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Nanoparticle-based drug delivery systems for cancer therapy

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Abstract

Nanoparticle-based drug delivery system (DDS) is considered promising for cancer treatment. Compared with traditional DDS, the nanoparticle-based DDS shows improved efficacy by: 1) increasing half-life of vulnerable drugs and proteins, 2) improving the solubility of hydrophobic drugs, and 3) allowing controlled and targeted release of drugs in diseased site. This review mainly focuses on nanoparticle-based DDS fabricated from chitosan, silica, and poly (lactic-co-glycolic acid). Their fabrication methods and applications in cancer treatment are introduced. The current limitations and future perspectives of the nanoparticle-based DDS are discussed.

Keywords

Drug delivery system; Nanoparticle; Controlled release; Targeted delivery; Cancer treatment

1. Introduction

Drug delivery system (DDS) has been used clinically and pre-clinically to deliver therapeutic substances for disease treatment [1]. Conventional DDS is administrated by either oral intake or injection. Despite many advantages of the conventional DDS, such as ease of administration and widely accepted by patients, it has its major limitations and disadvantages:

- Limited effectiveness: Many drugs have variable absorption rate when taken orally, also the low pH environment combined with digestive enzymes can break down some of the drugs before they enter blood circulation.
- Lack of selectivity: For drugs that need to target specific organs, oral drug delivery is not ideal due to its poor biodistribution. The drug uptake in the detoxification organs such as liver or kidney could be high and can induce toxicity to those organs.

Controlled drug delivery systems can overcome many of the disadvantages that conventional drug delivery systems face. For instance, chemotherapeutic agents used in cancer treatment are traditionally distributed non-specifically, harming both healthy cells and cancer cells,

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resulting in low effectiveness and high toxicities [2]. Controlled DDSs would be excellent carriers for chemotherapeutic agents, guiding the chemotherapeutic agents to the tumor site thus increasing the drug concentration in cancer cells and averting toxicity in normal cells [3,4]. Moreover, controlled DDSs protect the drugs from degradation and clearance, helpful for delivery of proteins and new therapeutic agents such as gene therapy and RNA interference. They can help DNA and siRNA evade uptake by reticuloendothelial or other tissues and enzymatic degradation [5].

The advancement of nanotechnology has made nanoparticles a promising candidate for controlled drug delivery systems. Nanoparticles often refer to particles with a diameter of around 10–1000 nm. When used as a DDS, nanoparticles can improve the efficacy of the drug by increasing drug half-life, improving the solubility for some hydrophobic drug, and releasing the drug in a controlled or sustained fashion. Stimuli-responsive nanoparticles can also help to lower the toxicity and to control the biodistribution of the drugs. Liposomes were the first discovered nanoparticles DDS and were used as carriers for drugs and proteins in the 1960s [6]. Since then, more and more materials are fabricated into nanoparticles and used as DDSs (Fig. 1). As reviewed by Bobo et al. [7] in 2016, FDA has approved 51 nanoparticles and 77 products are in clinical trials. Among all the approved materials for nanoparticles, large portions of them are polymeric and liposomal materials. However, researchers believe that more complex materials like micelle, metallic and protein-based materials also can be used as nanoparticles DDSs.

This review will focus on three different types of nanoparticles DDS that represent three different origins of materials for the fabrication of nanoparticles: chitosan nanoparticles, a group of nanoparticles made from natural polymeric material; silica nanoparticles, made from inorganic materials; and Polylactide-co-glycolic acid (PLGA) nanoparticles, made from synthetic polymeric material. Their fabrication methods and applications in drug delivery for cancer treatment will be introduced. The current obstacles that nanoparticles might face for clinical use and the future development for nanoparticles DDSs will also be presented.

2. Chitosan nanoparticles

Chitosan is a natural carbohydrate polymer obtained from the deacetylation of chitin, which is the main compound in crab, lobster, and shrimp shells. Due to its low price, good biocompatibility, low toxicity, and degradability in the body by chitinases, chitosan is considered suitable for pharmaceutical applications. The fabrication of nanoparticles from chitosan is often conducted in mild conditions as chitosan is soluble in acidic aqueous solutions at room temperature, no toxic organic solvents or heat is required. A broad category of drugs can be incorporated into chitosan DDS, including small molecules, proteins, and poly-nucleotides [8]. Chitosan can release the encapsulated drug in a controlled fashion. The free amine groups on chitosan also provide ionic crosslinking ability [9].

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2.1. Fabrication methods for chitosan nanoparticles

2.1.1. Ionotropic gelation method—Calvo et al. firstly reported the fabrication of chitosan-Polyethylene oxide (PEO) nanoparticles by the ionotropic gelation method [10]. Chitosan has positively charged amine groups and can go through a sol-gel transition when interacted with negatively charged polyanion to form nanoparticles under suitable conditions [11]. A commonly chosen polyanion is tripolyphosphate (TPP) [12,13]. Calvo et al. made different concentrations of chitosan in acetic acid aqueous solutions and TPP in purified water with the same concentrations as the chitosan solutions (0.05 wt%, 0.1 wt%, 0.5 wt%, and 1 wt%). The best condition for making chitosan nanoparticles was found by mixing various volumes of TPP with the chitosan solutions. Next, chitosan/PEO and chitosan/PEO-PPO nanoparticles were fabricated by adding TPP aqueous solution to chitosan solution containing PEO and PEO-PPO under constant stirring. The minimum particle size of the formed chitosan nanoparticles was 260 nm with a chitosan/TPP ratio of 5/1. The chitosan/PEO and chitosan/PEO-PPO nanoparticles showed particle sizes of around 300–1000 nm depending on different concentrations of PEO and PEO-PPO. The zeta potential of the chitosan/PEO and chitosan/PEO-PPO nanoparticles also decreased compared to chitosan nanoparticles, indicating increase stability of the chitosan/PEO and chitosan/PEO-PPO nanoparticles.

2.1.2. Emulsification solvent diffusion method—Emulsification solvent diffusion method was first discovered for the fabrication of poly D, L-lactide/glycolide (PLGA) nanoparticles [14], and was adapted to make chitosan nanoparticles by El-Shabouri [15]. The drug Cy-A and lecithin were first dissolved in methylene chloride and then added to acetone. The mixed solution was added into aqueous chitosan solution with magnetic stirring and high-pressure homogenization for 5 min. The suspension underwent low-pressure evaporation, filtration, centrifuge, resuspension in water, and re-centrifugation to achieve a particle size of about 150 nm.

2.1.3. Polyelectrolyte complex (PEC) method—Chitosan can also form nanoparticles with DNA via the polyelectrolyte complex (PEC) method. DNA and cationic chitosan can self-assemble to make nanoparticles when charge neutralization between them leads to a decrease in hydrophilicity [8]. Erbacher et al. [16] introduced chitosan/DNA complexes for gene delivery. The complexes were formed by mixing different equivalents of polymer with DNA phosphate. The reaction was completed within 15 min of incubation at room temperature with constant stirring. Dynamic light scattering (DLS) showed the particle sizes range from 80–500 nm for the DNA/chitosan ratio from 0.5–10. However, when zeta potential was close to zero, the particle size was around 1–5 μm. Transmission electron microscopy (TEM) showed that the complexes had a size of around 50–100 nm and shaped like donut and rod.

