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REVIEW ARTICLE

NANO FORMULATIONS AS DRUG DELIVERY SYSTEMS

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Abstract:
Classical drug forms are used frequently and in repeated doses. Undesirable situations may occur when the dose used for the concentration of the active substance released into the system falls below the sufficient amount or rises above the toxic level. As a result of the developments achieved in nanotechnological research, nanoparticles, which have many applications in the clinic, have made a significant impact in the pharmaceutical industry. The practical use of nanoparticles in applications such as direct binding to the active substance, entrapment and targeting in the pharmaceutical industry has made nanoparticles a preferred position. When implanted systems with nanocarriers reach the target area, uptake in organs, tissues and cells increases. These structures use active and passive targeting strategies to deliver the active substance to the targeted cells. The use of nanocarriers in drug delivery systems provides many advantages. The results obtained from the studies carried out so far are that, thanks to the targeting of cancer drug-loaded nanocarriers, treatment alternatives with higher selectivity have emerged. In this study, nanoparticles as drug delivery are discussed and how to increase bioavailability with nanoparticles is discussed with their advantages.

Keywords: Nanoparticles, Drug Delivery Systems, Nanotechnology

1. INTRODUCTION

Classical drug forms are used frequently and in repeated doses. Undesirable situations may occur when the dose used for the concentration of the active substance released into the system falls below the sufficient amount or rises above the toxic level Nanoparticles have unique optical, electrical and thermal properties and are reported to have an indispensable role in many fields such as medicine, diagnostics, imaging, sensing, genetics, artificial implants and tissue engineering (Danckwerts and Fassihi, 1991). The active substance concentration in the blood is kept constant for a long time at the desired therapeutic level and the elimination of the active substance in the body is reduced. Thus,

active substance use is realized and the benefit to be obtained from the drug is increased (Zhang et. al., 2008). One of the main problems in pharmaceutical and biotechnological fields is to transport the drug to the structure where it will act. Therefore, drug delivery systems have always been the focus of attention of researchers (Wang et. al., 2008). Developments in biotechnology and research in other branches of science related to this field help the discovery and rational design of new drugs (Chien and Lin, 2007). Today, new developing technologies are used to minimize the problems that arise in the use of drugs. For this purpose, researchers working in different disciplines are brought together and the developments obtained are transformed into clinical effectiveness. Targeted drug delivery systems enable drugs to be delivered to the target more effectively and more practically than today's drugs. Due to the fact that patients generally have a geriatric disorder, it becomes difficult to follow up on the patients' relatives and caregivers following their medications. As a result, the patient refuses the drug due to the agitation caused by the disease. As a result of the developments achieved in nanotechnological researches included in this study, nanoparticles, which have many applications in the clinic, have made a significant impact in the pharmaceutical industry. The practical use of nanoparticles in applications such as direct binding to the active substance, entrapment and targeting in the pharmaceutical industry has made nanoparticles a preferred position. Nanocarriers provide the delivery of targeted drugs to the diseased structure. Thanks to the nanoparticle researches, it is possible to diagnose and treat many diseases today. In addition, due to the potential of application in drug delivery systems, it shows a rapid development in the field of health. It is taking place more and more in drug delivery system technology with each passing day (Değim, 2011). The effect of other branches of science on the field of health and the process of replacing traditional drugs with new drugs has accelerated thanks to the developing nanotechnological applications. In this process, new drugs are produced thanks to the developments in nanotechnology and biotechnology, and pharmaceutical technology applications.

2. DRUG DELIVERY SYSTEMS

One of the main problems in pharmaceutical and biotechnological fields is the transfer of the drug to the structure where it will act. Today, newly developing technologies are used to minimize the problems that arise in the use of drugs. And thanks to the studies carried out, specific drug delivery systems are developed. Targeted drug delivery systems enable drugs to be delivered to the target more effectively and more practically than today's drugs. Thanks to all these developed systems, the patient's compliance increases and the half-life of the drug is extended. As a result, health expenditures are reduced. In recent years, there has been an increasing interest in drug delivery systems (Allen & Ansel, 2013).

