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Title: Nanoparticles / Nano platform to carry and deliver the drug molecules to the target site

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Abstract

Nanoparticles have become a major player in pharmaceutical research and drug design. By encapsulation of a drug into a nanostructure, its stability can be preserved, its solubility can be enhanced and its pharmacokinetic profile can be boosted as well. In addition, using a drug carrier can open the doors to different drug targeting strategies that improve the specificity of the drug and reduce toxicity and side effects accordingly. Many nanoparticles preparation methods exist, the most abundant are emulsion based, precipitation based and polymerization based methods. However, these particle types and delivery methods do not provide optimal delivery. Drug targeting strategies using passive approach must also be taken into consideration. In this chapter, the most abundant preparation methods will be discussed and examples for different kinds of nanoparticles will be given. Furthermore, the widely studied targeting strategies that are of paramount importance to drug delivery will be explained.

Keywords: nanoparticles, drug targeting, preparation methods, formulations, encapsulation, cancer.

Introduction

The emergence of nanocarriers has radically revolutionized drug delivery. Over the past decades, nanocarriers have become almost omnipresent in drug research. They are submicron structures that can be built from different kinds of materials and used as a cage or a carrier for different therapeutic molecules to boost, target, and control their effectiveness. By incorporating a drug within a nanoparticle (NP), major problems can be solved such as drug solubility, absorption, and pharmacokinetic profile as a whole. NPs can also promote specific targeting of a drug and therefore limiting any toxicity and side effects [1]. In addition, by using NPs as carriers, the release profile of the drug can be controlled to achieve a prolonged therapeutic duration. This is especially important for low dose high effect molecules. In fact, the following size decreasing of particles can cross certain barriers [2].

From the literature, many types of materials that were used as NP building blocks can be found. NPs were formulated from synthetic polymers, natural polymers, Protein, lipids, inorganic materials, and metals. This variety of NP types reflects the wide range of possibilities concerning drug delivery. Using one material or another (or sometimes hybrid materials) depends on the desired final product. Moreover, each type of NP offers certain advantages over the others. Polymeric based particles are easy to prepare and exhibit good biocompatibility. Protein and peptide-based particles have the advantage of biodegradability without having undesirable side products [3]. Lipid-based particles are important for carrying hydrophobic drugs and considered safe for administration and offer good cell internalization [4]. Finally, inorganic nanoparticles offer immune system invasion, thermal heating and the ability to respond to specific external stimuli (e.g. Magnetic field or near infra-red light) [5]. In addition, the presence of an extremely wide variety of active molecules invites the necessity of a wide variety of NPs. Drug properties such as hydrophilicity, hydrophobicity, solubility, etc. usually favors one type of particle over the other. Diversity gave us the ability to encapsulate almost all drug molecules regardless of their properties. Moreover, encapsulation is not exclusive for small therapeutic molecules. Macromolecules such as peptides and enzymes can also able to be encapsulated within polymer-based and lipid-based particles [6].

Encapsulation strategy gives researchers the privilege to target several diseases that are considered as a challenge. Anti-HIV, anti-diabetes, anti-inflammatory, and anti-cancer agents derived from encapsulated products are widely present in the literature. Furthermore, encapsulated formulations are already commercialized as therapeutic medicines. Doxil® composed from liposomal doxorubicin and Abraxane® containing paclitaxel-loaded albumin nanoparticles are market available potent agents against ovarian and breast cancer. Weissig et al. compiled a list of commercialized nanoformulations that originated from various kinds of nanoparticles [7].

Considering the different types of NPs and the large variety of drugs, different approaches including emulsification, precipitation, etc. must be pursued for drug encapsulation and NPs formulation. In this chapter, the most commonly used encapsulation methods of drugs within different Nano platforms are reviewed. Furthermore, the drug targeting strategies using these platforms are presented.

Encapsulation methods

When it comes to the preparation of drug-loaded nanostructures, the choice of one preparation method depends on a number of factors such as the properties of the drug to be encapsulated, the area of application of the formulation, the interaction between the drug and the building materials, and the

colloidal profile of the NPs. Since different preparation methods can yield different properties of NPs built from the same material (size, surface charge, morphology, etc.), defining the end goal of the formulation is crucial for choosing the preparation method. These techniques can be classified based on different criteria according to the author's point of view. They can be divided by categories of the base material (polymer-based particles, lipid-based particles, etc.), by the major phenomena occurring during the preparation (polymerization, precipitation, emulsification, etc.) or the necessity of using organic solvents. Usually, the use of organic solvents is less desired in pharmaceutical field since it may lead to toxic formulations and extra solvent removal steps. However, in some cases, the use of an organic solvent can be beneficial for the rapidity of the preparation or better control of the method. [8]–[10].

Emulsion polymerization

This method is the most common method for the preparation of polymeric nanoparticles from the fundamental monomer. Normally, the system consists of water, a monomer with low water solubility, an initiator, and a surfactant. When a monomer molecule encounters an active initiator (free radical or an ion), the initiation step begins to occur. The formation of solid particles may take place during or after the polymerization process (**Figure 1**). Different polymeric nanoparticles were prepared using this method such as poly(methyl methacrylate) (PMMA) [11], and poly[styrene/(dimethylamino)ethyl methacrylate] nanoparticles [12]. Recently, curcuminoid-loaded PMMA nanoparticles were prepared using emulsion polymerization in the presence of AIBN as initiator, and SDS as a surfactant. PMMA is well desired as a drug carrier since it is resistant to chemical hydrolysis, lacks toxicity, and possesses a high permeability. Loaded particles were produced with a size of 200 nm. In vitro tests showed that the encapsulated form of the drug demonstrated better affectivity and an enhanced pharmacokinetic profile as an anticancer agent [13].

