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Drug delivery and Nano carriers-A Review

Ahmed Al-Hussin, Raghda Alsayed, Emad Yousif

Department of Chemistry, College of Science, Al-Nahrain University, Baghdad, Iraq

Abstract

Recently, a significant number of researches have been conducted regarding drug delivery systems. This biomedical felid is one of the most potential fields that could be a promising area to heal illness without side effect. This review will try to cover drug deliver definition and preparation of drug delivery chemicals. Drug delivery nanotechnology systems will be the focus of this research including preparation, types and Nano carriers. This is due to the importance of the use of nanotechnology mainly in various science fields and particularly in medical treatment.

Keywords: Drug delivery, Nano carriers, Nanotechnology, pharmaceutical, Drug delivery

1. Introduction

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect ,It may involve scientific site-targeting within the body, or it might involve facilitating systemic pharmacokinetics; in any case, it is typically concerned with both quantity and duration of drug presence. Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Drug release is from: diffusion, degradation, swelling, and affinity-based mechanisms [1]. Delivering therapeutic compound to the target site is a major problem in treatment of many diseases. A conventional application of drugs is characterized by limited effectiveness, poor bio distribution, and lack of selectivity [2]. These limitations and drawbacks can be overcome by controlling drug delivery. In controlled drug delivery systems (DDS) the drug is transported to the place of action, thus, its influence on vital tissues and undesirable side effects can be minimized. In addition, DDS protects the drug from rapid degradation or clearance and enhances drug concentration in target tissues; therefore, lower doses of drug are required [2]. This modern form of therapy is especially important when there is a discrepancy between a dose and concentration of a drug and its therapeutic results or toxic effects.

The goal of drug formulation and delivery is to administer a drug at a therapeutic concentration to a particular site of action for a specified period of time. The design of the final formulated product for drug delivery depends upon several factors:

1. First, the drug must be administered using a narrow set of parameters that are defined by the therapeutic action of the drug. These parameters include the site of action (either targeted to a specific region of the body or systemic), the concentration of the drug at the time of administration, the amount of time the drug must remain at a therapeutic concentration, and the initial release rate of the drug for oral/controlled release systems.
2. The drug must remain physically and chemically stable in the formulation for at least 2 years.
3. The choice of delivery method must reflect the preferred administration route for the drug, such as oral, parenteral, or transdermal.

The most important goal in the delivery of a drug is to bring the drug concentration to a specific level and maintain it at that level for a specified period of time. Stability and solubility are two key physicochemical properties that must be considered when designing a successful drug formulation.

The physicochemical properties of the drug both in solution and in the solid state play a critical role in drug formulation. The solid-state form of the drug is often preferred, because it is often more chemically stable, easier to process, and more convenient to administer than liquid formulations. However, if the drug is in the solid state, it must dissolve before it can be

Corresponding author: Emad Yousif
Email Id: emad_yousif@hotmail.com

therapeutically active, and once it is in solution, it must be both sufficiently soluble and chemically stable [3].

There are several parameters that affect the solubility and chemical stability of a drug.

A. in solution:
   1. PH of the solution.
   2. Buffer concentration /composition.
   3. Ionic strength.
   4. Hydrophobic and hydrophilic natural.

B. in the solid state:
   1. Melting point.
   2. Heat of fusion using differential scanning calorimetric.
   3. Loss of solvent upon heating using thermo gravimetric analysis.
   4. A characterization of the molecular state of the solid using diffraction and spectroscopic techniques.

For many drugs, the therapeutic nature of the drug dictates the method of administration.

For example, oral drug delivery may be the most logical choice for gastrointestinal diseases. If drug release is systemic, then the choice of method often relies on the physicochemical and therapeutic properties of the drug. Transdermal drug delivery, although having the advantage of being non-invasive, has several criteria that must be met by the drug in order to be delivered properly, such as high potency, ready permeability through the stratum corneum, and nonirritation [2].

2. Nanotechnology systems

2.1 Nanoparticles

Nanoparticle drug delivery systems are nanometer carriers used to deliver drugs or biomolecules. Generally, nanometer carriers also comprise sub-micron particles with size below 1000 nm and with various morphologies, including Nano spheres, Nano capsules, Nano- micelles, Nano liposomes, and Nano drugs, etc. [4].

