7th International Conference on
Chemistry and Chemical Engineering
Tehran 2020

Various Types of Nanocarriers in Drug Delivery

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Abstract
In recent decades, significant research at the nano-technology field cause effective outcomes on different subfields and even daily life; since we can name the drug delivery field as a direct outcome of these recent achievements. Nanomaterials have many biological and medicinal applications in various fields such as drug delivery, tissue engineering, gene therapy, molecular imaging, etc. It is now possible to produce drug nanocarriers that can be utilized in a variety of innovative ways. Biodegradable polymeric nanoparticles, nanocapsules, nanospheres, fullerenes, nanotubes, nanorods, nanofibers, dendrimers, liposomes, liposphers, and micelles are some examples of drug delivery systems that are explained in this research.
Keywords: Drug delivery, Cancer treatment, Nanocarriers, Synthesis methods.

1. INTRODUCTION

Recently developed new cytotoxic drugs have not been efficient enough in tissue targeting. Using nanocarriers is the solution for conventional drugs which can solve this problem. Nanoparticles for drug delivery may be defined as submicron colloidal particles (10–1000 nm) that contain a therapeutic agent either dispersed in a polymer carrier matrix, encapsulated within a polymer shell, covalently attached or adsorbed to the particle surface, or encapsulated within a structure such as a liposome [1-4].
It is now possible to produce drug nanocarriers that can be utilized in a variety of innovative ways. The advantages of using nanocarriers for drug delivery applications result from their three main basic properties. First, nanocarriers, because of their small size, can penetrate through smaller capillaries, which could allow efficient drug accumulation at the target sites [4]. Second, the use of biodegradable materials for nanocarriers preparation can allow sustained drug release within the target site over a period of days or even weeks [5]. Third, the nanocarrier surface can be modified to alter the bio-distribution of drugs or can be conjugated to a ligand to achieve target-specific drug delivery [6]. Although a number of different materials have been investigated for formulating biodegradable nanocarriers.
So, utilization of this field in a new generation of medicines is more efficient in comparison with conventional ones due to accessing targeting tissues, and deep molecular targets, fewer side effects, and controlled drug release. As a result, several nanocarriers are suggested as drug delivery systems such as Biodegradable polymeric nanoparticles, fullerenes, nanotubes, nanorods, nanofibers, dendrimers, liposomes, liposphereres and micelles that were explained in next sections.

2. VARIOUS TYPES OF NANOPARTICLES IN DRUG DELIVERY

2.1. Biodegradable polymeric Nanoparticles

Polymeric Nanoparticles as therapeutic agents are excellent nanocarrier for delivery of a number of biomolecules, drugs, genes, and vaccines to the especial site. They can also be specifically designed for targeted drug delivery. There are two types of biodegradable nanoparticles depending on the preparation method: nanocapsules and nanospheres [7]. As illustrated in Figure 1 nanospheres have a monolithic-type structure (matrix) in which drugs are dispersed or adsorbed onto their surfaces. There are several methods to synthesis nanospheres such as Polymerization (Emulsification polymerization), Solvent Evaporation/ emulsion, Solvent displacement technique, Phase inversion temperature methods. However, nanocapsules exhibit a membrane-wall structure and drugs are entrapped in the core or adsorbed onto their exterior. Also,

they include high drug encapsulation efficiency due to optimized drug solubility in the core, low polymer content compared to other nanoparticulated systems such as nanospheres [8]. In general, there are six classical methods for the preparation of nanocapsules: nanoprecipitation, emulsion–diffusion, double emulsification, emulsion-coacervation, polymer-coating, layer-by-layer method.

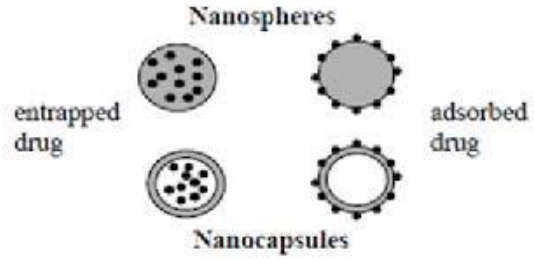

Figure 1. Various type of drug-loaded nanoparticles [7]

Polymeric NPs can be categorized into two groups based on their source: natural and synthetic in Table 1 you can find a comprehensive comparison between these two different polymeric NPs.