Moreover, successfully surfactant-free emulsion polymerization was reported in the literature [14]. Usually, the stabilization of the particles is due to the use of ionizable initiators or ionic co-monomers while particle size in the conventional emulsion polymerization depends on the type and amount of the surfactant added. In the surfactant-free emulsion polymerization, the size depends on the solution dielectric constant, and the solubility of the monomer. In a recent study, surfactant-free emulsion polymerization was adopted to produce multi-responsive amphiphilic copolymer particles using methyl methacrylate (MMA), butyl acrylate (BA) and N, N-diethylacrylamide (DEAA). Particles were obtained with an average size of 380 nm, and possessing a salinity, temperature, and pH responsivities, making them good candidates for controlled drug release cases [15].

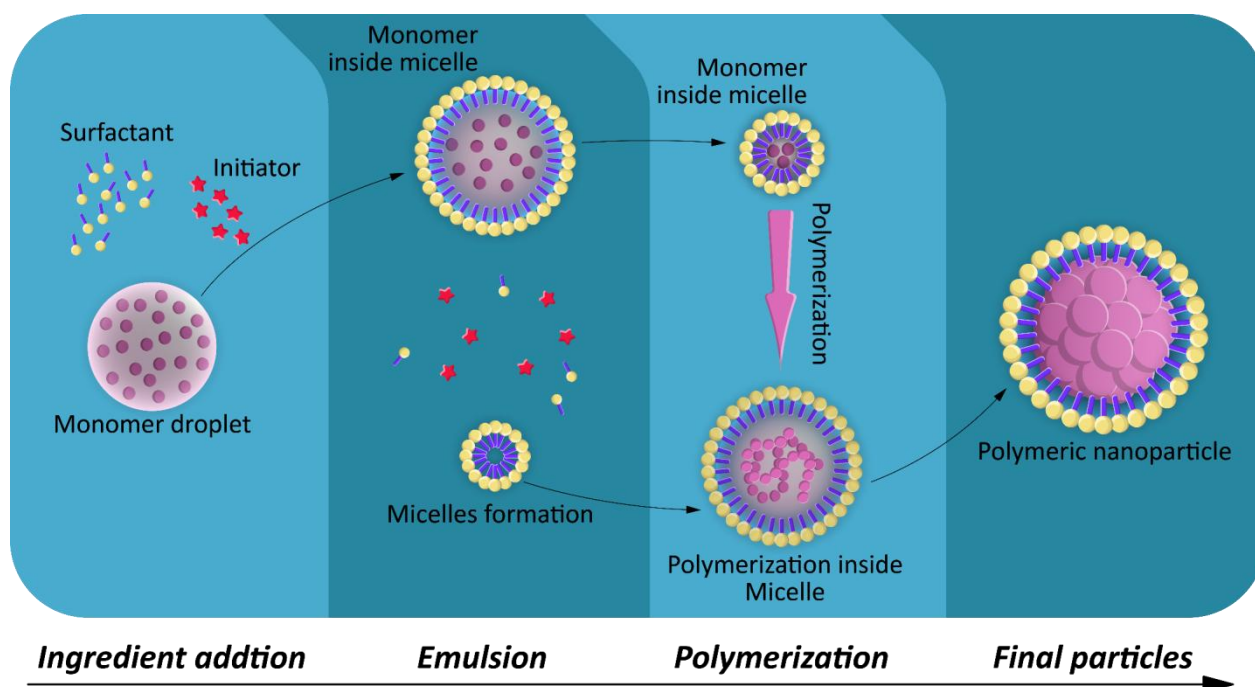


Figure 1 Nanoparticles formation by emulsion polymerization

Miniemulsion polymerization

Another emulsion-based technique for the synthesis of polymeric NPs for monomer solutions is called miniemulsion. This polymerization method uses a high-shear device such as ultraturrax or a high shear mixer by which two immiscible phases can be dispersed, and the use of a low molecular mass co-stabilizer. In this method, only a small amount of surfactant is required. By applying a high shear force such as homogenizer or ultrasonicator, monomer droplets stabilized by surfactant will be formed in the aqueous phase. Droplets size are usually ranged from 50 to 500 nm. These droplets will then be converted to polymeric particles by chain-growth polymerization in the presence of a water-soluble initiator, yielding highly monodispersed nanostructures [9] (**Figure 2**). Moreover, this method offers certain advantages over other polymerization-based technique. Droplets produced by miniemulsion were proven to be stable against coalescence. Schaeffel et al. proposed the use of dual-color fluorescence cross-correlation spectroscopy (DC FCCS) to study coalescence and aggregation during particle formation. Among the three studied systems, it was found that polystyrene nanoparticles prepared by miniemulsion are not exposed to coalescence during preparation process [16]. Moreover, miniemulsion polymerization can be used for conducting reactions that require high temperature [17].

In a recent study, 10-hydroxycamptothecin-loaded poly (n-butyl cyanoacrylate) nanoparticles were prepared. *In vitro* evaluation of these particles indicated a great release profile, cellular uptake, and rapid absorption in Caco-2 cells, suggesting that this formulation can be interesting for controlled release delivery of the antitumor agent 10-hydroxycamptothecin in oral drug delivery system [18].