Of the three fabrication methods of chitosan nanoparticles, ionotropic gelation method has the least steps and all steps are conducted in mild and non-toxic aqueous conditions. It is considered as the simplest and most applicable method. The emulsification method is very useful when the drug used is hydrophobic, but also has drawbacks such as the use of high

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pressure and toxic solvents. PEC method provides chitosan nanoparticles the ability to be used in gene delivery.

2.2. Applications of chitosan nanoparticles in drug delivery

Chitosan nanoparticles have been widely studied for their application in cancer therapies. Chitosan nanoparticles can target tumors on specific organs through passive targeting (also known as enhanced permeability and retention (EPR) effect [17]), active targeting, and physical targeting through stimuli-sensitive targeting.

2.2.1. Passive and active targeting of tumors using chitosan nanoparticles

—Jain and Jain [18] developed hyaluronic acid (HA) coupled chitosan nanoparticles by ionotropic gelation. 5-fluorouracil (5FU) was chosen as the drug for colon cancer treatment. HA was incorporated into the chitosan nanoparticles DDS due to an elevated level of HA receptors around tumor tissues. Therefore, nanoparticles can target colon tumors via both the EPR effect and the binding of HA to HA receptors. The chitosan nanoparticles loaded with 5FU synthesized in this study had a diameter of around 135 nm, after conjugating HA with free amino groups on chitosan (Scheme 1), the particle size increased to around 150 nm. Compared with uncoupled chitosan nanoparticles, HA coupled nanoparticles showed suppressed drug release in 24 h due to the double barrier created by an additional HA layer on the nanoparticles. The HA coupled nanoparticles also showed higher cell uptake rate by cancer cells within 4 h of incubation time at 37 °C, suggesting that the HA-conjugated chitosan nanoparticles are promising carriers for targeted delivery of the drug to colon tumor.

2.2.2. Stimuli-sensitive targeting of tumors using chitosan nanoparticles—

Stimuli-sensitive chitosan nanoparticles are also widely used in cancer therapies. pH and temperature are often chosen as physiological signals as inflamed or neoplastic tissues will exhibit acidosis or hyper-thermia. Zhang et al. [19] reported a design of a pH-mediated chitosan-based microgel drug delivery system for cancer therapeutics. Chitosan powder was first dissolved in water at 85 °C and then was reacted with Glycidyltrimethylammonium chloride to yield N-[(2-hydroxy-3-trimethylammonium)propyl]chitosan chloride (HTCC). Nanoparticles of HTCC were fabricated using the ionotropic gelation method with TPP. When pH decreased from 7.4 to 5.0, the diameter of chitosan nanoparticles increased from less than 200 nm to around 400 nm (a 2.2-fold increase), the relative volume of the nanoparticles increased 11-fold. It is implied that after internalization into the cell, the microgels will show strong swelling and thus will stay in the diseased region and release the drug. After loading with methotrexate disodium (MTX), the loading efficiency, release kinetics, and cell viability/-mortality were determined. Microgels showed a faster drug release rate at pH = 5.0 (93% after day 1), whereas about 30% of the drug was trapped in microgel after 5 days at pH = 7.4. In cell viability experiments, MTX-loaded HTCC showed the highest mortality on HeLa cells compared with the pure drug group and non-conjugated MTX-chitosan nanoparticles group.

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3. Silica nanoparticles

Silica xerogels haven been widely used as inorganic materials for drug delivery. It is biocompatible, highly porous and easy to modify for functionalization. In 1992, Kresge et al. [20] first reported the fabrication of mesoporous silica nanoparticles (MSNs), compared with silica xero-gels, MSNs has many advantages in its use as drug delivery systems: i) when materials are made to be nano-sized, it has a larger surface area (often exceeds 1000 m^2/g) and pore volume, making it superior for adsorption and loading of drugs into the pores [21]; ii) the drug loading and release kinetics of the nanoparticles can be adjusted by changing the size of the nanoparticles [22]; iii) surface modification of MSNs is easy to achieve, which enhances the targeting ability of nanoparticles, leading to an increase in drug delivery efficacy and a decrease in systemic toxicity [23,24]; iv)when combined with magnetic materials or luminescent compounds, MSNs can be used as drug delivery systems and bioimaging probes [25,26].

3.1. Fabrication of MSNs

3.1.1. Solution-based method for MSNs synthesis—MCM-41 with hexagonal mesopores is one of the most known types of MSNs. When Kresge et al. first reported the synthesis of MSNs through a liquid-crystal template mechanism [20], the particle sizes are in the scale of microns. However, many researchers modified their methods of MCM-41 synthesis and now the particle size of MCM-41 can be around 50 nm. As reported by Meng and coworkers [27], MSNs with mesoporous silica core of 50 nm were synthesized. A solution of pluronic F127, n-Cetyltrimethylammonium bromide (CTAB), and water were heated at 80 °C for 0.5 h. tetraethyl orthosilicate (TEOS) was then mixed with N-(2-Aminoethyl)- 3-aminopropyltrimethoxysilane (NAPTS) with a volume ratio of 5:1 and then added into F127 and CTAB mixed solution. Twenty minutes later, trihydroxysilypropyl methylphosphonate was added. After filtration through a 220 nm filter, the solution was mixed with methanol and NH_4NO_3 to remove CTAB at 70 °C for 30 min. The synthesized MSNs were then centrifuged and washed with methanol. TEM tests showed that the synthesized MSNs has particle sizes around 50 nm, after coating with PEG, the hydrodynamic size of MSNs is around 70 nm. This synthesis uses alkylammonium salt (usually CTAB) as a liquid crystal template, which can self-assemble into micelles when its concentration is above critical micelle concentration (CMC), and form liquid crystal mesophases when its concentration is even higher [28]. Silica precursors can then concentrate to form amorphous silica mesophases due to electrostatic interactions and hydrogen bonding.

3.1.2. Evaporation-induced self-assembly (EISA) method—The evaporation-induced self-assembly (EISA) method was first discovered by Lu et al. to make mesoporous silica films [29]. First, TEOS was mixed with ethanol and hydrochloric acid (HCl) and refluxed at 60 °C for 90 min. Second, more water and HCl were added to increase the concentration of HCl. The two-step process was designed mainly to lower the rate of siloxane condensation in the solution. After stirring for 15 min and aging for another 15 min, the solution was diluted 1:3 with ethanol. Surfactant CTAB was added into the solution with a concentration much smaller than CMC. The mesoporous film was developed by

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dip-coating at 7.6 cm/min. During the dip-coating process, ethanol evaporation leads to an increase in surfactant concentration to finally above CMC, and the self-assembly of silica in the micelle began. The film became steady only after a few seconds.

After two years, Lu and coworker modified the EISA method they developed and fabricated silica mesoporous nanoparticles with stable hexagonal or cubic pore mesostructures [30]. TEM tests showed that the diameter of the synthesized nanoparticles was around 200–300 nm. The process began with a solution of silica, ethanol, water, and surfactant initial concentration lower than CMC. An aerosol dispersion was then generated in a tubular reactor, during a 6-s process, alcohol evaporated and induced micelle formation, resulting in solid silica-surfactant self--assembled MSNs (Fig. 2).