Table 1. Comparison of Natural and Synthetic polymers [9]

Natural Polymers		**Synthetic Polymers**	
Cellulose, starch, chitosan, carrageenan, alginates, xantham gum, gellan gum, pectins.		Polylactic acid (PLA), poly orthoesters, poly cyanoacrylates (PACA), poly anhydrides, polyacrylic acid, polyamides, polyethylene glycol, polyvinyl alcohol (PVA), poly isobuylcynoacrylates (PIBCA), polyethylene oxide (PEO), etc.	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
Less toxic Biocompatibility Biodegradable Easily available	1-The high degree of variability in natural materials derived from animal sources 2-Structurally more complex 3-The extraction process is very complicated and high cost	Biocompatibility	Toxic Non-degrable Synthetic process is very complicated and high cost

2.2. Nanocapsules

As previously mentioned, generally, nanoparticles are defined as solid colloidal particles that include both nanospheres and nanocapsules. They can be prepared by both polymerization methods and synthesis with preformed polymers. One of their fundamental characteristics is their size, which is generally taken to be around 5–10 nm with an upper size limit of ~1000 nm, although the range generally obtained is 100–500 nm. As asserted by different authors, nanoparticulated systems show promise as active vectors due to their capacity to release drugs; their subcellular size allows relatively higher intracellular uptake than other particulate systems; they can improve the stability of active substances and can be biocompatible with tissue and cells when synthesized from materials that are either biocompatible or biodegradable.

First of all the nanocapsules can be likened to vesicular systems in which a drug is confined in a cavity consisting of an inner liquid core surrounded by a polymeric membrane. However, seen from a general level, they can be defined as nano-vesicular systems that exhibit a typical core-shell structure in which the drug is confined to a reservoir or within a cavity surrounded by a polymer membrane or coating. The cavity can contain the active substance in liquid or solid form or as a molecular dispersion. Likewise, this reservoir can be lipophilic or hydrophobic according to the preparation method and raw materials used. Also, taking into account the operative limitations of preparation methods, nanocapsules can also carry the active substance on their surfaces or imbibed in the polymeric membrane [10].

Generally, there are six classical methods for the preparation of nanocapsules:

- nanoprecipitation
- emulsion–diffusion
- double emulsification
- emulsion-coacervation
- polymer-coating
- layer-by-layer

2.3. Nanospheres

Nanospheres have a homogeneous structure in the whole particle but nanocapsules exhibit a typical core-shell structure. The mean diameter of nanospheres ranges between 10-200 nm. Basically, the drug is dissolved, entrapped, encapsulated or attached to the matrix of these spherical polymers. In the matrix system of polymer, the drug is physically and uniformly dispersed. Nanospheres can be amorphous or crystalline in nature and also, they have the ability to protect the drug from enzymatic and chemical degradation. Nanospheres polymers have two main responsibility at the drug delivery systems: controlling the particle size and releasing of pharmacologically active agents to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.

At practical applications of nanospheres polymers at drug delivery systems there may be some advantages and disadvantages. Table 2 exhibits some major advantages and disadvantages of nanospheres:

Table 2. Advantages and disadvantages of nanosphere polymers at DDSs

Advantages of nanospheres
• Easily pass through the smallest capillary vessels due to their **ultra-tiny** volume • Avoiding the rapid clearance by phagocytes and prolongation of residence time in bloodstream • Eas**y penetration** to the cells and tissues gap in order to arrive at target organs eg. liver, spleen, lungs, spinal cord and lymph's • Having controlled release property • Site specific targeting by attaching the ligands to the surface of the spheres • Easily administration by various routes including oral, nasal, parenteral etc. • Toxicity degradation features
Disadvantages of nanospheres
• Having difficult physical handling in liquids and in dry form due to the smaller size and larger surface area • Having major limitations at drug loading and releasing due to the smaller size and larger surface area

There are various methods to produce nanospheres. The most common methods are:

- Polymerization (Emulsification polymerization)
- Solvent Evaporation.emulsion-coacervation
- Solvent displacement technique
- Phase inversion temperature methods

2.4. Fullerenes

Fullerenes have shown some of the greatest promises in physical manipulation and synthesis for optimal drug conjugation and transport [11]. Fullerenes are the only kind of carbon allotropes that can be solved into solvents at room temperature which has the shape of hollow spherical, ellipse or tube. These colloidal particles can be produced via a plasma arc between two electrodes in an inert media which results in carbon

ash that carries fullerene, after the cooling process the purified fullerene can be extracted. The C60 fullerene known as Buckyball (Figure 2), named in honor of Buckminster Fuller is one of the most famous fullerenes [12].

Figure 2. 3D structure of C60 [12]

2.5. Nanotubes

Carbon nanotubes (CNTs), first discovered by Iijima in 1991 [13], are cylindrical macromolecules with a maximum length of 20 cm that have shown high potential biological applications such as nanocarrier, DNA and protein biosensors, ion channel blockers, bio-separators and biocatalysts [14]. Generally, there are two groups of nanotubes: single-walled (SWNTs), which consist of one layer of cylinder graphene which illustrated in Figure 3 and multi-walled (MWNTs), which contain several concentric graphene sheets. Having high loading capacity for cargo molecules, ultra-high surface area, low toxicity, and unique electronic, mechanical and thermal properties make the CNTs as the best candidates to be used at drug delivery systems [15]. There have been reported many methods for synthesizing carbon nanotubes which include: self-assembly of precursor compounds, vapor deposition, and template synthesis.