2.1.1 Properties of nanoparticles

Nanoparticle drug delivery systems have outstanding advantages, some of which include [5]:

1. They can pass through the smallest capillary vessels because of their ultra-tiny volume and avoid rapid clearance by phagocytes so that their duration in blood stream is greatly prolonged.
2. They can penetrate cells and tissue gap to arrive at target organs such as liver, spleen, lung, spinal cord and lymph.
3. They could show controlled- release properties due to the biodegradability, pH, ion and/or temperature sensibility of materials.
4. They can improve the utility of drugs and reduce toxic side effects. As drug delivery system.

Nanoparticles can entrap drugs or biomolecules into their interior structures and/or absorb drugs or biomolecules onto their exterior surfaces. Presently, nanoparticles have been widely used to deliver drugs, polypeptides, proteins, vaccines, nucleic acids, genes and so on. Over the years, nanoparticle drug delivery systems have shown huge potential in biological, medical and pharmaceutical applications [6].

2.1.2 Preparation of nanoparticles

2.1.2.1 Nano suspensions

Nano suspension refers to production of sub-micron-sized particles by subjecting the combination of drug and a suitable emulsifier to the process of milling or high-pressure homogenization. Nano suspension formulations can be used to improve the solubility of poorly soluble drugs. A large number of new drug candidates emerging from drug discovery programs are water insoluble, and therefore poorly bioavailable, leading to abandoned development efforts. These can now be rescued by formulating them into crystalline nan suspensions. Techniques such as media milling and high-pressure homogenization have been used commercially for producing Nano suspensions.

The unique features of Nano suspensions have enabled their use in various dosage forms, including specialized delivery systems such as mucoadhesive hydrogels. Nano suspensions can be delivered by parenteral, per- oral, ocular, and pulmonary routes [7].

A typical procedure for preparing Nano suspension involves, preparing an aqueous suspension of drug in surfactant solution, this is then passed through a high pressure of typically 1500 bar at 3–20 homogenization cycles. The suspension is then passed through a small gap in the homogenizer of typical width 25 mm at 1500 bar. Due to build up cavitation forces that are created drug particles are broken down from micro to nanoparticles [8].

It has been reported that, Nano suspension particles in most cases have an average size ranging from 40 to 500 nm with a small (0.1%) proportion of particles larger than 5 mm [4].

2.1.2.2 Polymeric nanoparticles

Polymeric nanoparticles can be identified as submicronic (size< 1μm) colloidal carriers. Compared to other colloidal carriers polymeric Nanoparticles hold significant promise for the advancement of treating diseases and disorders. They have attractive physicochemical properties such as size, surface potential, and hydrophilic-hydrophobic balance and for this reason they have been recognized as potential drug carriers for bioactive ingredients such as anticancer drugs, vaccines, oligonucleotides, peptides, etc.

Although various biodegradable nanoparticles of natural polymers such as starch, chitosan, liposomes etc., are largely in use as drug carriers in con- trolled Drug-delivery technology [9]. Nanoparticles can be prepared from polymerization of monomers or from preformed polymer with the possibility of performing many chemical modifications. The polymerization reaction in these systems generally occurs in two steps: a

nucleation phase followed by a growth phase and the process can be carried out in two ways either as emulsion polymerization or as interfacial polymerization. When nanoparticle preparation involves polymerization, it is undesirable to have residual monomers and initiators in the final nanoparticle formulation. A critical step of the process is the purification and removal of residual monomers. It is also very important to separate free drugs from the drug loaded nanoparticle suspension. A potential challenge for polymeric nanoparticles is associated with residues from organic solvents and polymer toxicity. If the drug to be incorporated in nanoparticles is hydrophobic, the drug is dissolved or dispersed into the polymer solution.

The polymer solution is then added to an aqueous solution, followed by high-speed homogenization or sonication to form an oil-in-water emulsion. Nanoparticle preparation is usually facilitated and stabilized with the aid of an emulsifier or stabilizer. If the drug to be incorporated in nanoparticles is hydrophilic, the drug is added to the aqueous phase and entrapped into nanoparticles through a double emulsification method to form water-in-oilin- water emulsion [8]. Residual organic solvent can be removed by evaporation or a decreased pressure or under a vacuum environment with or without the aid of inert gas flow. Solid nanoparticles are cured from the suspension by centrifugation, filtration or freeze drying.