Drug delivery systems provide the followings (Tiwari et al., 2012):

i. They make active substances with low solubility soluble and thus increase their bioavailability.
ii. Drugs are delivered to the target tissue by crossing various anatomical and biological structures such as the blood-brain barrier, bronchioles in the respiratory system and tight junctions in the skin.

iii. Having the size of nanoparticles allows them to accumulate in areas with weak vascularity.
iv. Specific ligands can be targeted by binding.
v. They can be produced in large quantities, easily and reproducibly.
vi. They can protect the active substance in them from inactivation in the biological environment and undesirable side effects are not observed.

Drug delivery systems are divided into various classes as micelles, dendrimers, liposomes, nanoparticles and carbon nanotubes (Tanbour et. al., 2016). Nanocarriers, when the implanted systems reach the target area, uptake in organs, tissues and cells increases. These structures use active and passive targeting strategies to deliver the active substance to the targeted cells. The use of nanocarriers in drug delivery systems provides many advantages. For example, it is preferred in the release of cancer drugs because it reduces the toxic effect of drugs and prevents multi-drug resistance. The results obtained from the studies carried out so far are that treatment alternatives with higher selectivity have emerged thanks to the targeting of cancer drug-loaded nanocarriers (Zhou et. al., 2013). Thanks to this selective targeting, unwanted side effects of drugs are reduced and the most appropriate therapeutic response is obtained.

2. 1. Features Drug Required by Drug Delivery Systems

If we summarize the features that drug delivery systems should have, in items (Kolate et al.,2014); Must not interact with the active substance they carry, must be inert,

i. It should be compatible with the body, it should be degradable in the body, it should not be toxic,
ii. It should be able to carry the active substance in the required time until it reaches the targeted area,
iii. It must be durable in physiological conditions,
iv. It should be pharmaceutically stable,
v. It should be able to carry the required amounts of active substances that are dissolved in both water and oil.
vi. Since they are generally used parenterally, they should be suitable for sterilization.

2. 2. Implantable Drug Carrier Systems

Drug delivery systems, by carrying drugs or radiocontrast agents, ensure safe, controlled and effective delivery of diagnostic imaging and/or therapeutic (theranostic) materials to the target organ or tissue. The most important studies in the field of biopharmaceuticals in recent years are colloidal drug carrier systems and they exist in two forms as semi-solid and solid. When colloidal delivery systems are used, the amount of drug required for treatment is lower than the free drug (Pawar et. al., 2012). Therefore, side and toxic effects of drugs are reduced. Although the preparation technology of colloidal carrier systems is expensive, the reduction of side and toxic effects reduces the cost.

The nanoparticle system consists of the carrier portion and the drug loaded on it. The carrier portion is prepared from synthetic polymers or natural macromolecules (protein, cellulose, etc.). If the system is to be used for diagnostic purposes only, it is not expected to decompose under physiological conditions. However, disintegration is required for those used for treatment. It is expected to be broken down by lysosomal enzymes in the cell it enters by phagocytosis, to provide controlled release and to show its effect (Van Rooij et. al., 2015).

Nanoparticles, nanospheres, nanocapsules, liposomes that are the ancestors of drug delivery systems, niosomes polymeric systems, dendrimers, colloid gold, nano-sized semiconductor crystal structures (quantum dots-QDs), micelles, sphingosomes, microbubbles, microspheres and supermagnetic particles are some of the carrier systems (Wunderlich et. al., 2010). Among the different carrier systems, liposomes are the most remarkable and have the most suitable features for both diagnostic imaging and treatment (Silindir et. al., 2012).

2. 3. Vesicular systems

In cell biology, a vesicle is a relatively small intracellular sac consisting of a closed membrane that stores or transports substances. It is separated by at least one lipid bilayer that separates the vesicle from the cytosol. Drug delivery systems are divided into various classes as micelles, dendrimers, liposomes, nanoparticles and carbon nanotubes. Thanks to these systems, the active substance concentration in the blood is kept constant for a long time at the desired therapeutic level and the elimination of the active substance in the body is reduced (Kirthi et. al., 2011).

2. 3. 1. Liposomes

Liposomes are carrier systems between 30 nm – 1000 nm, containing phospholipids, resembling a cell structure, having hydrophilic and lipophilic parts, and amphiphilic (both oil and water-loving) (Nakayama et. al., 2015). It is the best model for biological membranes. Since it resembles cell structure, it can easily place active substances in the body. Thanks to these features, they are preferred in many areas as drug carriers from dermocosmetics to biotechnology. In terms of cosmetics and dermatology, liposomes have some features (Allen and Cullis, 2013);

1. They have a membranous structure like the barrier layer of the skin. Since they are modeled like artificial cells, they do not have compatibility problems with the skin and cell mem branes in the body.
2. Its membranes easily integrate into the barrier layers of the skin without changing the physical structure.
3. Since they can carry the phosphatidylcholine group to the lower layers of the epidermis, they are effective in the regeneration of the skin.

