of nanoparticles is the Bottom-up approach. It relies on the principle of supersaturation for the control of particle size. Various methods of preparation for nanoparticles exist, such as solvent evaporation, HPR, nanoprecipitation, salting out, microemulsion ball milling, and process of detergent removal also been used. The substantial growth in the field the other methods for the preparation of nanoparticles are also evolved (Wang *et al.*, 2016).

Solvent Evaporation

Solvent evaporation techniques are mostly used in the preparation of polymer-based nanoparticles. There are two main types of procedures used when the preparation of nanoparticles through the Solvent Evaporation technique which includes single emulsion and double emulsion. Single emulsion preparation involves the Oil in water (O/W) type, and double emulsions preparation involves the water in oil in water (W/O/W) types.

The step by step process of Solvent Evaporation technique includes,

The polymers and required amount of drug of choice is dissolved into the organic solvent. The aqueous phase is prepared separately, which contains the stabilizers or emulsifiers. The organic phase is transferred to the aqueous phase, and the mixture is homogenized and constantly stirred for several minutes for the organic phase to be evaporated, and hardened nanoparticles are formed. The resulting solutions undergo centrifugation or filtration to separate out the nanoparticles (Nagavarma *et al.*, 2012).

High- Pressure homogenization (HPR)

High- Pressure homogenization technique is mainly used in the preparation of solid lipid nanoparticles and liposomes. There are mainly two methods in the homogenization technique the preparation of nanoparticles can be done by either hot or cold process. The solid lipid nanoparticles are prepared by hot High- Pressure homogenization techniques the nanoparticles are prepared as lipids are melted above its melting point, and the drug of choice is dissolved in the melted lipids. Then the melt is dispersed on the hot aqueous surfactant solution that is

heated to the same temperature. Then the resulting solution is homogenized to form the hot oil in water nanoemulsion and cooled in room temperature to obtain the SLN's. In the cold process of the HPR technique, the melt is prepared with a drug of choice and cooled and grounded to form the micro lipid particles. The micro lipid particles are dispersed in a cold aqueous surfactant solution and homogenized below the room temperature that facilitates the formation of SLN's (Rupenagunta *et al.*, 2011).

Salting Out method

In this method, the Polymer is dissolved in the organic phase of suitable solvents and drug of choice. The aqueous phase are prepared with the surfactant, and the saturated solution of electrolytes the electrolytes should not be soluble in the organic solvent. The electrolytes are added to decrease the ionic-strength. Then the organic phase is emulsified in the aqueous phase by constant stirring. Then the organic solvents migrate from the oil phase to the aqueous phase. It results in the formation of nanoparticles. The salting-out agent is eliminated using centrifugation, and then the samples are purified.

Surface properties of nanoparticulate system

Mohanraj and Chen (2006); Rizvi and Saleh (2018), The surface characteristics of Nanoparticles plays a major role in designing an effective drug delivery system. Surface characteristics of the nanoparticles that affects the drug targeting are

1. Size of the particle
2. Hydrophobicity
3. Zeta potential of the particles.

Size of the particles

The size of the particles determines the distribution, toxicity, and their targeting ability. The size of the particle also influences their stability, drug loading, and drug release. Nanoparticles have higher intracellular uptake and are available to a wide range of the biological target. Due to their small size had a greater uptake than microparticles. Drug release is also affected by particle size. Larger particles have large cores more amounts of the drug can be encapsulated, and the drug can be diffuse out slowly, whereas in smaller particles have a large surface area, and the drug is associated to or near the particle surface that leads to faster release of the drug. Larger size particles, when enters the body it is recognized by the immune system and considered as a foreign particles and engulfed by a Macrophages.

Hydrophobicity

The hydrophobicity of the nanoparticles determines the amount of blood components that binds the surface, and it also influences the *In vivo* fate of nanoparticles. Surface non-modified nanoparticles are rapidly opsonized and cleared by the mononuclear phagocytes system(MPS).To increase the rate of success in drug targeting, the opsonization has to be minimized to prolong the circulation time. This is achieved by formulating the nanoparticles with biodegradable polymers with hydrophilic properties. Or coating it with hydrophilic polymers.