When comparing the particle size of MSNs synthesized by the liquid-crystal template method and the EISA method, one can find that the former can synthesize MSNs with a smaller size, while the latter has a more regular shape and more stable hexagonal or cubic pore mesostructures (Fig. 2). Another potential advantage of EISA could be that nonvolatile drugs can be easily encapsulated in the silica-surfactant mesophase. However, it is worth noting that CTAB in the EISA method is not removed, this might cause toxicity issues in *in vivo* application. Isomaa and coworkers [31] have found out that rats drinking water with 45 mg/kg/day dosage of CTAB for 1 year showed a decrease in growth rate.

3.2. Applications of silica nanoparticles in drug delivery

3.2.1. Application of MSNs in gene delivery for cancer treatment—MSNs have been studied as a promising carrier for gene delivery. Compared with other drug delivery systems, MSNs have a mesoporous structure which provides a homogeneous distribution of drug through the matrix system, the pore size of MSNs can also be tailored to fit different molecular sizes of drugs (Scheme 2) [32]. Compared with chitosan and other polymers, MSNs also has a higher drug loading capacity [33]. When used in gene delivery, gene molecules are hidden deeply in the mesopores and thus can avoid from nuclease degradation before reaching the targeting area [34].

To increase the binding and loading capacity of negatively charged nucleic acids, the surface of MSNs is often modified to be positively charged. Xia et al. studied the effects of coating polyethyleneimine (PEI), a cationic polymer, on MSNs. Their results showed that the surface coating of PEI increased the binding avidity of DNA and SiRNA, and cell uptake rate of the nanoparticles. SiRNA bonded to the MSN-PEI surface can achieve knockdown of GFP in HEPA-1 cells. The delivery of plasmid DNA using the MSN-PEI system is comparable to the commercial drug delivery system. However, one of the drawbacks of PEI coated MSNs is that toxic PEI coating can increase the cytotoxicity of the MSNs delivery system [35].

Yang et al. [36] showed for the first time that the combined delivery of miRNA-204–5p, a tumor suppressor miRNA, with anti-cancer drug Oxaliplatin (OXL) in PEI/hyaluronic acid-assembled mesoporous silica nanoparticles (Oxmi-HSMN) showed a synergistic anticancer effect in the treatment of colon cancers. As discussed before, PEI was attached to the MSN via electrostatic interaction to increase the loading of miRNA, and the hyaluronic

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acid (HA) was covalently conjugated on the MSN surface to allow the selective targeting of CD44 receptors on the colon cancer cells. The particle size of Oxmi-HMSN was about 138 nm, with a narrow distribution (PDI = 0.165), suitable for passive delivery to the cancer site via the EPR effect. *In vitro* release study showed a faster release of the drug from OXL-MSN compared with the release from OXmi-HMSN, possibly because of the PEI polymer assembly on the surface of Oxmi-HMSN hinders the diffusion of the drug into the release medium. Cellulate uptake study showed OXmi-HMSN exhibited higher cell uptake compared with non-targeted OXmi-MSN. *In vitro* experiments on HT-29 tumor-bearing mice revealed that OXmi-HMSN showed the strongest inhibition of tumor growth when compared with OXL and OXL-MSN group ($P < 0.0001$). Furthermore, blank OXmi-HMSN with no drug and siRNA showed high cell viability (>80%) even when exposed to 100 μg/ml of the nanoparticles.

3.2.2. Application of MSNs to achieve zero premature release in the treatment of cancer—

In tumor treatment, many drugs used are toxic to other organs or tissues. It is therefore very important to ensure “zero premature release” [33], which means the drug distribution in non-targeted sites is close to zero. Mal et al. [37] first modified MSNs with coumarin group to actively photo-control the accessibility of the pores using UV irradiation. The coumarin substituents are considered as “hinged double doors”. When the MSNs are irradiated with 310 nm wavelength UV light, the coumarin groups photopolymerize to make cyclobutane coumarin dimmers and the doors are closed, blocking any drug absorption into the pores. When the MSNs are irradiated with 250 nm wavelength UV light, photocleavage of the dimers can happen and the doors are open, allowing access to the interior of the MSNs. Controlled release study of coumarin modified MSNs with steroid cholestane (its small molecular size allows it to be stored in the pores of MSNs) showed that 28 wt% of cholestane was absorbed in the irradiated coumarin modified MSNs after washing with n-hexane while no cholestane remained after washing in coumarin modified MSNs without irradiation. Despite photo-stimulation, other stimuli such as pH [38], enzymes [39], and magnetic fields [40] have been studied to achieve zero premature release in MSNs.

4. Polylactide-co-glycolic acid (PLGA) nanoparticles

Polylactide-co-glycolic acid (PLGA) is a copolymer of polylactic acid (PLA) and polyglycolic acid (PGA) synthesized through ring-opening polymerization of lactide (LA) and glycolide (GA). As biomaterials, PLGA has many advantages to be used as drug delivery systems. Firstly, it has already been approved by the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for its use in the human body [41]. Secondly, as a synthetic polymer, it has higher purity, tailorable molecular weight, and higher reproducibility than many natural polymers. Thirdly, PLGA is biodegradable, when it undergoes hydrolytic cleavage in the body, it will be degraded into lactic acid and glycolic acid and will be metabolized via the Krebs cycle and turned into CO_2 and water [42]. Fourthly, compared with PLA and PGA, the copolymer is more stable against hydrolysis and thus can be used for continued drug release up to days, weeks or months.

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4.1. Fabrication of PLGA nanoparticles

4.1.1. Emulsion evaporation method—The emulsion evaporation method is one of the most common techniques for the fabrication of PLGA nanoparticles [43]. Depending on the solubility of the drug in water, two different emulsion methods can be applied. Single-emulsion (oil-in-water, o/w) is suitable for encapsulation of hydrophobic drugs, while double-emulsion (water-in-oil-in-water, w/o/w) is suitable for encapsulation of hydrophilic drugs. In the single-emulsion method, PLGA polymer and the hydrophobic drug are first dissolved in an organic solvent, and then the emulsion is formed by adding water and a surfactant into the organic phase. Sonication or high shear stress such as rapid stirring are often used to prevent the aggregation of emulsion droplets [41,43]. Finally, the organic solvent is removed by evaporation or extraction, the formed nanoparticles can then be collected via centrifugation (Scheme 3) [44,45]. For the encapsulation of hydrophilic drugs, the above method is modified to make a double emulsion. After mixing the organic solvent with an aqueous solution to make the first emulsion, the mixture is then added to an aqueous solution with a stabilizer.

The emulsion evaporation method is suitable for laboratory fabrication of PLGA nanoparticles, but not for large-scale fabrication. Mainly because of the high energy input needed for high-speed homogenization and sonication [45]. The nanoparticles made from double emulsion evaporation also have several drawbacks such as larger particle size and low drug loading efficiency.

4.1.2. Salting out method—To make PLGA nanoparticles from the salting out method, PLGA first needs to be dissolved in a water-miscible organic solvent, such as acetone. Next, the polymer solution is added into an aqueous phase containing emulsifier and high concentration of salts (such as calcium chloride) under high-speed stirring. The formation of PLGA nanoparticles is induced by dilution of salt concentration, as it increases the diffusion speed of the organic phase into the aqueous phase. The organic solvent and salts are removed by centrifugation or cross-flow filtration (Scheme 4).

Salting out method is suitable for encapsulation of peptide or protein as it minimizes tension [47]. The whole process can be conducted at ambient temperature, making it ideal for encapsulation of heat-sensitive drugs [48]. The disadvantages of this method are that it can only encapsulate hydrophobic drugs, and the additional washing steps needed to remove salts [49,50].