When phospholipids are added to water, their hydrophilic regions move towards the water, while their hydrophobic regions move away from the water and take the form of vesicles. Hydrophobic interactions between phospholipid and water molecules and van der Waals interactions between phospholipid molecules provide the formation of the bilayer liposome structure. The methods used to prepare liposomes generally involve 3 basic steps (Anwekar et al., 2011):

i. Drying of lipids dissolved in organic solvent
ii. Formation of liposomes in aqueous medium
iii. Analysis of the resulting liposomes

With the understanding that intravenously administered liposomes are digested by the phagocytic system, liposome-mediated drug delivery to macrophages has been achieved. In this way, liposomes have played a role in the development of treatments against parasites in phagocytic cells. Liposomes can also be used for grafting. While preparing the liposome vaccine, water-soluble substances are added to the aqueous region inside the liposome, while lipid-soluble substances are mixed into the lipid layer during vesicle formation (Değim, 2011). These liposomes are absorbed by many cells and release the substances they contain when they enter the cell. These vaccines generally target macrophages and other phagocytic cells (Coelho et. al., 2010). After the liposomes are given to the body by adding the appropriate antigen, they release the antigen in them as soon as they enter the cell. Cells that encounter the antigen produce an immune response.

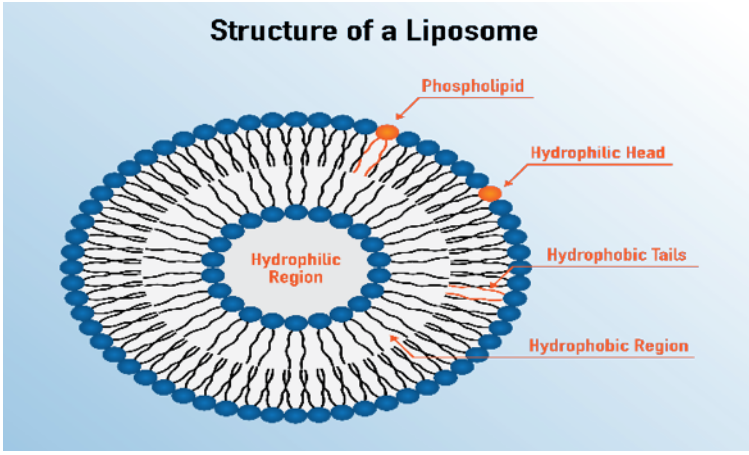

Figure 1. Structure of lipozome (Taghavi et. al., 2013).

2. 3. 2. Niosome

The first use of niosome technology in cosmetics was studied in Loreal's patented products in the 1970s and 1980s. It is expressed as proniosome when introducing the product. The missing point of

this design was that sensitive extra processing was required before using it in the cream, since some steps were skipped in the synthesis of the niosomes (Ge et al., 2019). However, in the new generation niosomes, when it is applied to the skin and interacts with the skin, its activation is provided on its own. The structure called niosome consists of spherical (vesicular) structures synthesized in small sizes. These spheres can also be called smart spheres. Because it is designed to find the damaged area by crossing the skin barriers between the thick layers of your skin.

2. 3. 3. Erythrocyte

The erythrocyte membrane is semi-permeable. It is made up of cholesterol and phospholipids. As a result of the researches, it has been found that cholesterol is effective in the form of erythrocyte. Again, in the membrane structure, there are proteins that form the skeleton of the membrane. Cell organelles such as the endoplasmic reticulum and lysosome in the erythrocyte are also present in the cell at a certain concentration to provide the erythrocyte flexibility. All these structures need to be protected from damage during targeting operations (Dong, 2018). Depending on the active ingredient loading method used, minor changes in the biochemical structure of erythrocytes, such as removal of some sialic acid residues from cell proteins from the cell surface, separation of glycoproteins, increased membrane stiffness, oxidation of sulfhydryl groups in the membrane, can greatly change the general circulation time and biological behavior of these cells in the organism (Xia et. al., 2019).