Zeta Potential

The zeta potential is used to characterize the surface charge property of the nanoparticles.it is the electric potential of the particles is influenced by medium in which is dispersed and composition of the particles. For the stable suspension, the zeta potential must be above (+/-) 30 mV since the aggregation is prevented by the surface charge. The zeta potential is used to determine whether the charged material is encapsulated in the centre of the nanoparticle or present on the surface of the particle.

Characterization of nanoparticulate system

The nanoparticles are classified based on the analysis of various physicochemical properties as Morphological, structural, Particle size and surface area characterization (Cooper *et al.*, 2014; Pal *et al.*, 2011; Khan *et al.*, 2017).

Morphological characterization of Nanoparticles

The morphological characters of the nanoparticles plays an important role in determining their property. This characteristic of the nanoparticles are analyzed by mainly two techniques, such as SEM and TEM techniques.

SEM technique works on the basis of the electron scanning principle. It provides all the information related to Nanoparticles; it also helps in the study of Morphology and also the dispersion of Nanoparticles in the matrix or bulk. The SEM produces the reports due to the scattering of photons.

TEM technique works on the basic principle of the transmission of electrons. It provides the information of the nanoparticles from the characteristic of bulk material to the very low magnification. If the nanoparticles are present in layers, it also reported by TEM as micrographs.

Structural characterization of Nanoparticles

The structural properties plays an important role in the study of the composition and nature of bonding

materials in the nanoparticles. It provides information about the bulk properties of the nanoparticles. Some of the techniques involved in the analysis of the structural characteristics includes XRD, energy dispersive X-ray (EDX), XPS, IR, BET, and Zeta size analyzers.

XRD is the important technique it reveals the information of nanoparticles crystallinity nature and the different phase and it also partially provides the idea about the particle size. This is done using the Debye Scherer formula, and it works well in single and multiphase Nanoparticles identification. The better diagnosis of the nanoparticles are done by comparing the diffractograms. XPS is another technique used to describe the elemental ratio and the bonding nature of elements of the nanoparticles. XPS works on the basis of spectroscopic principles.

Vibrational characteristics of the nanoparticles are determined by using FT- IR and Raman spectroscopic methods. In this, the fingerprint region of the nanoparticles describes the properties of them, and FT- IR describes the functionalization of the nanoparticles.

Particle size and surface area characterization of Nanoparticles

There are various techniques available for the analysis of the size and surface characteristics of the nanoparticles that involves SEM, TEM, XRD, AFM, dynamic light scattering (DLS). Especially the Zeta potential size analyzer/ (DLS) can determine the nanoparticles size till the lower levels, and they aids in determining the size variations. In case of incapability of (DLS) to produce accurate results leads to high -resolution technique of differential centrifugal sedimentation (DCS). Then the biological molecules Nanoparticle tracking analysis (NTA) is used. They produce better results than (DLS).

Necessity of nanoparticulate system

Traditionally available dosage forms like oral and injectables suffer from certain drawbacks like high dose, and low solubility and bio availability, first-pass effect, intolerance, instability, and some drugs exhibit plasma drug level fluctuations and do not provide controlled release, and degradation of fragile molecules (proteins). The efficiency of most drug delivery system depends directly on their particle size. This created the necessity for the nanoparticles because it has small particle size and show increase in solubility and improved bioavailability, and they have the ability to cross the Blood-Brain Barrier(BBB) and can be absorbed through tight junction and can penetrate through the pulmonary system and can stay more time in the circu-

lation by avoiding entry to Reticuloendothelial system. The development of a new drug delivery system increases the profit of the Pharmaceutical company and patient compliance (Mohanraj and Chen, 2006).

Self-assembly of nanoparticulate system

Yu *et al.* (2016), The nanostructures formed as a result of self-assembly of nanoparticles is a force balance process in which well-defined structures are formed without human intervention. The self-assembly process takes place by Noncovalent interactions, electrostatic interactions, hydrophobic effect, van der Waals interactions, hydrogen bonding, steric and depletion forces, coordination bonding, solvation, and hydration forces, π - π stacking interactions. The noncovalent interactions have a significant influence on the self-assembling nanostructures, synergistically, or separately.