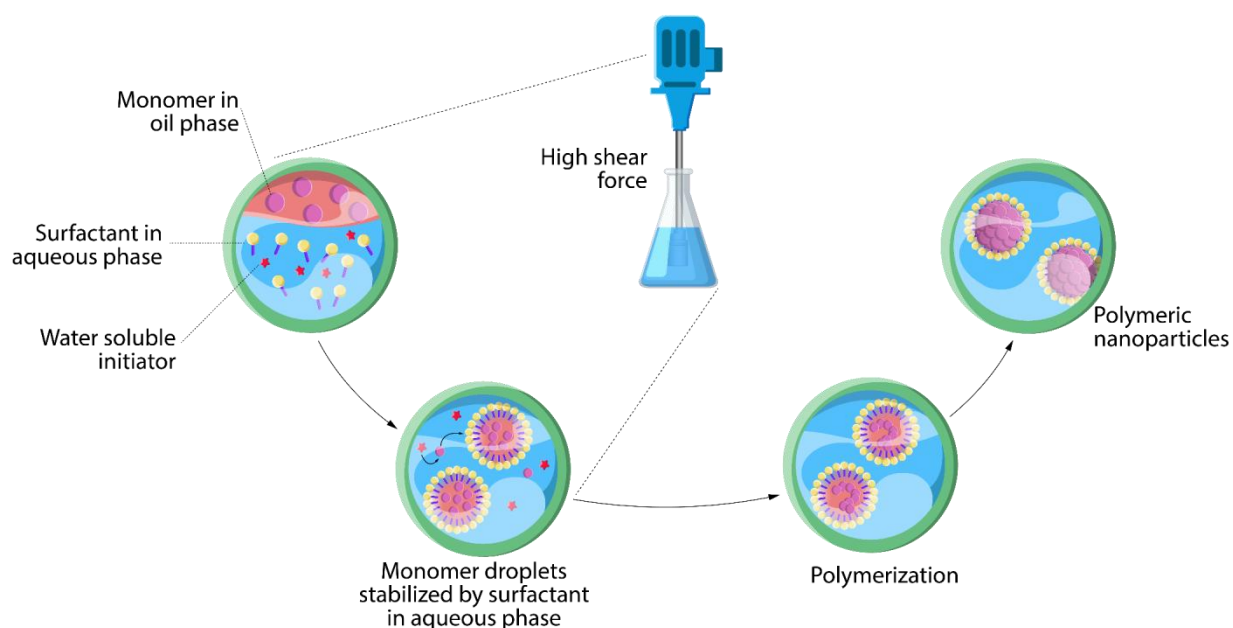


Figure 2 Nanoparticles formation by miniemulsion polymerization

Emulsion-evaporation

In this method, particles are prepared from an already existing and purified polymer in a two-step procedure. The first step is based on the emulsification of a solvent phase containing the polymer, into an additional continuous phase. The second step is the evaporation of the solvent in droplets leading to the formation of solid NPs. The drug can be dissolved in any of the phases depending on its solubility profile, making this method suitable for the encapsulation of hydrophobic and hydrophilic molecules (**Figure 3**).

Typically, biodegradable polymers such as polylactic acid (PLA), poly(lactide-co-glycolide) acid (PLGA), and polycaprolactone (PCL), are dissolved in a low boiling point solvent such as ethyl acetate, dichloromethane, or chloroform. This organic phase is added to a continuous aqueous phase containing the emulsifier, emulsified using homogenization or sonication techniques, leading to the formation of polymer droplets in the size range between 20 and 200 nm. The organic solvent will then be evaporated at atmospheric pressure or under vacuum, a step in which the organic solvent leaks from the droplets to the aqueous phase before getting evaporated. Allowing the manipulator to obtain oil-in-water (o/w) single emulsions. Modification of the procedures by using different materials can lead the formation of water-in-oil (w/o) or oil-in-oil (o/o) emulsions suitable for the encapsulation of a large spectrum of drugs with different solubility profiles. However, despite the simplicity, single emulsion suffers from low encapsulation efficiency of hydrophilic molecules. This is caused by the rapid partitioning into the aqueous phase. Therefore single emulsion is known for the encapsulation of hydrophobic molecules [9], [10].

Hypocrellin A (HA), a natural compound with various therapeutic activities, was encapsulated within PLGA nanoparticles using a single emulsion evaporation method. The achieved drug loading and encapsulation efficiency were 7% and 57% respectively, the release profile was pH-dependent, and the

solubility of the encapsulated form of HA was 35-fold that of the native HA [19]. In another study, single emulsion-evaporation was successfully used to prepare PEGylated biodegradable/biocompatible magnetic carriers. The oil phase consisted of magnetic gel added to the polymer in dichloromethane solution. This oil phase was then added to the aqueous phase containing PVA and emulsified using Ultra Turrax. The evaporation step was done at room temperature using a paddle mixer. Particles were obtained with a small size, high magnetization, and good spherical morphology. This added to their biocompatibility and biodegradability, makes these particles a suitable candidate for *in vivo* magnetically guided drug delivery [20].