4.1.3. Nanoprecipitation method—Nanoprecipitation method is also known as solvent diffusion or solvent displacement method [41]. In this one-step method, PLGA polymer is dissolved in water-miscible and polar solvent, such as acetone or THF, the solution is then added dropwise into an aqueous solution with stabilizer under constant rapid stirring. Nanoparticles precipitate out as the organic solvent diffuses rapidly into the aqueous phase. The remaining solvent can be removed by nitrogen or air blowing or reduced-pressure evaporation (Scheme 5).

The nanoprecipitation method can be used to encapsulate both hydrophobic and hydrophilic drugs. However, the loading efficiency for hydrophilic drugs will be quite low. The size

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of the formed nanoparticles from the nanoprecipitation method can be affected by various factors, such as the concentration of the polymer solution [51], the molecular weight of the polymer [41], the stabilizer used [14], and the stirring speed [52].

4.2. Applications of PLGA nanoparticles in cancer treatment

Due to the observed insufficient delivery of nanodrugs into tumors during the passive delivery using EPR effects, most of the applications of PLGA nanoparticles utilizes active targeting strategy for the delivery of chemotherapeutic agents in the treatment of cancer. Targeting ligands are often coated or grafted on the surface of PLGA nanoparticles. The chosen ligands provide a specific binding to receptors that are often overexpressed by cancer cells or tumoral endothelial cells.

Hyaluronic acid (HA) is a naturally occurring polysaccharide and a suitable targeting moiety for PLGA nanoparticles DDS in cancer treatment because it binds to CD44 receptors, which are overexpressed on some tumor types. Furthermore, compared with other targeting ligands, HA has many advantages, it is non-toxic, biocompatible and biodegradable, and non-immunogenic. Cerqueira et al. developed PLGA nanoparticles engineered with HA on the surface for the targeted delivery of paclitaxel (PTX) to treat triple-negative breast cancer. The PLGA nanoparticles were fabricated by single emulsion method, cetrimide was added to the aqueous phase to make positively charged PLGA nanoparticles. After complete evaporation of the solvent dichloromethane (DCM), the surface charge was modified by adding negatively-charged sodium hyaluronate. The effect of formulation parameters such as the PVA concentration, the sonication time, the polymer concentration, and the polymer type on the nanoparticles has been investigated. It is observed by the authors that the increase of PVA concentration from 0.5% to 2% can decrease the size and polydispersity index (PDI) of the nanoparticles. When the sonication time increased from 1 min to 4 min, the particle size decreased, and both the encapsulation efficiency (EE%) and drug loading (DL%) of PTX have improved. The best formulation with the highest EE% (90.8 ± 1.5) was found out to be 100 mg of 50:50 PLGA and 2% w/v PVA. The size of the nanoparticles with 0.05% w/v is around 250 nm and the zeta potential after modification with sodium hyaluronate is about −37.5 mv. The *in vitro* release study showed that PTX was released faster from the HA-coated PLGA nanoparticles than the bare PLGA nanoparticles. This is because the HA layer creates a porous surface on the PLGA nanoparticles, increasing the hydrolysis of PLGA by increasing the water absorption. Cell viability results showed HA-PTX-PLGA nanoparticles have a decreased IC50 than PTX-PLGA nanoparticles, indicating greater cellular uptake of HA-PTX-PLGA nanoparticles, which is possibly due to the interaction between HA and the overexpressed CD44 receptors in MDA-MB-231 cells.

Another approach for active targeting is to utilize outside stimuli such as a magnetic field to guide the nanoparticles toward the tumor site [53, 54]. Cui et al. [55] developed dual-targeting magnetic PLGA nanoparticles for the treatment of brain tumors. The choice of chemo drug for glioma treatment has been greatly limited due to the restriction of the blood-brain barrier (BBB). The authors developed dual-functional PLGA nanoparticles DDS (MNP/T7-PLGA NPs) to address this challenging situation for glioma treatment. The human transferrin receptor-binding peptide T7 was selected to provide ligand-mediated

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active targeting, and the magnetic nanoparticles (MNP) were entrapped into the PLGA NPs by a single-emulsion solvent evaporation method to provide magnetic-guided targeting. Paclitaxel (PTX) and curcumin (CUR) were chosen as the drug for tumor treatment. *In vitro* cell uptake experiment was conducted with human malignant glioma U 87 cells and mouse brain endothelial cell line bEnd.3. Confocal image results showed that the primary mechanism responsible for intracellular delivery was T7-mediate intracellular delivery. To study the *in vivo* brain targeting effect of the MNP/T7-PLGA NPs, mice bearing orthotopic glioma were treated with the Cy5-labeled NPs. IVIS imaging showed that 4 h after tail vein injection, MNP/T7-PLGA NPs + MAG (with the magnetic field) showed the highest fluorescence intensity in the brain. In a 35-day experimental course, the MNP/T7-PLGA NPs + MAG group also showed the highest inhibition of glioma growth and highest survival rate (100%), compared with groups with no magnetic field, or with free CUR + PTX.

5. Obstacles of nanoparticles for clinical use

Despite many advantages of nanoparticles as drug delivery systems, only a few nanoparticle drugs are available now (Table 1.) on the market for cancer treatment. Many limitations and disadvantages of nanoparticles DDS still exist.

5.1. Scaling up problems

Many current fabrication methods for nanoparticles are only suitable for the lab-scale synthesis of nanoparticles. Low-energy-input methods need to be developed for large-scale production of nanoparticles. Besides, due to the small size and large surface area of nanoparticles, dry forms of nanoparticles are easy to aggregate, making them difficult to handle.

Chitosan is a natural polymer comes from many different sources, this results in variations in the molecular weight, molecular weight distribution, and purity levels of chitosan materials. Chitosan is also highly susceptible to environmental factors: exposure to high relative humidity (>60%) can result in a significant increase in water content of chitosan, lowering its mechanical properties [59,60]; exposure to high temperature (>40 °C) can increase the degradation rate of chitosan [61,62].

5.2. Toxicity and biodistribution

Nanoparticles have many unique properties that are different from bulk materials. Therefore, the toxicological profile of the nanoparticles is not the same as the bulk materials [63]. Our current procedure and tests for evaluation of drug toxicity may not apply to nanoparticles. The biodistribution of nanoparticles is also a concern. Researchers have reported that nanoparticles with a diameter of 50–100 nm have a higher accumulation in liver, spleen, and lung [64,65], leading to nonspecific accumulation of nanoparticles. This could be toxic to those organs if the drug carried within the nanoparticles is harmful to normal cells. A thorough understanding of the biological behavior of nanoparticles is still lacking [63].

Concerns over the cytotoxicity and *in vivo* toxicity have hindered the application of silica nanoparticles as DDSs. One of the possible contributors to the toxicity of silica is the silanol groups, which can cause membranolysis. Another contributor is the radicals on the silica

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surface, which can react with water to form reactive oxygen species (ROS) and further lead to cell death. Many studies on the toxicity of MSNs showed contradictory results [66–68]. Therefore, it is still not safe to say that MSNs have no toxicity when used as DDS. Despite acute toxicity, studies on the long-term toxicity of MSNs also need to be conducted before clinical application.