Hydrophobic effect

The hydrophobic effect is important among the non-covalent interactions in the self-assembly process. The presence of both polar and non-polar groups aids the amphiphilic molecules to self-assemble, and it occurs through microphase separation. In aqueous solutions, the nonpolar regions of the molecules will collapse and aggregate together to form hydrophobic area in aqueous solutions while the polar regions attempts to increase their interaction with water and this makes the molecules get self-assembled.

Electrostatic interactions

It is the interaction between the charged ions, atoms, or molecules. It involves both attractive and repulsive forces. This interaction has a strong influence on the self-assembly process. Cationic polymers interact with the anionic molecules and forms the stable nanoparticles in the aqueous solution.

Hydrogen bond

It is the electrostatic interactions between the hydrogen atom and a high electronegative atom (N, O, F). Hydrogen bond attractions can either occur as intermolecular and intramolecular, and it is common in both organic and inorganic molecules. Non-covalent interactions play an important role in the self-assembly of nanoparticles.

CONCLUSIONS

Over the past few decades, the interest in the use of the Nanoparticulate drug delivery system increased progressively in the field of medicines. Nanoparticles are used as potential carriers in drug targeting, Bioimaging, wound dressing, diagnosis, and treat-

ment of the various diseases, and it possess more advantages over the conventional dosage forms. It offers the site-specific delivery of the drugs, thus can reduce the maximum of side-effects and improves the therapeutic index of the drugs that benefits the patients. In this review, we presented the systemic and detailed overview about the Nanoparticles and necessity of Nanoparticles, classification, method of synthesis, surface properties, characterization, self-assembly principle, mechanism of drug release, and strategies of drug targeting. Further, the nanoparticulate drug delivery systems has to be improved as that helps in the advanced drug delivery and for practical applications.