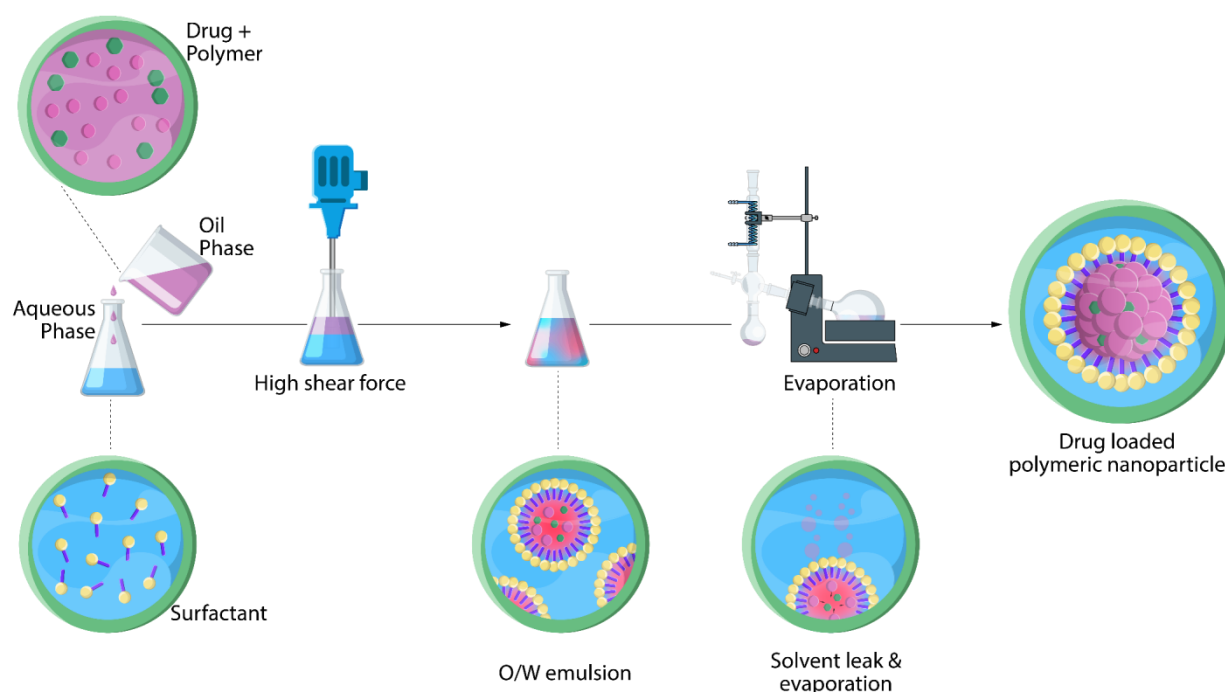


Figure 3 Formation of O/W emulsion by single emulsion evaporation

Another approach in the emulsion-evaporation method is the preparation of a double emulsion system. As its name indicates, this system consists of an emulsion droplet with smaller droplets made within. Starting from an emulsifier-free o/w emulsion, another oil phase is added with the emulsifier to create o/w/o emulsion, followed by an evaporation step. Moreover, w/o/w emulsion can also be prepared by a simple modification of the protocol. The double emulsion can fix the problem of low encapsulation efficiency of hydrophilic drugs in o/w emulsion since hydrophilic molecules are often encapsulated using w/o/w emulsion method. Several studies have reported the interest of using a double emulsion-evaporation process in drug delivery [9], [21]. Recently, w/o/w emulsion was produced to encapsulate Memantine, an approved anti-Alzheimer agent, into PLGA nanoparticles. Particles were obtained with an average size of 150 nm, monomodal size distribution, and negative zeta potential. In-vitro and in-vivo studies showed that these particles were able to cross the blood-brain barrier without inducing cytotoxicity on brain cell lines. Moreover, treated mice showed a decrease in memory impairment [22]. Another recent study uses this technique to encapsulate the anti-cancer agent Letrozole into poly(D,L-lactide) NP in order to solve the problems of poor solubility, rapid metabolism, and controlling the side effects. Obtained particles were spherical in shape with a size of 350 nm. High entrapment efficiency was obtained (96%) and the release profile was significantly improved [23].

Emulsion diffusion

Emulsion diffusion has several advantages over other preparation methods, including the use of pharmaceutically acceptable organic solvents, that yields a high encapsulation efficiency, is easily reproducible and is easily scaled-up. It is a two-step procedure and requires the use of three liquid phases. The first step is the production of a normal o/w emulsion. The second step, which is the elimination of the organic phase is done by the diffusion into the third liquid aqueous phase (dilution phase) (**Figure 4**). Once the organic solvent is diffused into the dilution phase, it can be eliminated by evaporation under reduced pressure. The organic solvent in this method should have a partial solubility in water for the diffusion step to occur, one of the favorable solvents is ethyl acetate. Nanocapsules are formed during the diffusion step upon the fact that the organic solvent went out of the droplets leaving the solid polymer particles. The size of the final particles was proven to be a function of the chemical composition of the organic phase and the size of the initial droplets [24].