5.3. Poor control over loading and releasing of drugs

For many polymeric nanoparticles, a low rate of drug loading is one of the major pitfalls [43,69]. Many studies have reported a loading rate of less than 10% [70–72]. Initial burst release is also a big concern for nanoparticles as drug delivery systems. It often happens during the first few minutes when the nanoparticles contact the external environment [73]. This phenomenon happens on nanoparticles fabricated from different materials. For example, Janes et al. [12] reported a 17% burst release of dextran sulfate encapsulated in chitosan nanoparticles over 2 h; Suh et al. reported a 40% burst release of an antiproliferative drug in polyethylene oxide-PLGA nanoparticles in the first three days. As a result of burst release, which is mainly attributed to the adsorption of the drugs bound to the surface, the drugs may not be able to reach the targeted site, resulting in loss of drug efficiency.

5.4. Physiological barriers

Another obstacle for nanoparticles DDSs in cancer treatment is the physiological barriers between nanoparticles and tumor cells. After systemic administration, nanoparticles go through the microvessel wall, extracellular matrix, and plasma membrane of cells for drug delivery; each of the three barriers hinders nanoparticle delivery in a specific way via disruptions in transvascular, interstitial, and transmembrane transport, respectively [74]. Although the EPR effect is often present in tumors, regions with low or no permeability microvessels also exist, resulting in heterogeneity in the distribution of nanoparticles [75]. Once the nanoparticles reach the interstitial space, they then encounter transport difficulty due to the low convective transport driving force in the solid tumors. Due to these hindrances, the systemically administered nanoparticles are often found only in the perivascular and peripheral regions in solid tumors [74].

6. Future of nanoparticles as drug delivery systems

Nanoparticles have many advantages compared with traditional drug delivery strategies. However, for wider application of nanoparticles in the pharmaceutical market, more *in vivo* studies and clinical trials are needed to understand the toxicity and long-term biological behavior of nanoparticles.

Recently, more and more studies are focusing on the surface modification of nanoparticles to increase the retention time of nanoparticles. Polyethylene glycol has been a popular choice for nanoparticle surface modification. When grafted onto the surface of nanoparticles [76], The formation of a hydrating layer on the nanoparticles can help increase the circulation lifetimes after intravascular injection. Another top-down biomimetic approach, cell membrane coated nanoparticles, has also been intensively researched [77–82]. The

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isolated cell membranes still retain the original membrane proteins and the lipid bilayer structure, thus can still perform the function of natural cell membranes. The cell membrane camouflaged nanoparticles could have the advantages of suppressed immune reaction and improved biodistribution over naked nanoparticles.

The development of multi-functional nanoparticles is also a blooming research field (Fig. 3). This field is driven by the growing medical needs. During cancer treatment, nanoparticles are needed to not only deliver drugs but also to provide diagnosis and drug monitoring. One example could be image-guided drug delivery, which incorporates magnetic resonance imaging (MRI) with drug delivery nanoparticles to monitor the biodistribution, circulation, and targeting behavior of nanoparticles.

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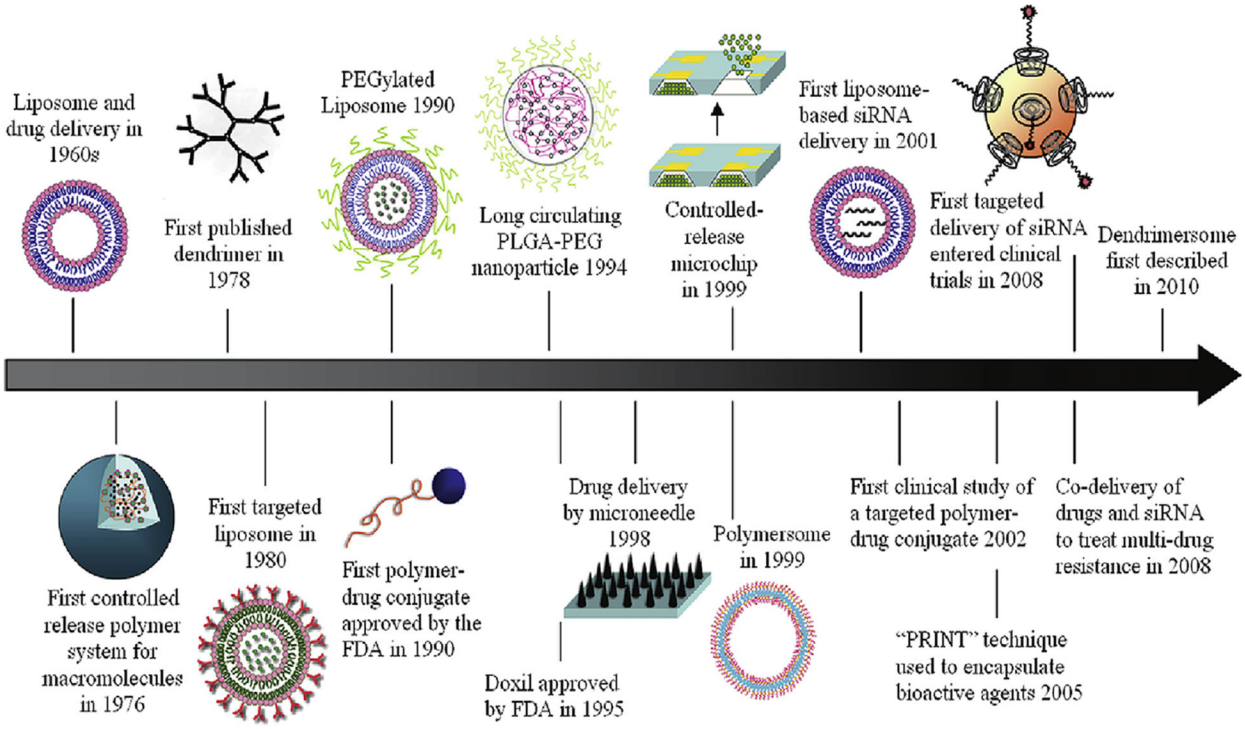

Fig. 1.

Timeline for the development of nanoparticle drug delivery systems. Reprinted with permission from [5]. Copyright (2010) American Chemical Society.