REFERENCES

- Aggarwal, D., Nautiyal, U. 2016. Ethosomes: A review. *International Journal of Pharmaceutical and Medicinal Research*, 4(4):354–363.
- Akbarzadeh, A., Rezaei-Sadabady, R., Davaran, S. 2013. Liposome: classification, preparation, and applications. *Nanoscale Res Lett*, 8:102–102.
- Banerjee, S., Kundu, A. 2018. Lipid-drug conjugates: a potential nanocarrier system for oral drug delivery applications. *DARU Journal of Pharmaceutical Sciences*, 26(1):65–75.
- Bozzuto, G., Molinari, A. 2015. Liposomes as nanomedical devices. *International Journal of Nanomedicine*, (10):975–999.
- Chatterjee, K., Sarkar, S., Rao, K. J., Paria, S. 2014. Core/shell nanoparticles in biomedical applications. *Advances in colloid and interface science*, 209:8–39.
- Chilkwar, R. N., Nanjwade, B. K., Nwaji, M. S. 2015. Bilosomes Based Drug Delivery System. *Journal of Chemistry & Applications*, 2(1):5–6. Idris SM, Mohamied AS.
- Cooper, D. L., Conder, C. M., Harirforoosh, S. 2014. Nanoparticles in drug delivery: mechanism of action, formulation, and clinical application towards the reduction in drug-associated nephrotoxicity. *Expert Opinion on Drug Delivery*, 11(10):1661–1680.
- Dewan, N., Chowdhary, G., Pandit, S., Ahmed, P., Dasgupta, D. 2016. Review on-Herbosomes, A new arena for drug delivery. *Journal of Pharmacognosy and Phytochemistry*, 5(4):104–108.
- Drbohlovova, J., Adam, V., Kizek, R., Hubalek, J. 2009. Quantum Dots - Characterization, Preparation, and Usage in Biological Systems. *International Journal of Molecular Sciences*, 10(2):656–673.
- Fahmy, T. M., Fong, P. M., Goyal, A., Saltzman, W. M. 2005. Targeted for drug delivery. *Materials Today*, 8(8):71033–71039.
- Fang, C. L., Al-Suwayeh, A., Fang, J. Y. 2012. Nanostructured Lipid Carriers (NLCs) for Drug Delivery and Targeting. *Recent Patents on Nanotechnology*, 7(1):41–55.
- Gohla, S. 2000. Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(1):161–177.
- Gokhale, M., Somani, R. 2015. Mini-Reviews in Organic Chemistry. *Fullerenes: Chemistry and Its Applications*, 12.
- Gulati, M., Singh, S., Kishore, U., Kumar, R. 2015. Potential Applications of Aquasomes for Therapeutic Delivery of. *Proteins and Peptides*, 4:439–453.
- Gurpret, K., Singh, S. K. 2018. Review of Nanoemulsion Formulation and Characterization Techniques. *Indian Journal of Pharmaceutical Sciences*, (5):80–80.
- Hanafy, N., El-Kemary, M., Leporatti, S. 2018. Micelles Structure Development as a Strategy to Improve Smart Cancer Therapy. *Cancers*, 10(7).
- Horikoshi, S., Serpone, N. 2013. Microwaves in Nanoparticle Synthesis. *Fundamentals and Applications*, pages 1–24.
- Ibrahim, K. N., Krishnakumar, B., Dineshkumar, Smitha, K., Nair 2018. An overview on nanosphere drug delivery. *European journal of pharmaceutical and medical research*, 5(4):192–198.
- Inamdar, N. A., Gajanan, V., Pulgamwar, Kalyani, A., Jadhav 2015. Virosomes: New Frontier for Targeting Drugs and Biological Molecules. *Asian Journal of Pharmaceutical Technology & Innovation*, (12):92–103.
- Jain, S., Jain, V., Mahajan, S. C. 2014a. Lipid-Based Vesicular Drug Delivery Systems. *Advances in Pharmaceutics*, pages 1–12.
- Jain, S., Jain, V., Mahajan, S. C. 2014b. Lipid-Based Vesicular Drug Delivery Systems. *Advances in Pharmaceutics*, pages 1–12.
- Khan, I., Saeed, K., Khan, I. 2017. Nanoparticles: Properties, applications, and toxicities. *Arabian Journal of Chemistry*, pages 1–24.
- Li, Q., Cai, T., Huang, Y., Xia, X., Cole, S., Cai, Y. 2017. A Review of the Structure, Preparation, and Application of NLCs, PNPs, and PLNs. *Nanomaterials*, 7:122–122.
- Lombardo, D., Kiselev, M. A., Caccamo, M. T. 2019. Smart Nanoparticles for Drug Delivery Applica-