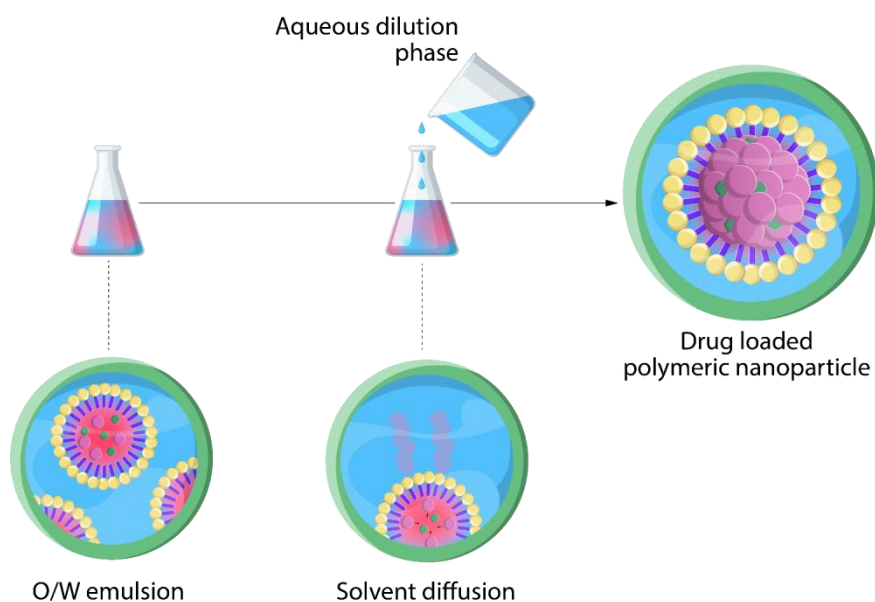


Figure 4 Nanoparticles formation by emulsion diffusion

Curcumin was encapsulated within PLGA nanoparticles using an emulsion-diffusion technique using ethyl acetate as an organic solvent. The obtained particles were spherical in shape with an average size of 260 nm. The entrapment efficiency and loading of curcumin were 76% and 15% respectively. In fact, the oral bioavailability of curcumin was increased 9-fold after encapsulation [25]. This method was also used to encapsulate fish oil into polycaprolactone (PCL) particles using ethyl acetate as an organic solvent. The encapsulation yields a high entrapment and loading, and PCL protected the fish oil because of its water insolubility [26].

Nanoprecipitation

Nanoprecipitation, also known as solvent displacement, was first developed by Fessi et al. [27]. This method has many advantages over other preparation methods. It is a fast, one-step procedure that yields a good control submicron particle with narrow size distribution [28]. In addition, this technique avoids the use of large amounts of toxic solvent or external energy sources. Two different phases are needed in the method. Solvent phase, in which polymer molecules are dissolved [29]. A non-solvent phase that is miscible with the solvent, serves as a bad solvent for the polymer in which polymer is not

soluble. Upon addition of the solvent phase to the non-solvent phase, the quality of the mixture as a polymer-solvent will be reduced, and the polymer will be precipitated as nanoparticles (**Figure 5**). The organic solvent can then be removed by evaporation or any other separation method [28]. Despite the simplicity of this technique, it has many experimental parameters that should be controlled to produce particles with desired characteristics. Factors such as polymer concentration, solvent/non-solvent volume ratio, solvent addition speed, agitation, salinity, etc. proved their effect on the colloidal properties of bovine serum albumin nanoparticles prepared by nanoprecipitation method [30].

Because of its simplicity, nanoprecipitation was heavily adopted for the preparation of nanocarriers. Recently, PLGA nanoparticles loaded with Fluticasone Propionate, a glucocorticoid used for the treatment of inflammation of nasal symptoms, were prepared. Precipitation was done by dissolving both the polymer and the drug in acetone, and then added dropwise to water under stirring. Acetone was evaporated overnight under stirring. The obtained particles have a size of 128 nm, a zeta potential of -19 mV, and the encapsulation efficiency and drug loading capacity were 68% and 4% respectively. The *in-vitro* studies showed a sustained release over a 10 days period, and cell assays on C2C12 myoblast cells show a decrease in inflammation, and effectiveness at 10 times lower concentration of the encapsulated form compared with the free form of the drug [31]. In another study, PEGylated PLGA nanoparticles loaded with paclitaxel, an anticancer agent, were synthesized with the aim of in-vivo administration. The same preparation protocol was adopted. *In-vivo* results in NMRI mice showed a noticeable antitumor efficacy and enhanced survival rate comparing with already commercialized anticancer agents [32].

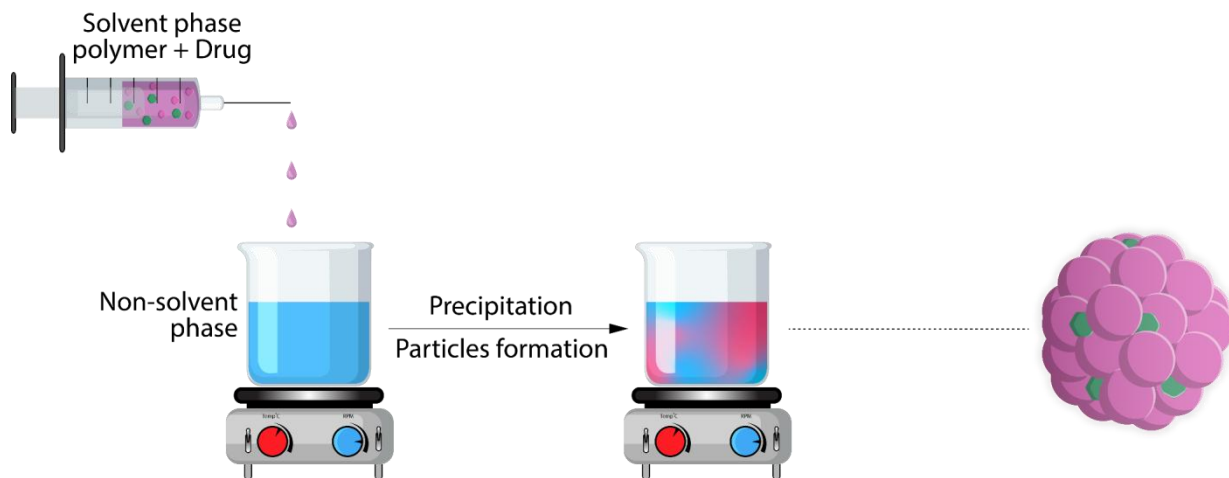


Figure 5 Nanoprecipitation method

Salting out

Salting-out is an emulsification process that has the advantage of avoiding the use of surfactants and chlorinated solvents. Instead, the emulsification occurs by adding a high concentration of salt. The salting-out agents used can be electrolytes such as magnesium chloride, calcium chloride, and magnesium acetate or non-electrolyte such as sucrose. In brief, the polymer is dissolved in an organic phase that is miscible with water and the aqueous phase should be saturated with a salting-out agent. These two phases are emulsified together and a dilution step is followed to decrease the ionic strength of the electrolyte. Leading to the formation of the particles by the migration of organic solvent from the oil phase to the aqueous phase (**Figure 6**). The salting out agent can then be eliminated with an extensive washing step [33], [34]. Allémann et al. were able to prepare poly(vinyl alcohol) nanoparticles using ethyl

cellulose as a salting-out agent. In this work, the effect of process parameters on the size of the particles was investigated. Variables such as polymer amount, homogenization method, internal to external phase ratio and stirring speed, showed an important effect on the size of particles. Proving that this method can be tweaked according to the the desired pharmaceutical application [35].