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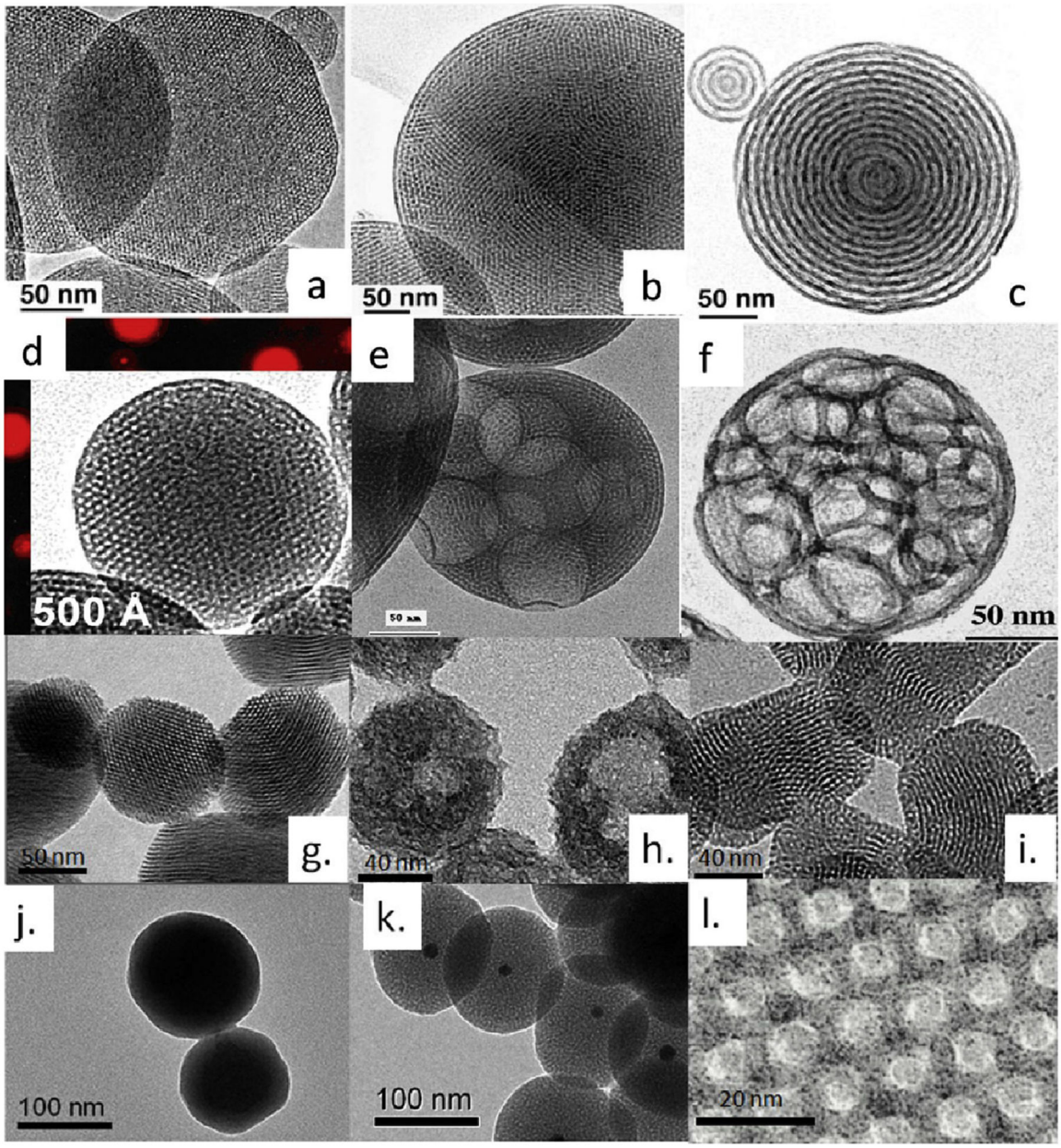

Fig. 2.

TEM images of MSNs prepared by EISA (a.-d.) and solution-based methods (e.-l.). Reprinted with permission from [28]. Copyright (2013) American Chemical Society.

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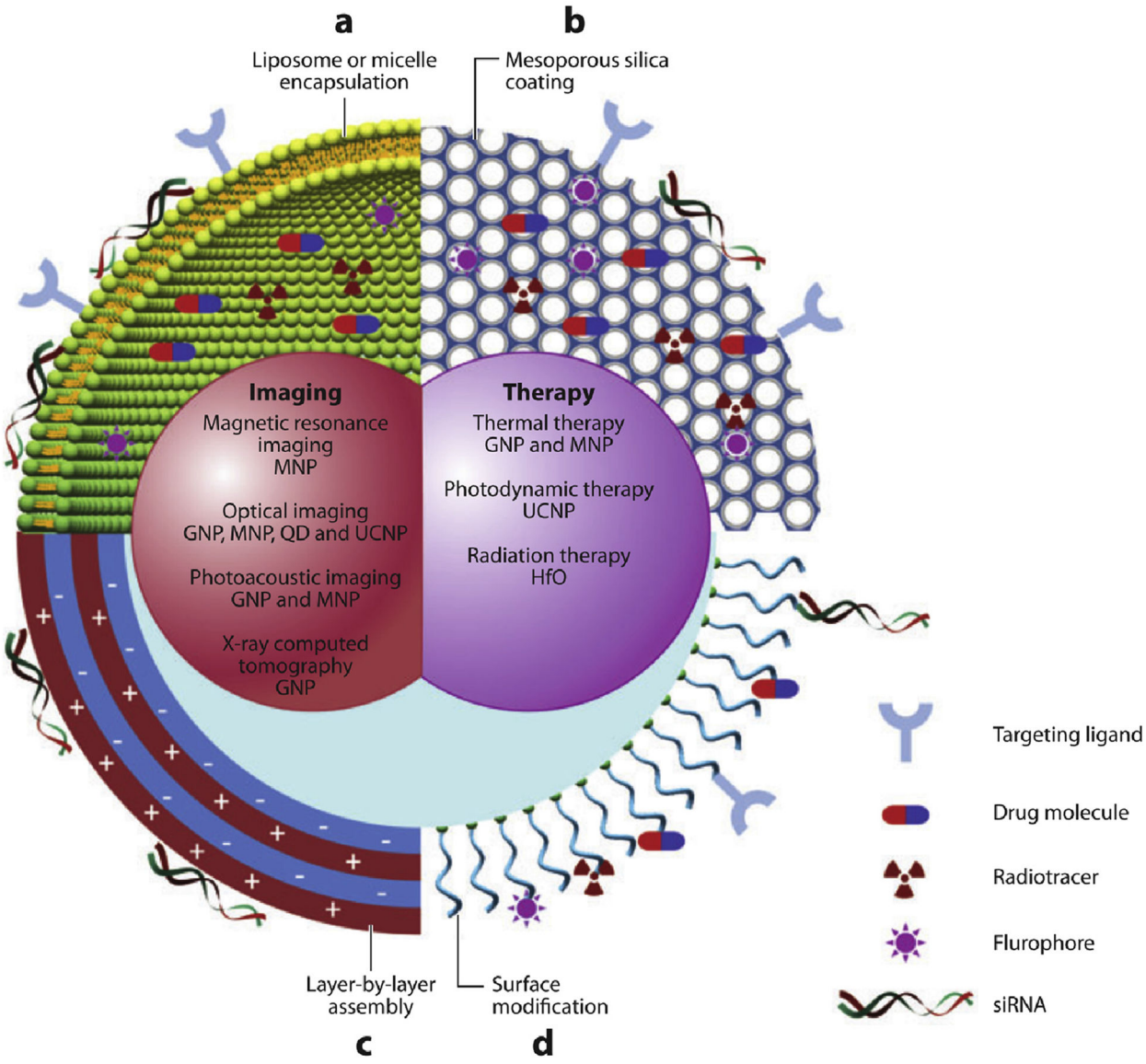

Fig. 3.

Schematic diagram for future multifunctional nanoparticles. Republished with permission of Annual Reviews, Inc, from [83]; permission conveyed through Copyright Clearance Center, Inc. Abbreviations: GNP, gold nanoparticles; MNP, magnetic nanoparticles; QD, quantum dot; HfO, hafnium oxide nanoparticles; UCNP, upconversion nanoparticles.