Loading of active substance into erythrocytes can be done by three methods. These (Luk et al., 2016):

i. Hypoosmotic lysis method
    a. Dilution
    b. Diluting first by swelling,
    c. Dialysis
    d. isoionic osmotic lysis
ii. Electric shock method
iii. Endocytosis method

2. 4. Solid Particulate Systems

Solid lipid nanoparticles are one of the drug delivery systems developed as an alternative to liposome, emulsion and polymeric nanoparticles. The advantage of solid fat over oil in emulsion is that it can provide controlled release. In addition, the stability of the system is high due to the solid oil. The size of solid lipid nanoparticles ranges from 10 to 1000 nm. The substances in their structures are biocompatible and biodegradable (Cancer Research, 2018). In short, solid lipid nanoparticles have great potential to be used as a drug delivery system and to be targeted to the desired region. In recent years, new generation solid lipid nanoparticles have been developed and they are called nano lipid carrier systems (NLC) and lipid-drug conjugates (LDC). These systems consist of a mixture of solid and liquid lipids. In addition to

the properties of solid lipid nanoparticles, they have higher drug loading capacity (Lang et al., 2012). They can be produced in different ways.

2. 4. 1. Microspheres

Microspheres are drug delivery systems in which the active ingredient is dispersed at the molecular level or as macroscopic particles, with a diameter distribution ranging from a few μm to mm, and providing controlled release in the form of solid, spherical particles (Prajapati et al., 2015). It can be used to target the active substance to the site of action by injection into the bloodstream. Thus, it is aimed to reduce the dose of the active substance and to reduce its side effects. Many different materials are used in the preparation of microspheres (non-magnetic).

There are several techniques in which it is used (Schirrmacher, 2019):

1) Solvent Evaporation Method
2) Protein Gelation Methods
    a. Denaturation By Heat
    b. Chemically Crosslinking
    c. Desolvation
3) Emulsion Polymerization Methods
    a. Starch Microspheres Cross-Linked With Epiclohydrin
    b. Cross-Linked Polyacryl Microspheres.

2. 5. Nanoparticles

Nanoparticles are solid colloidal particles ranging in size from 10 to 1000 nm, which release the dissolved, trapped or adsorbed active substance in a controlled manner.

Nanoparticles exist in two forms

c. nanospheres and
d. nanocapsules

Properties expected from nanoparticles (McNamara and Tofail, 2017);

e. Controlled release of the active substance
f. Collecting the active substance in the area where they are expected to affect
g. No stability problems
h. Decomposition of the carrier in the physiological environment and non-toxicity of the degradation products
i. Ability to be sterilized

2. 5. 1. Polymeric Micelles

Polymeric micelles are formed from amphiphilic polymers. Amphiphilic polymers are copolymers containing hydrophilic and hydrophobic units. Polymeric micelles are spherical particles with a size of 100 nm and less formed in the core of hydrophobic blocks and the surrounding hydrophilic corona (Nicolai et. al., 2010). The amphiphilic unimers that make up the micelles exist as polymer chains alone under a certain temperature and concentration. The self-organizing micelle formation of these unimers occurs when entropically above a certain temperature and concentration in aqueous solutions. Theoretically, the formation of micelles occurs with the reduction of free energy (Carpenter et. al., 2012)

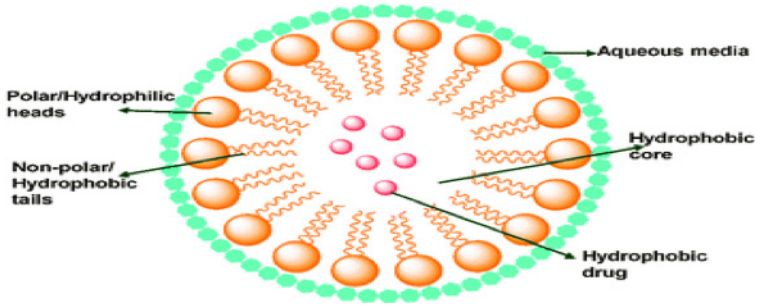

Figure 2. Structure of micelle which polar hydrophilic heads ,non polar hydrophobic talls,aqueous media,hydrophobic core. (Kurtar, 2011)