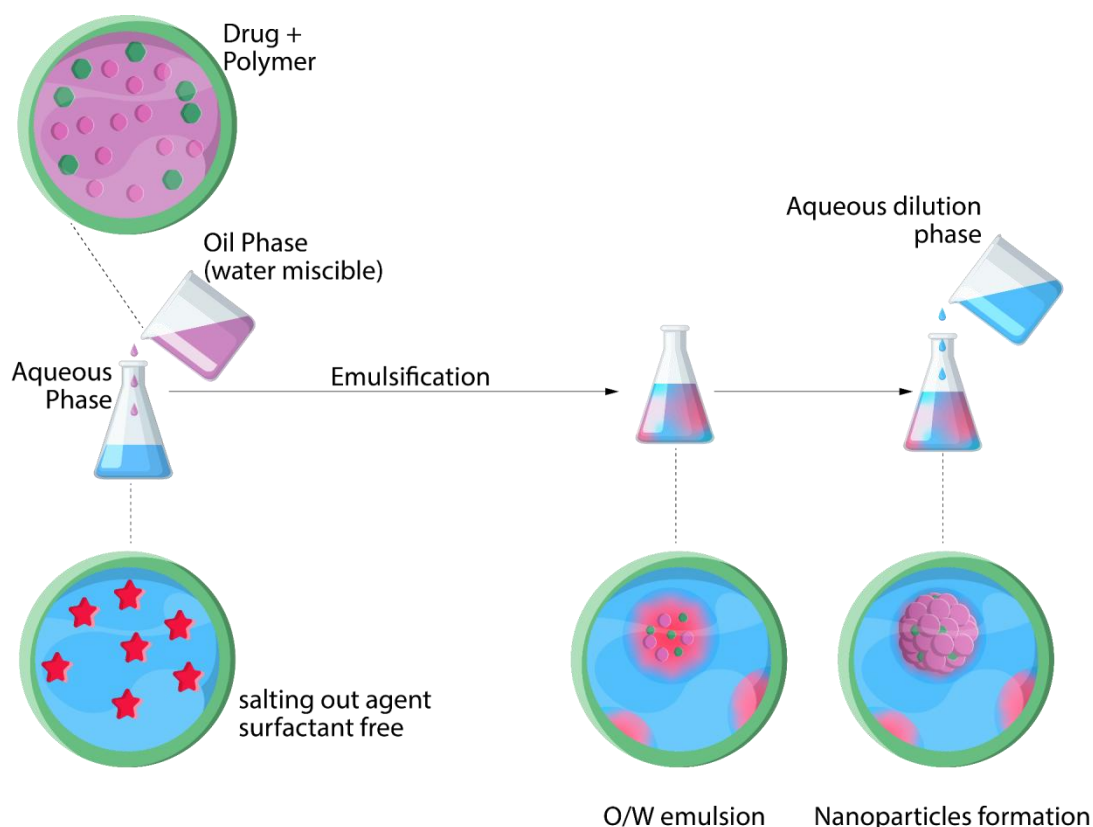


Figure 6 Salting out method for nanoparticles preparation

Cabazitaxel (Cbz), that is an active chemotherapy drug for taxane-resistant metastatic castration-resistant prostate cancer was encapsulated within human serum albumin nanoparticles with a salting-out method using disodium hydrogen phosphate as salting out agent. Particles were produced with a narrow size distribution, a drug loading capacity of 4.9% and high blood compatibility. *In-vivo* studies on prostatic cancer xenograft-bearing nude mice showed a prolonged blood circulation, and higher accumulation of the drug in tumors compared to the current clinical formulation based on Tween 80. Salting-out method not only produced more capable particles but also reduces their toxicity compared to Cbz-Tween due to the avoidance of using chlorinated organic solvent [36]. In another study, GSK 678361A, Inhibitors of p38 mitogen-activated protein kinase (MAPK) were encapsulated within PLGA nanoparticles using this technique. Polymer-drug mixes were added dropwise to the aqueous phase containing 45% MgCl_2 and 2.5% PVA. Particles with a size of 115 nm, polydispersity index of 0.13, drug loading of 10 μg per mg polymer and entrapment efficiency were produced. *Invitro* studies showed a controlled release and large inhibition of the production of pro-inflammatory cytokines compared to the free drug [37].

Ionic gelation

This method is known in the literature as the preparation of polysaccharides nanoparticles (alginate, pectin, chitosan), most famously chitosan. It is based on the ionic crosslinking of chitosan amino group (positively charged) and negatively charged polyanion such as tripolyphosphate (TPP). It attracted attention due to its simplicity and due to the fact that crosslinking by electrostatic interaction instead of chemical crosslinking can avoid toxicity and other undesirable effects [38]. In ionic gelation, chitosan is dissolved in an acidic aqueous solution (e.g. acetic acid diluted solution). This chitosan solution is added dropwise to a TPP solution under stirring. Due to the cationic properties of chitosan and anionic properties of TPP, a complexation between species will lead to ionic gelation and therefore, precipitation and formation of nanoparticles [38] (**Figure 7**).