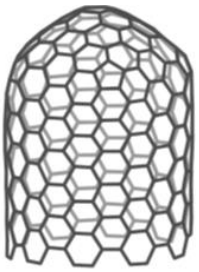

Figure 3. 3D structure of single-walled carbon nanotube with a fullerene-like cap [14]

2.6. Nanorods

Nanorods (NRs) have unique chemical, electrical, magnetic, and optical anisotropy which allows them to interact with cells, tissues, and biomolecules [16]. There are two common methods to produce nanorods: template synthesis [14] and chemical synthesis [16]. The template method is more beneficial in comparison with the chemical method because of two main reasons: producing more monodisperse NRs and controlling the capability of some properties such as aspect ratio [17]. Recently, gold nanoparticles (GNPs) have been extensively studied due to their unique optical properties that arise from the surface plasmon resonance phenomena (Figure 4). In particular, gold nanorods (GNRs) are one of the most studied nanoparticle systems because of the ease of their synthesis in aqueous media. Furthermore, the experimental protocols used in the synthesis of GNRs allow tuning their surface plasmon resonance into the biological window of the electromagnetic spectrum. Aside from high stability and low toxicity, other advantages of the gold nanorods are that the particles can be prepared easily and they can be attached readily to molecules of biological interest [18].

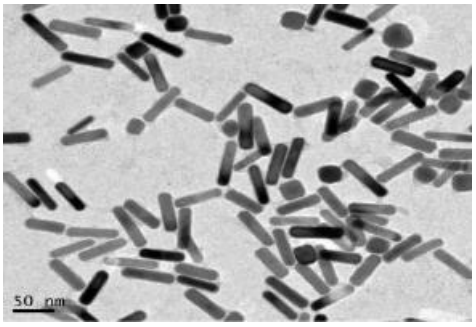

Figure 4. TEM image of gold nanorods (GNRs) [19].

2.7. Nanofibers

In the areas of tissue engineering and drug delivery, nanofibers have emerged as biocompatible, biodegradable scaffolds, and nanocarrier vehicles. The use of nanofibers as illustrated in Figure 5 in tissue restoration can potentially produce an efficient, compact organ with a rapid recovery process. This is because of the large surface area that polymer and protein-based nanofibers possess. These nanofibers have potential applications in the promotion of cell adhesion and growth, targeted drug delivery, tissue engineering, and filtration systems for toxic chemicals [20].
Nanofibers can be created from synthetic polymers, such as polylactides or polyamides, as well as natural polymers, such as collagen, silk, and celluloses. The polymers are spun into nanofibers using organic solvents like chloroform, ethanol, or formic acid, and water is used in the spinning solution.

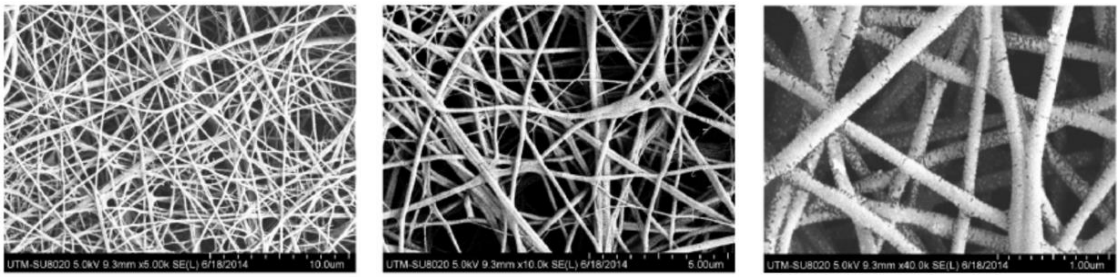

Figure 5. FESEM micrographs of 14% w/v PCL/GE-based nanofibers at different magnification [21]

2.8. Dendrimers

Dendrimers are generally referred to as hyperbranched polymers that have various biological applications such as multi-functional nanocarriers at drug delivery systems [22]. The term “dendrimer” is a combination of two Greek words dendron means “tree” and meros means “part”, which exactly reflects their branched structure [23]. In comparison with conventional polymers, dendrimers offer numerous benefits which include: low polydispersity, the exact number of surface end groups, tailor-made structure; controlled size and shape; ability to covalently attach or physically sequester drug molecules and ligands, multiple attachment sites, and efficient cellular uptake. Poly amido amine (PAMAM), poly propylene imine (PPI) and poly L-lysine (PLL) are some of the most frequently used dendrimers for drug delivery purposes [24]. As you can see in Figure 6, there are four well-defined components at the structure of a dendrimer which include: a central core, branching units, surface end groups and internal cavities [24].