2. 5. 2. Dendrimers

Dendritic structures are one of the most common structures on earth. In the biological world, the branches and roots of trees, the vascular systems and neurons of animals and plants are the best examples of branched structures. However, it is possible to see this structure in inanimate systems (for example, snow crystals) as well as in living systems (Boas et. al., 2006). In biological systems, these dendritic structures can be in meters like trees, centimeters/millimeters like fungi, or microns like neurons. However, it is still debated whether these structures are evolutionary structures optimized to provide a large interface for energy (Thompson, 2006). Dendrimer consists of a nucleus, branching units around the nucleus, and surface groups, also called functional groups. The diversity of dendrimers is provided by functional groups. Branching units, on the other hand, ensure the repetitive growth of dendrimers (Newcome et. al., 1985). The degree of polymerization of dendrimers is indicated by the concept of generation number, which expresses the repetition cycle.

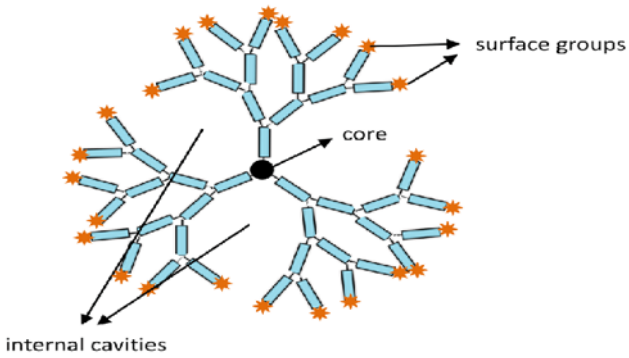

Figure 3. Dendrimer core (Taghavi et. al., 2013).

Having too many chain ends in dendrimers gives dendrimers high solubility and miscibility. The higher the chain ends, the higher the activity. The solubility of dendrimers is directly related to the groups on the surface. Dendrimers ending in hydrophilic groups dissolve well in polar solvents, while dendrimers ending in hydrophobic groups dissolve in nonpolar solvents (Tomalia et al., 1985). Dendrimers have many advantages because they have a spherical structure and have an internal cavity in the middle. The most important of these is that molecules can be trapped in this gap (Martinho et al., 2014). In this way, both the protection of the active substance is ensured and the controlled release of the active substance is achieved. Thanks to their multi-branched structure, groups that provide targeting and structures that increase solubility can be added to dendrimers at the same time. Thanks to the added groups, cytotoxicity can be reduced and biocompatible dendrimers can be obtained. However, it can be ensured that they cross the epithelial barrier. It is possible to add fluorescent substances to the dendrimer structure by conjugation with dendrimers (Gillies and Frechet, 2005).

i. Dendrimers terminate with many functional groups. Various groups can be attached to these functional groups for targeting to a particular part of the body

ii. Dendrimers may show greater permeability and retention to tumor cells than small molecules. Therefore, they can be used in tumor targeting

iii. Another advantage of dendrimers is that they can be synthesized or designed for specific applications. They are ideal drug delivery systems due to their flexible topology, features and dimensions. However, the particle size of dendrimers is quite close to some biological polymers such as DNA (Wei et. al., 2009)

2. 5. 3. Microsponges

Microsponges are patented, microscopic, polymer-based, porous, microspherical systems that can be applied mostly topically, but oral use has also been mentioned in recent studies (Stephen et al.,

2021). Particle size, pore diameter, pore volume and viscoelastic properties of microsponges may vary depending on the properties of the active substance and the desired release time. Pharmaceutical preparations such as creams, soaps, lotions, powders, tablets and capsules can be prepared after the active ingredients are confined to microsponges. Especially when applied to the skin, they cannot pass through the stratum corneum due to their large particle size. They can stay on the skin surface and release the active substance in a controlled manner. Microsponges, which are biologically inert, do not cause toxicity, allergic reaction and irritation (Pan et al., 2009). If we compare microsponges with other microencapsulation products, liposomes and microcapsules, we see that they are more advantageous systems. Since microcapsules control the exit of the active substance with the capsule wall, all of the active substance in the content can be released uncontrollably when this wall is damaged, whereas in microsponge systems, the active substance is released through the pores of the polymeric structure and the system skeleton remains intact (Sobel et al., 2014).