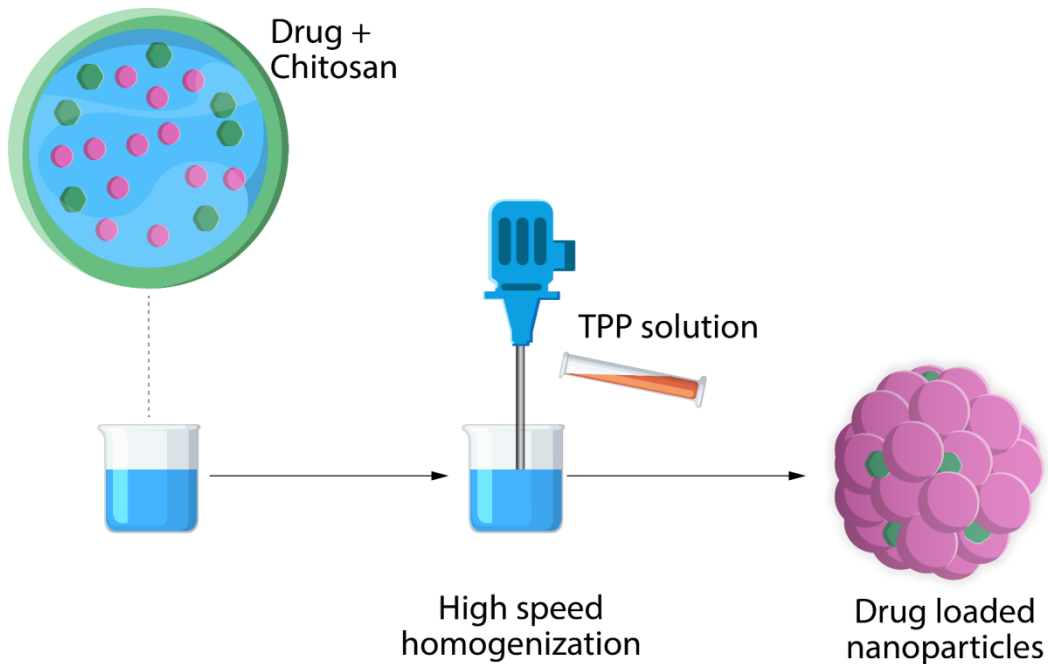


Figure 7 ionic gelation for nanoparticle preparation

Avadi et al. were able to prepare insulin-loaded chitosan/Arabic gum nanoparticles using the ionic gelation method with the aim of enhancing oral protein delivery. In this study, the effect of process variables was evaluated. It was found that these variables have an effect on the particle colloidal properties and insulin release profile, with the chitosan and Arabic gum concentrations being the most important factors that affect the association efficiency of the particles [39]. Another study used ionic gelation technique for the preparation of chitosan-ibuprofen-gellan nanogel for the transdermal delivery of ibuprofen. Chitosan-ibuprofen nanoconjugates are with a size of 14 nm due to the interaction between both. *Ex vivo* delivery across pig skin showed an enhanced skin penetration, permeability and transdermal release rate of ibuprofen [40]. Additionally, a recent study successfully prepared chitosan nanoparticles loaded with isoniazid and rifampicin separately as inhalable anti-tuberculosis agents. Particles were prepared by ionic gelation. Chitosan and the drugs were added to a TPP solution under stirring followed by a spray drying step to obtain an inhalable powder. Particles were produced with an average size of 230 nm and a decent polydispersity index. An *in vivo* study on female Balb/c mice showed that both drugs are detectable until 24 hours post nebulization in lungs, liver, spleen and kidneys [41].

Co-precipitation

Co-precipitation as a simple technic is usually used for the preparation of inorganic and metal-based nanoparticles. Iron oxide nanoparticles are widely famous in the biomedical field for their several advantages, and they are frequently synthesized using co-precipitation method. This method has several advantages such as high product yield, environmentally friendly solvent and narrow size distribution. Generally, the species forming the particles are dissolved in an aqueous medium (in the case of iron oxide nanoparticles the species are $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$). The precipitation is induced by the addition of a base under stirring at room temperature under a non-oxidation atmosphere, leading to the formation of nanoparticles. The process variables that can govern the colloidal properties of the final particles are the type and ratio of salt used, reaction temperature, pH and the ionic strength [42].

In order to obtain biocompatible and injectable nanocarriers with anti-cancer activity, co-precipitation was used to prepare iron oxide nanoparticles, coated with a polymer and loaded with doxorubicin. The obtained particles had a size of 35 nm and an antiproliferative effect on cancer cells. *In vivo* biodistribution study showed an accumulation of the drug in the tumor region and reduced cardiotoxicity compared to free doxorubicin [43]. In another study, calcium carbonate nanoparticles were prepared by a co-precipitation technique incorporating a granulocyte colony-stimulating factor. The incorporated molecule was chemically stable with a slow-release profile. Moreover, subcutaneous injection of CaCO_3 particles containing betamethasone phosphate gives rise to a smaller initial increase in plasma concentration and a subsequent sustained release compared with free betamethasone phosphate suggesting calcium carbonate particles as a promising candidate for hydrophilic drug delivery [44].

Nanoparticles Properties

The behavior of nanoparticles is based on their characteristics. The most frequently sought characteristics include size, shape and surface charge, dispersion pH, shell thickness, encapsulation efficiency, drug release, *in vivo* and *in vitro* performance and stability.