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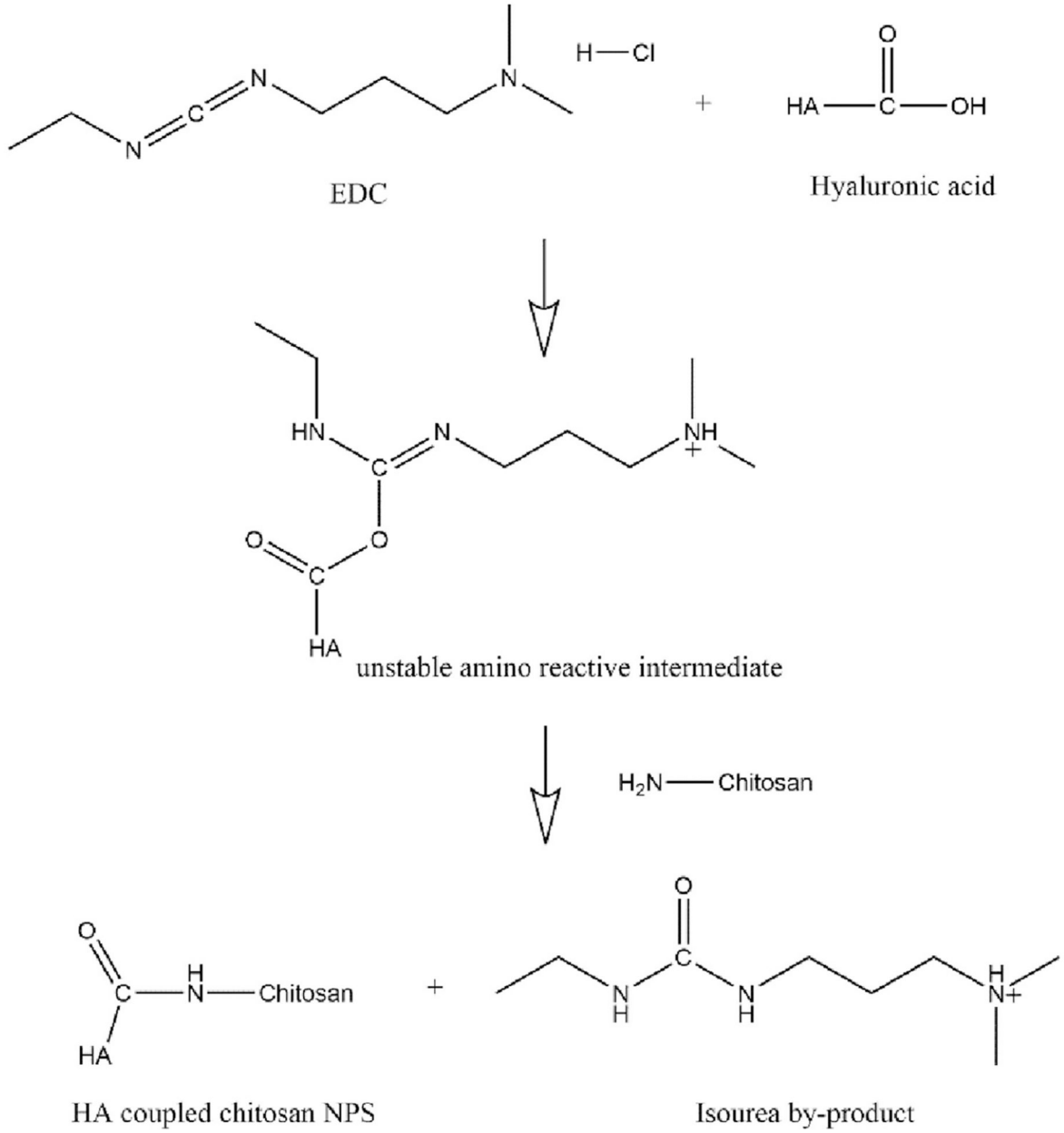

Scheme 1.
Coupling of hyaluronic acid with chitosan nanoparticles.

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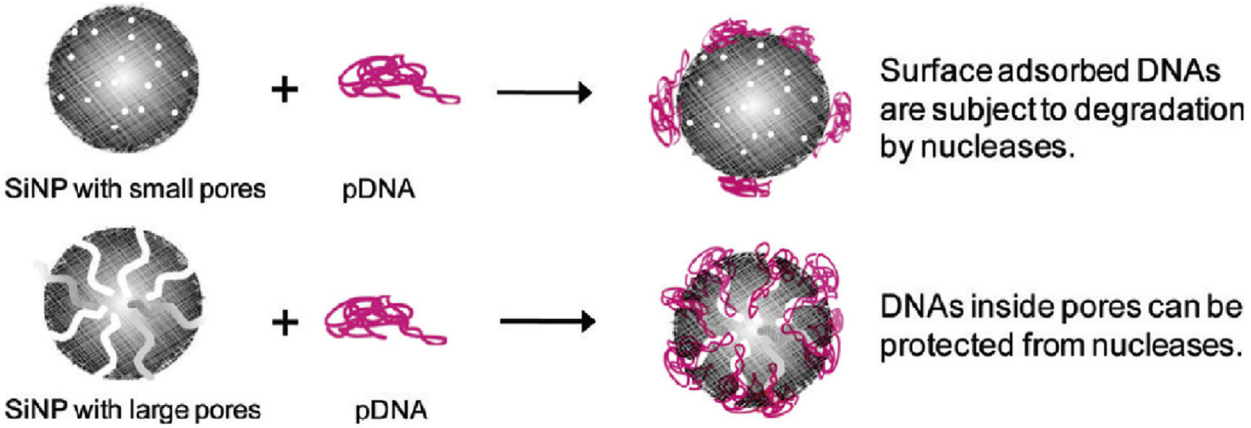

Scheme 2.

Monodispersed MSN (MMSN) can be tailored to have a large pore size (>15 nm) for increased plasmid DNA loading capacity and better protection from nucleases. Reprinted with permission from [32]. Copyright (2011) American Chemical Society.

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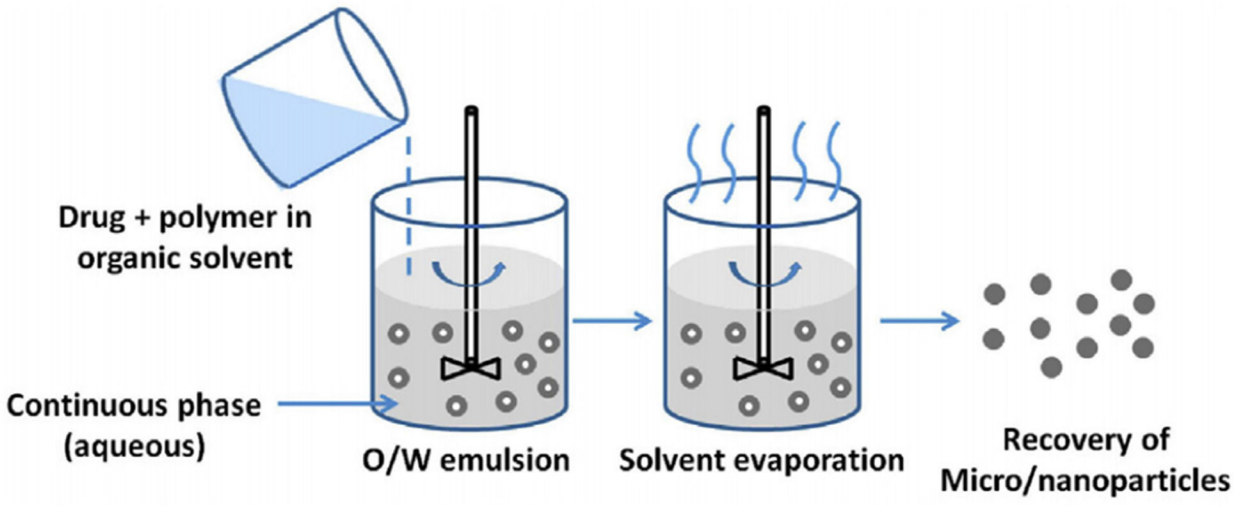

Scheme 3.