In general, the controlling factors in the nanoparticle formulation process, which are adjustable for an ideal design, are the polymer type and its molecular weight, the copolymer blend ratio, the type of organic solvent, the drug loading level, the emulsifier/stabilizer and oil–water phase ratio, the mechanical strength of mixing, the temperature and pH.

3. Polymers for gene delivery

The delivery of nucleic acid into cells in vitro and in vivo is a critical technique for the study of genes and development of potential gene therapies. Current nucleic acid delivery falls into two major categories, viral and nonviral. In nonviral gene delivery, cationic lipids or polymers are used to both protect nucleic acids from degradation and facilitate entry into the target cells. The resulting complexes self-assemble via electrostatic interactions to form stable aggregates. Recent reports have discussed the promise of lipid-DNA (lipoplex) and polycation-DNA complexes (polyplexes) as potential therapeutics, including recent efforts to incorporate bio responsive chemistries for increased effectiveness. Successful gene transfer requires sufficient stability of DNA during the extracellular delivery phase, A molecular architecture that achieves all the requirements will most likely consist of a virus like layered structure incorporating several components. Though nonviral gene vectors can be efficient in vitro and in vivo, their uncontrolled and often undefined interactions under physiological conditions still represent a major obstacle to their use in gene therapy. In particular, it has been shown that nonviral gene vectors or their constituents interact strongly with negatively charged serum proteins and other blood components. Such opsonization alters the physicochemical characteristics of vectors, may interfere with vector targeting, and is of concern if vectors are to be applied in humans [10].

Consequently, one major objective in nonviral vector development is to devise vectors that are inert in the in vivo environment during the delivery phase. Poly (ethylene glycol) (PEG) has often been used to confer to these drug carriers the desired stability during the extracellular delivery phase. The incorporation of PEG to lipo- or polyplexes has been proven effective in reducing undesired effects such as immune response, unspecific interactions, and degradation. PEGylating can be implemented by using PEGylated components in the initial complex formation. Alternatively, PEG shielding can be applied to preformed complexes in a secondary processing step by using either electrostatic self-assembly or chemical grafting. While PEGylating is a necessity to improve extracellular stability and circulation half-life, it often decreases the transfection efficiency due to reduced specificity and inhibited cell association and uptake. Incorporating receptor targeting or using bio responsive linkers to release PEG have proven useful to overcome these intracellular barriers to efficient delivery [11].

Certain issues must be addressed in the development of DNA particles with cationic polymers. These are:

(i) Potential toxicity of cationic polymers especially when administered at high concentrations.
(ii) Instability of particles on storage.
(iii) Instability of DNA particle size and particle size distribution leading to undesirable particle aggregation.
(iv) Poor transfection efficiency.
(v) Poor stability in blood circulation.
(vi) High cost of scaling up the process to achieve reproducible product quality.

4. Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) are particles made from solid lipids with mean diameters ranging between 50–1000nm and represent an alternative to polymeric particulate carriers. The main advantage offered by lipid carriers in drug delivery is the use of physiological lipids or lipid molecules with a history of safe use in human medicine, which can decrease the danger of acute and chronic toxicity [12].

Up until today, only a few methods are described in the literature for SLN preparation, including high pressure hot homogenization and cold homogenization techniques micro emulsion-based preparation and solvent emulsification/evaporation method. Particularly, the emulsification/evaporation method concerns the preparation of nanoparticles dispersions from O/W emulsions: the lipophilic material is dissolved in a water-immiscible organic solvent that is emulsified in an aqueous phase [12]. Upon evaporation of the solvent, nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. Depending on the composition and the concentration of the lipid in the organic

phase, very low particle sizes can be obtained, ranging from 30–100nm, but a clear disadvantage of this method is the use of organic solvents, whose toxicity cannot always be neglected. Recently, an emulsification–diffusion technique was developed using non-toxic and physiologically compatible solvents and monoglycerides or waxes as components of the disperse phase of oil-in-water emulsions obtained at 50 oC [13]. According to the moderate water solubility of the solvents employed, the dilution of the emulsions determined the diffusion of the organic solvent from the droplets to the continuous phase with the consequent instant solidification of lipophilic material. The emulsion compositions and process parameters used were the results of a formulated study aimed to develop optimized non-sphere formulations, whose mean sizes were below 200nm.