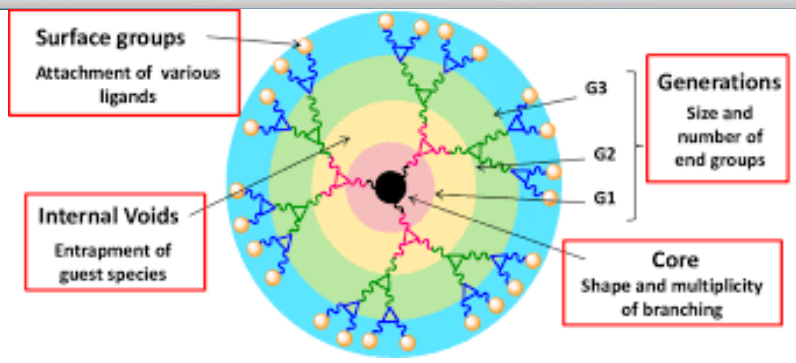

Figure 6. Structural components of dendrimers [24]

2.9. Liposomes

Liposomes are composite structures made of phospholipids and may contain small amounts of other molecules. The term "liposome" is a combination of two Greek words lipo means "fat" and soma means "body", which is due to its major component. Recently, there have been numerous pharmaceutical researches on liposomes such as vaccine adjuvants, artificial blood, gene therapy vehicles, etc. [25].
The most important capability of liposomes is their ability to encapsulate both hydrophilic and hydrophobic drugs. But it's some unignorable disadvantages including short circulation time in the body after par-enteral administration and the possibility of chemical degradation, aggregation, and fusion during storage. To enhancing the stability of liposomes both in vivo and in vitro, they are coated with some polymers such as chitosan, pectin, poly (N-isopropyl acrylamide (PNIPAAM)-co-methacrylic acid), and alginate via electrostatic deposition method [26].

2.10. Lipospheres

Lipospheres are fat-based encapsulation system, developed for parenteral and topical drug delivery of bioactive compounds. Lipospheres consist of water-dispersible solid microparticles, which have their diameter between 0.1 and 100 mm. These are composed of a solid hydrophobic fat core (triglycerides) stabilized by a layer of phospholipid molecules embedded in their surface. The internal core contains the bioactive compound, dissolved or dispersed in the solid fat matrix. Lipospheres have several advantages over other delivery systems such as emulsions, liposomes, and microspheres such as: better physical stability, low cost of ingredients, ease of preparation and scale-up, high dispersibility in an aqueous medium, high entrapment of hydrophobic drugs, controlled particle size, and extended-release of entrapped drug after a single injection, which can last from a few hours to several days [25].

2.11. Polymeric micelles

Polymeric micelles (PMs) have gained considerable attention as a multifunctional nanotechnology-based delivery system for poorly water-soluble drugs due to their ability to solubilize hydrophobic drugs in large amounts and achieve site-specific delivery. PMs are self-assembled core-shell nanostructures formed in an aqueous solution consisting of amphiphilic block copolymers (Figure 7). The formation of micelles in aqueous solution occurs when the concentration of the block copolymer increases above a certain concentration named the critical aggregation concentration (CAC) or critical micelle concentration (CMC). At the CAC or CMC, hydrophobic segments of block copolymers start to associate to minimize the contact with water molecules, leading to the formation of a vesicular or core-shell micellar structure [27].

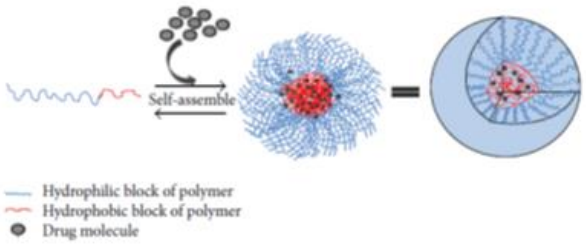

Figure 7. Formation and drug loading of PMs by self-assembly of amphiphilic block copolymers in aqueous solution [27]

3. CONCLUSIONS

In summary, nanocarriers as drug delivery systems offer unique properties as compared to traditional systems such as:

- Nanocarriers provide a container that can hold agents within
- Nanometer size provides improved cell entry and extravasation
- Protection of the therapeutic agent from the biological milieu
- Decreased renal elimination
- Large surface area to the volume ratio provides a surface for chemical modification
- Improved bioavailability of the therapeutic agents
- Increased solubility of water-insoluble anticancer agents

However, to achieve personalized nanocarriers, there are still many obstacles to overcome. Formulations of nanomedicines with precisely controlled parameters (i.e., drug loading, size, and release kinetics) in large quantities are still challenging.

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