Fabrication of nanoparticles by emulsion evaporation method. Reprinted with permission from [46].

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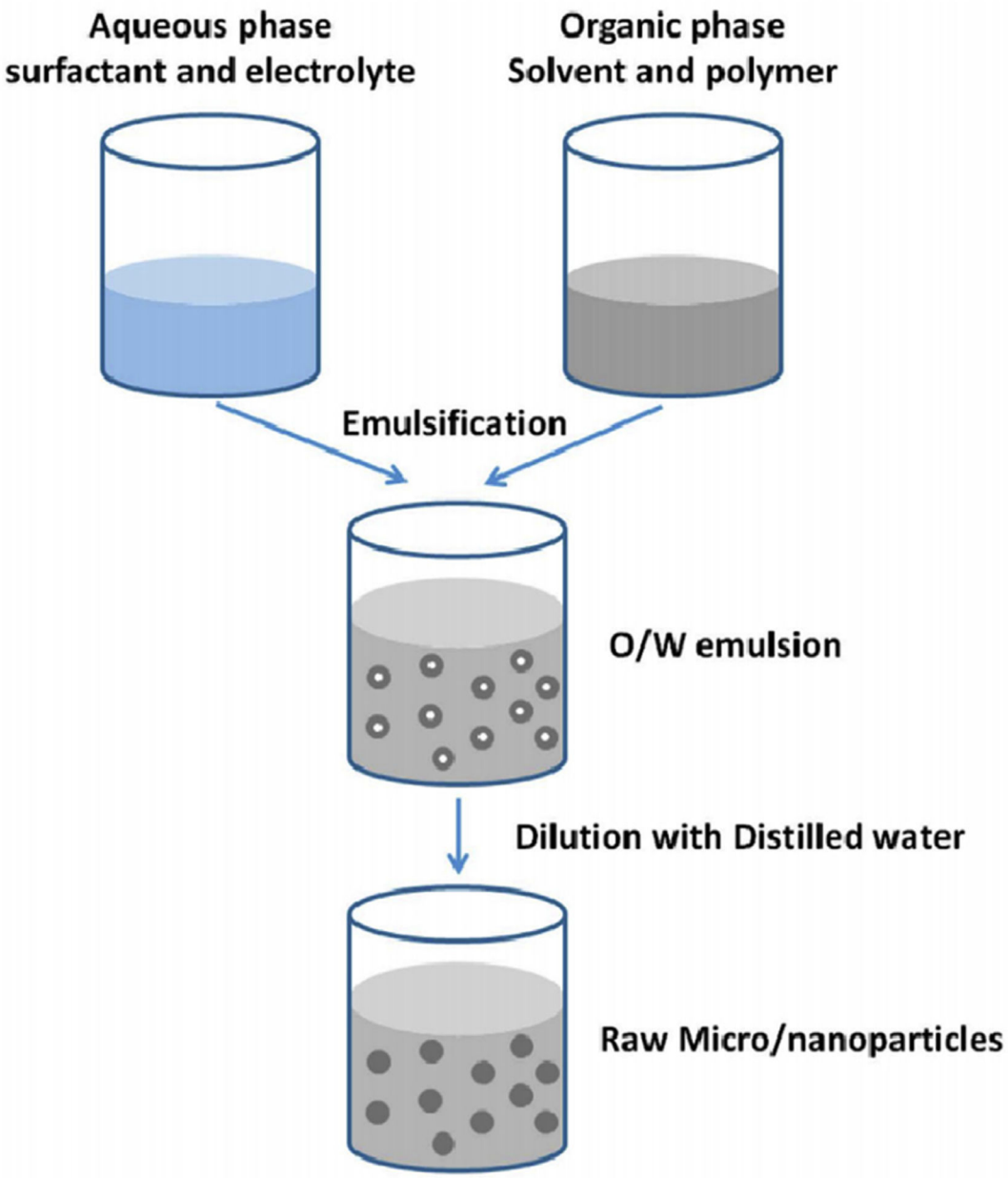

Scheme 4.
Fabrication of nanoparticles by emulsion evaporation method. Reprinted with permission from [46].

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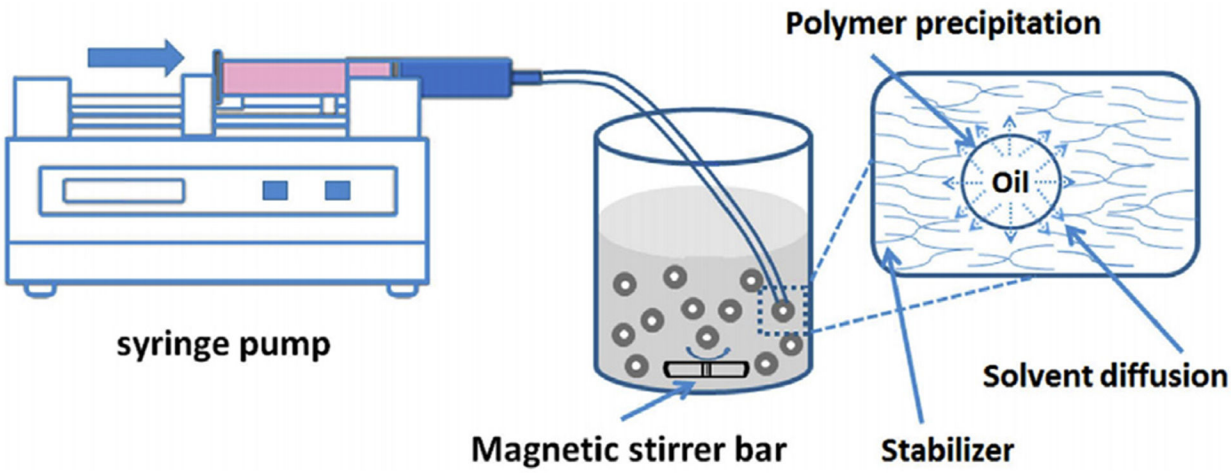

Scheme 5.
Fabrication of nanoparticles by emulsion evaporation method. Reprinted with permission from [46].

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Table 1

List of FDA-approved nanomedicines for cancer treatment [7,56,57,58].

Tradename	Material	Drug	Company	Indication	Year(s) approved
Doxil®	Liposome-PEG	doxorubicin	Janssen	Metastatic breast cancer, metastatic ovarian cancer	1995
Eligard®	PLGA	Leuprolide acetate	Tolmar	Prostate Cancer	2002
Abraxane®	Albumin	Paclitaxel	Celgene	Metastatic breast cancer	2005
				Pancreatic cancer	2013
Genexol PM®	mPEG-PLA	Paclitaxel	Samyang Corporation	Metastatic breast cancer	2007
Onivyde®	Liposome	Irinotecan	Merrimack	Pancreatic cancer	2015

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