Of recent, SLN has become a popular drug delivery system for ophthalmic application. It is gaining prominence as promising approach to improve the poor ocular bioavailability of biomolecules. In particular, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), regarded as the first and second generation of lipid nanoparticles are currently being applied [14].

NLC consist of a mixture of especially different solid and liquid lipids molecules, resulting in a structure with more imperfections in crystal lattice to accommodate drugs [15].

As drug delivery devices, NLC show great promise for the eye, due to their better biocompatibility, modified drug release kinetics, reduction of drug leakage during storage, avoidance of organic solvents during production process and feasibility of large scale production [16].

Solid lipid nanoparticles are obtained upon lipid recrystallization at room temperature. Some of the process variables that will affect the particle size of nanoparticles as well as drug loading are:

i. The type of homogenization technique.
ii. Speed of homogenization.
iii. Rate of cooling in hot homogenization.

5. Nano drug delivery carriers

5.1 Liposomes

Liposomes have been the first to be investigated as drug carriers. Liposomes are small spherical vesicles in which one or more aqueous compartments are completely enclosed by molecules that have hydrophilic and hydrophobic functionality. Liposomes vary with composition, size, surface charge and method of preparation. They can be single or in multiple bilayers. Those containing one bilayer membrane are termed small unilamellar vesicles or large unilamellar vesicles based on their sizes [17].

Drugs associated with liposomes have markedly altered pharmacokinetic properties compared to free drugs in solution. Liposomes are also effective in reducing systemic toxicity and preventing early degradation of the encapsulated drug after administration.

Liposomes can also be conjugated to antibodies or ligands to in order enhance target-specificity.

A drug is incorporated in liposomes by the encapsulation process (Fig. 1).The release of a drug from liposomes depends on the liposome composition, pH, osmotic gradient, and the surrounding environment [18]. Additionally, a prolonged residence time increases the duration of action of such particles, but decreases their number. Interactions of liposomes with cells can be realized by: adsorption, fusion, endocytosis, and lipid transfer. There are a lot of drug examples in liposomal formulations, such as anticancer drugs [18], neurotransmitters (serotonin) [19], antibiotics [20], anti-inflammatory [21], and ant rheumatic drugs [22].

Modified liposomes are an interesting type of such lipid structures. The multifunctional liposomes, containing the specific proteins, antigens, or other biological substances, can be used to design drugs which act selectively on a particular tissue. It is a promising approach for targeted delivery of therapeutics [23].

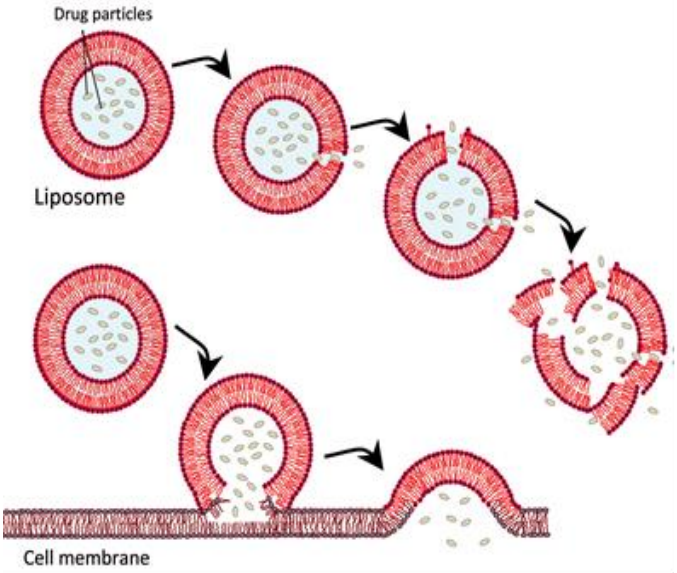

Fig1. Drug delivery by liposomes [24].

5.2 Dendrimer Nano carriers

Dendrimers are unique polymers with well-defined size and structure. Dendritic architecture is one of the most popular structures observed throughout all biological systems. Some of the examples of nanometric molecules possessing dendritic structure include: glycogen, amylopectin, and proteoglycans [24].