- tion: Development of Versatile Nanocarrier Platforms in Biotechnology and Nanomedicine. *Journal of Nanomaterials*, pages 1–26.
- Mirza, A. Z., Siddiqui, F. A. 2014. Nanomedicine and drug delivery: a mini review. *International Nano Letters*, 4(1).
- Mishra, N., Pant, P., Porwal, A., Jaiswal, J., Samad, M., Tiwari, S. 2016. Targeted Drug Delivery: A Review. *American Journal Of PharmTech Research*, 6.
- Mohanraj, Y. V., Chen 2006. Nanoparticles : A Review. *Tropical Journal of Pharmaceutical Research*, 5(1):561–573.
- Mudshinge, S. R., Deore, A. B., Patil, S., Bhalgat, C. M. 2011. Nanoparticles: Emerging carriers for drug delivery. *Saudi Pharmaceutical Journal*, 19(3):129–141.
- Nagavarma, B. V. N., Yadav, H. K. S., Ayaz, A., Vasudha, L. S., Shivakumar, H. G. 2012. Different techniques for preparation of polymeric nanoparticles- A review. *Asian Journal of Pharmaceutical and Clinical Research*, 5(3):16–23. Suppl.
- Ochekpe, N., Olorunfemi, P., Ngwuluka, N. 2009. Nanotechnology and Drug Delivery Part 2: Nanostructures for Drug Delivery. *Tropical Journal of Pharmaceutical Research*, 8(3).
- Pal, S. L., Jana, U., Manna, P. K., Mohanta, G. P., Manavalan, R. 2011. Nanoparticle: An overview of preparation and characterization. *Journal of Applied Pharmaceutical Science*, pages 228–234.
- Pandita, D., Poonia, N., Kumar, S., Lather, V., Madaan, K. 2014. Dendrimers in drug delivery and targeting: Drug-dendrimer interactions and toxicity issues. *Journal of Pharmacy and Bioallied Sciences*, 6(3):139–139.
- Patel, S., Aundhia, C., Seth, A., Shah, N., Pandya, K., Patel, D. 2018. Aquasomes: a novel approach in the drug carrier system. 3:198–201.
- Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V. R., Rodriguez-Torres, M., Acosta-Torres, S., Torres, L. D., Grillo, R. 2018. Nano based drug delivery systems: recent developments and future prospects. *Journal of Nanobiotechnology*, 16(1).
- Rajera, R., Nagpal, K., Singh, S. K., Mishra, D. N. 2011. Niosomes: A Controlled and Novel Drug Delivery System. *Biological & Pharmaceutical Bulletin*, 34(7):945–953.
- Rajkumar, G. A., Gayathri, R., Vishnupriya, V. 2017. Targeting the target using nanoparticles - a review. *Asian J Pharm Clin Res*, 10:6–10. Issue.
- Rizvi, S. A. A., Saleh, A. M. 2018. Applications of nanoparticle systems in drug delivery technology. *Saudi Pharmaceutical Journal*, 26(1):64–70.
- Rupenagunta, A., Somasundaram, I., Ravichandiram, V., Kausalya, J., Senthilnathan, B. 2011. Solid lipid nanoparticles-A versatile carrier system. *J Pharm Res*, 4(7):2069–2075.
- Sachan, R., Parashar, T., Singh, V., Singh, G., Tyagi, S., Patel, C. 2013. Drug carrier transfersomes: a novel tool for transdermal drug delivery system. *International journal of research and development in pharmacy and life sciences*, 2:309–316.
- Savale, S. K. 2015. A Review - Self Nanoemulsifying Drug Delivery System (Snedds). *International Journal of Research in Pharmaceutical and Nano Sciences*, 4(6):385–397.
- Singh, A., Singh, V., Rawat, G., Juyal, D. 2015. Self-emulsifying systems: A review. *Asian Journal of Pharmaceutics*, 9(1):13–13.
- Singh, N., Gautam, S. P., Kumari, N., Kaur, R., Kaur, M. 2017. Virosomes as Novel drug delivery System: An Overview. *PharmaTutor*, 5:47–55.
- Singh, S., Pandey, V. K., Tewari, R. P., Agarwal, V. 2011. Nanoparticle-based drug delivery system: Advantages and applications. *Indian Journal of Science and Technology*, 4(3):177–180.
- Usman, M. R. M., Ghuge, P. R., Jain, B. V. 2017. Niosomes: A Novel Trend of Drug Delivery. *European Journal of Biomedical and Pharmaceutical sciences*, 4(7):436–442. European Journal of Biomedical.
- Velavan, P., Karuppusamy, C., Venkatesen, P. 2015. Nanoparticles as drug delivery systems. *Journal of Pharmaceutical Sciences and Research*, 7(12):1118–1122.
- Verma, N. 2015. Liposomes: A Targeted Drug Delivery System- A Review. *Acta Medica Scientia*, 2(3):65–70.
- Wakaskar, R. R. 2017. Passive and Active Targeting in Tumor Microenvironment. *International Journal of Drug Development and Research*, 9(2):37–41.
- Wang, Y., Li, P., Tran, T. T.-D., Zhang, J., Kong, L. 2016. Manufacturing Techniques and Surface Engineering of Polymer-Based Nanoparticles for Targeted Drug Delivery to Cancer. *Nanomaterials*, 6(2).
- Wanigasekara, J., Witharana, C. 2016. Applications of nanotechnology in drug delivery and design - an insight. *Current Trends in Biotechnology and Pharmacy*, 10(1):78–91.
- Yu, X., Trase, I., Ren, M., Duval, K., Guo, X., Chen, Z. 2016. Design of Nanoparticle-Based Carriers for Targeted Drug Delivery. *Journal of Nanomaterials*, pages 1–15.