3. NANOPARTICLES AS DRUG DELIVERY SYSTEMS

Healthy cells in living things have the ability to divide in a controlled manner. Thanks to this feature, dead cells are replaced by new ones. With its divisibility, it is possible to repair injured tissues. These systems, which operate smoothly, can be disrupted when under the influence of any disease. As a result of the disease, the need for repair occurs in organs, tissues and cells. In this case, mostly chemical treatment methods are used. As a result of the use of chemical treatment method, healthy cells are also exposed to chemical effects (Wei et. al., 2015). To prevent this, nanocarrier systems have been developed today. Thanks to these structures, damage to healthy organs and cells is prevented and the drug concentration in the cells is increased. Nanocarriers used today make it possible to detect diseases as soon as possible, thanks to a number of diagnostic and diagnostic systems. However, there is a risk of infection to the patient during the application of nanosystems (Rao et. al., 2020). In addition, the patient may feel discomfort due to the procedure performed with the needle. In these systems, the correct symptoms cannot be obtained until the disease reaches a certain level. For this reason, developments in nanotechnology and nanomedicine, which have attracted attention in recent years, have come to the fore. Thanks to research, advances have been made in early diagnosis and treatment in many health fields, thus opening new horizons. An important part of the studies in the field of nanomedicine is to develop nanomaterials with high sensitivity and tissue targeting properties that allow early diagnosis (Nyström and Fadeel, 2012). Nanomedicine is defined as early detection of pathological processes, taking precautions and using them in targeted treatments, and making use of the physical, chemical, electrical, optical and biological properties of organic or synthesized nano-sized materials. Passive and active targeting methods have been developed to ensure that nanocarrier systems reach their target exactly (Attia et. al., 2019). The dendrimers used for this purpose have high solubility and miscibility because there are too many chain ends. The higher the chain ends, the higher the activity rate. Dendrimer solubility is directly related to surface groups. Dendrimers ending in hydrophilic groups dissolve well in polar solvents, while dendrimers ending in hydrophobic groups dissolve better in nonpolar solvents.

3. 1. Advantages of Nanocarriers in Drug Transport

There are some advantages of using a drug delivery system in nanoparticles (Mou et al., 2015). It is possible to define them as follows (Batrakova and Kim, 2015; Su et. al., 2018; Van Rooij et. al., 2015);

a. A nanocarrier can carry both the active substance and the imager at the same time.
b. It can bind to more than one active substance and targeting molecule on a nanocarrier.
c. Thanks to theronostic structures, the release and distribution of the drug can be followed, and the effectiveness of the treatment can be monitored.
d. As a result of increasing the bioavailability of the drug, an effective drug treatment is provided.
e. Targeting is easy due to their nano size.
f. Since it is in nanoparticle size, it easily passes into the veins and mixes into the circulation.
g. As a result of the preparation of nanoparticle formulations, their solubility increases. It increases the absorption of the particle and, accordingly, the bioavailability.
h. Nanoparticles can be targeted to the sick site or to the designated cell, tissue or organ.
i. Drugs, imaging agents, targeting molecules, magnetic materials, temperature and pH sensitive substances can be attached to nanocarriers.
j. Thanks to the polyethylene glycol or polyoxyethylene molecule bonding, it can remain in circulation for a long time.
k. It is suitable for making surface modifications.
l. Providing an effective drug therapy by increasing the bioavailability of the drug. Thus, they are developed to be used in the diagnosis, treatment and monitoring of diseases.
m. It provides a more reliable treatment opportunity when its side effects are reduced.

4. CONSLUSION

In this study, when the chemical structure of nanoparticles is examined, they are formed by adding various molecules, especially phospholipids such as phosphatidylcholine, phosphotidylethanolamine, phosphotidylserine and phosphotidylglycerol, and main lipids such as cholesterol, at different rates. Clinical studies on the efficacy ,these double membrane particles being tested the potential to carry hydrophobic and hydrophilic drugs separately or together and deliver them to the target cell due to their polar and nonpolar properties.The nanoparticles mentioned in this study are; nanospheres, nanocapsules, liposomes, which are the ancestors of drug delivery systems, niosomes polymeric systems, dendrimers, colloid gold, nano-sized semiconductor crystal structures (quantum dots-QDs), micelles, sphingosomes, microbubbles, microspheres and supermagnetic particles are some of the carrier systems. Thus, the accumulation of the drug in healthy tissues decreases, allowing the drug levels in the tumor tissue to increase. The aim of this is to summarize how far nanotechnology has progressed and the latest developments. how to increase bioavailability with nanoparticles is discussed with their advantages.

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