In the structure of dendrimer, in contrast to the linear polymer, the following elements can be distinguished: a core, dendrons, and surface active groups. The core is a single atom or molecule,

Selection of a core, type of a monomer and surface functional groups determine the usability of dendrimers in medical applications. Cytotoxicity of dendrimers and their so-called polyvalence is particularly relevant for biomedical purposes.

Dendrimers cytotoxicity depends on the core material and is strongly influenced by the nature of the dendrimers surface. For example, changing the surface amine groups into hydroxyl ones may result in lower levels of cytotoxicity.
There are a few ways of connecting biologically active compounds to dendrimers. The drug may be encapsulated in the internal structure of dendrimers [25] or it can be chemically attached or physically adsorbed on dendrimers surface [26]. The choice of the immobilization method depends on the drug properties. Encapsulation is used when drugs are labile, toxic, or poorly soluble. In turn, chemical attachment provides the possibility to control quantity of drugs on dendrimers surface by controlling the number of covalent bonds [27]. The selectivity of both methods may be enhanced by attaching on the dendrimers surface such targeting agents as folic acid [25, 27] or epidermal growth factor [28].
The surface of dendrimers provides an excellent platform for an attachment of specific ligands, which may include folic acid [27], antibodies [29], cyclic targeting peptides – arginine-glycine-aspartic acid (RGD) [30], the attached compounds can improve surface activity as well as the biological and physical properties of dendrimers.

5.3 Silica materials

Silica materials used in controlled drug delivery systems are classified as xerogels [31] and mesoporous silica nanoparticles (MSNs). They exhibit several advantages as carrier systems, including biocompatibility, highly porous framework and an ease in terms of functionalization [32]. Among inorganic nanoparticles, silica materials are the carriers which most often are chosen for biological purposes [33].
Silica xerogels possess an amorphous structure with high porosity and enormous surface area. A porous structure (shape and pore dimensions) depends on synthesis parameters [34] Sol-gel technique is frequently used to form silica xerogels loaded with drugs.
The best-known types of mesoporous silica nanomaterials are MCM-41 with a hexagonal arrangement of the mesopores and SBA-15 with a well-ordered hexagonal connected system of pores [35].
The mechanism of drug loading into mesoporous silica material is a chemical or physical adsorption [36]. By these processes, diverse types of drugs, including anticancer drugs [36, 37], antibiotics [38], and heart disease drugs [39], have been embedded into MNSs.
The MSNs properties make them an excellent material for various pharmaceutical and biomedical applications. The structure of MSNs enables the incorporation of both small [30] and large molecules [40], adsorption of DNA [41], and gene transfer [42]. This gives a possibility of using these nanomaterials in a combined therapy [37].
Silica nanoparticles have an impact on a generation of oxidative stress in cells *via* formation of reactive oxygen species, elevated production of malondialdehyde [43], decreasing glutathione level [44], and induction of antioxidant enzymes, including superoxide dismutase (SOD) and heme oxygenase 1 (OH-1) [45].

5.4 Carbon nanomaterials

Carbon Nano carriers used in DDS are differentiated into nanotubes (CNTs) and Nano horns (CNH).
CNTs are characterized by unique architecture formed by rolling of single (SWNCTs – single walled carbon nanotubes) or multi (MWCNTs – multi walled carbon nanotubes) layers of graphite with an enormous surface area and an excellent electronic and thermal conductivity [46]. Biocompatibility of nanotubes may be improved by chemical modification of their surface [47].
There are three ways of drug immobilization in carbon Nano carriers, which are: encapsulation of a drug in the carbon nanotube [48, 47], chemical adsorption on the surface or in the spaces between the nanotubes (by electrostatic, hydrophobic, *p-p* interactions and hydrogen bonds) [49, 50], and attachment of active agents to functionalized carbon nanotubes (f-CNTs). Encapsulation has the advantage over the two remaining methods as the drug is protected from degradation during its transport to the cells and is released only in specific conditions [51].
Drug release from carbon nanotubes can be electrically or chemically controlled. To prevent the unwanted release of the drug, the open ends of CNTs were sealed with polypyrrole (PPy) films [52]. Homing devices, i.e., folic acid [53] and epidermal growth factor [54], were attached to improve selectivity of such drug delivery systems.
The toxicity of carbon nanomaterials also depends on their unique well-defined geometric structure [55]. The toxic potential of carbon nanotubes can result from the high length to diameter ratio and the toxicity of the sole material, which is graphite. In addition, some impurities, such as residual metal and amorphous carbon, contribute to the level increase of reactive oxygen species (ROS), thus, inducing the oxidative stress in cells [56].

5.5 Magnetic nanoparticles

Magnetic nanoparticles exhibit a wide variety of attributes, which make them highly promising carriers for drug delivery. In particular, these are: easy handling with the aid of an external magnetic field, the possibility of using passive and active drug delivery strategies, and enhanced uptake by the target tissue resulting in effective treatment at the therapeutically optimal doses [57].
However, in most of the cases where magnetic Nano carriers have been used, difficulties in achieving these objectives appeared. It is most likely associated with inappropriate features of magnetic nanoparticles or inadequate magnet system. Magnetic nanoparticles, for instance, tend to aggregate into larger clusters losing the specific properties connected with their small dimensions and making physical handling difficult. In turn, magnetic force may not be strong enough to

overcome the force of blood flow and to accumulate magnetic drugs only at target site [58].

Therefore, designing magnetic drug delivery systems requires taking into consideration many factors, e.g., magnetic properties and size of particles, strength of magnetic field, drug loading capacity, the place of accessibility of target tissue, or the rate of blood flow [59].

Depending on magnetic properties, MNPs can be divided into pure metals (such as cobalt [60], nickel [61], manganese [62], and iron [63], their alloys and oxides. However, narrowing the area of MNPs applications only to biomedicine reduces significantly the choice of magnetic material. Such a restriction results from the lack of knowledge of the negative effects which the majority of these nanomaterial have on the human body.

Iron oxide nanoparticles, due to the favorable features they exhibit, are the only type of MNPs approved for clinical use by Food and Drug Administration.

These attributes are: facile single step synthesis by alkaline co-precipitation of Fe2+ and Fe3+ [64], chemical stability in physiological conditions [65] and possibility of chemical modification by coating the iron oxide cores with various shells, i.e., golden [66], polymeric [67], silane [68], or dendrimeric [69] (Fig. 2). In addition, iron oxides – magnetite and maghemite – occur naturally in human heart, spleen and liver [70]. This indicates their biocompatibility and non-toxicity at a physiological concentration. It is essential to estimate a safe upper limit of MNPs for biomedical use.

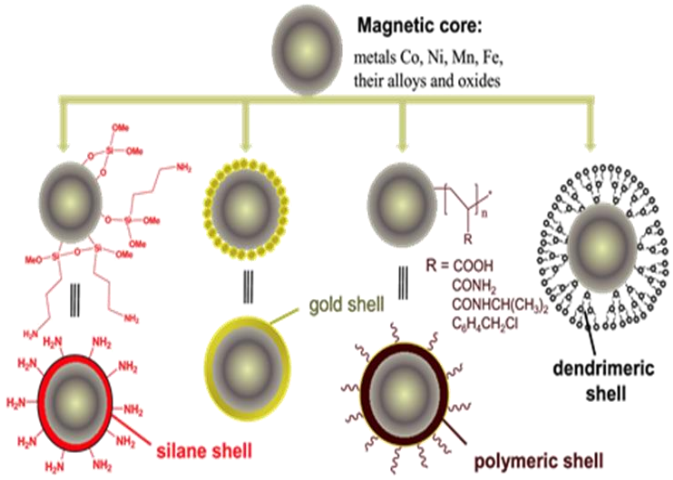

Fig.2. Magnetic nanoparticles with various shells [24]

Magnetic nanoparticles can be quickly opsonized by plasma proteins, recognized and subsequently removed from the bloodstream by macrophages of the reticuloendothelial system [71]. The greatest overall uptake of nanoparticles can be observed in liver and spleen [72].

6. Conclusion

The drug delivery cover a very broad area related to biomedical science chemistry and biology, this review was a try to present several aspects about this science including general definition, types and Nano carriers however, this area still need a lot work to be investigated.

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