The average size of nanocapsules obtained from preformed polymers is between 250 and 500 nm. Depending on the employed preparation technique, there are many factors that influence the size of nanoparticles. Nanoparticles, thanks to their tiny size, can penetrate biological membranes and find access accordingly into the cells, tissues, and organs. Indeed, the unique physical and chemical properties of nanomaterials make them so attractive to cross biological barriers and to carry out target drug delivery accordingly [45].

The zeta potential of nanoparticles is influenced by the polymer chemical nature, stabilizing agent chemical nature, and medium pH. In fact, up to now regarding nanoparticles' zeta potential, no specific trend has been brought to light. Generally, nanoparticles dispersion pH ranges between 3.0 – 7.5 when nanoprecipitation, emulsion-diffusion or layer-by-layer techniques are used while there is no available data for the other nanoparticles' preparation methods. As described earlier, nanoparticles dispersion pH dictates the zeta potential of the dispersion and impacts their stability. Obviously, nanoparticles dispersion medium pH has a crucial impact on the nanoparticles' size and biodistribution. Shell thickness is a key factor in active molecule protection and probably in release profile of designed nanoparticles. Based on different studies shell thickness values are around 10 nm and 20 nm.

Nanoparticles' encapsulation efficiency is different based on the employed method. To generalize, nanoparticles release profile it would be rash because it depends on many variables including active substance concentration and physicochemical characteristics, polymer nature, degradability, molecular weight and concentration; and etc. Nanoparticles stability can be influenced by many factors including

nanoparticles composition, preparation method related parameters and storage conditions. Furthermore, nanoparticles' performances face many challenges such as nanoparticles' administration for targeting a specific organ permitting site-selective action and obtaining sustained delivery of drug to provide enhance therapeutic efficiency. In fact, it is not easy to tackle these challenges because when the nanoparticles enter the blood, they are promptly removed by the mononuclear phagocytic system (MPS). In addition, the extent and nature of nanocapsule opsonization is based on the physicochemical properties of nanoparticles including size, surface charge and surface hydrophobicity [46].

Nanoplatforms and drug targeting

As has been shown in the above-mentioned studies, the use of nanoparticles as drug carriers are capable to alter drug pharmacokinetics, enhance biodistribution, prolonge plasma half-life and avoid or reduce any toxicity or side effects. However, one of the main benefits of using nanosystems is the specific targeting of tumors, inflamed tissues, or any desired site [46]. **Table 1** shows different targeting strategies for carriers prepared using various preparation methods.

Table 1 Targeting strategies of nanoparticles prepared by various preparation methods.

NPs type	Encapsulated drug	Preparation method	Aim	Targeting strategy	Ref
Lipid NPs	paclitaxel	melt emulsion technology	prolong the circulation time in blood and increase the accumulation in the tumor.	Coating with hyaluronic acid	[64]
Solid lipid NPs	Sclareol	hot homogenization	Growth inhibition of A549 human lung epithelial cancer cells	Passive targeting	[53]
Solid lipid NPs	Curcumin	hot homogenization	Growth inhibition of breast cancer cells	Passive targeting	[65]
Solid lipid NPs	resveratrol	high shear homogenization	Targeting the blood-brain barrier	Functionalization with apolipoprotein E to target LDL receptors overexpressed on the blood–brain barrier	[66]
Solid lipid NPs	Paclitaxel & α -tocopherol	Emulsification solvent evaporation	synergistic effect in the suppression of cervical tumor cell growth, lower toxicity in vivo.	Modify with trans-activating transcriptional activator	[67]
Polymeric nanoparitcles	FITC-Dx	Emulsion polymerisation	Increase blood circulation time	Passive targeting	[68]
Polymeric nanoparticles	Paclitaxel	Nanoprecipitation	Growth inhibition of breast tumor cells	Functionalization with hyaluronic acid	[69]
Polymeric nanoparticles	-	Salting out	Specific targeting of human ovarian cancer cells and Daudi lymphoma	Coating with anti-HER2 and anti-CD20 monoclonal antibodies	[54]

			cells separately		
Chitosan nanoparticles	5-Amino Salicylic Acid	Ionic gelation	Colon delivery	pH-sensitivity of coated polymer	[70]
Iron oxide nanoparticles	-	Co-precipitation	Glioma targeting	External magnetic field	[61]

Passive targeting

In general, the size and surface properties of nanoparticles can be involved in passive targeting strategies that can be applied to all non-sized carriers. Due to their small size, nanoparticles can exploit the enhanced permeability and retention effect (EPR) that can be observed in certain pathologies, especially cancer. This excessive formation of vesicles will lead to a discontinuous endothelial cell barrier with pores ranging from 100 nm to 3000 nm [47]. In addition, diffusion limitation can be overwhelmed by the overexpression and activation of vascular permeability factors. This is usually accompanied by dysfunctional lymphangiogenesis leading to a longer presence of interstitial fluid in tumors compared to normal tissues. Therefore, it was shown that nanoparticles can actually increase the fraction of drug dose penetrating the tumor tissues and not in healthy ones, preventing the danger of side effects [48]. Such an effect can be clearly observed with Doxil®, a pegylated liposomal doxorubicin formulation. While free doxorubicin is known to have a significant risk of cardiomyopathy, Doxil® was shown to have a lesser risk at a cumulative dose in excess of 500 mg/m² [49].

However, despite the advantages of nanoparticles exploiting the EPR effect, there is still some limitation that prevents a therapeutic agent to reach its targeted site. Due to fenestrated vasculature, plasma fluid and proteins can leak from the capillaries of tumor or inflamed tissues. In addition, the increase of colloidal pressure caused by the high protein content in the interstitial space and the contraction of the latter caused by stromal fibroblast leads to an interstitial fluid pressure (IFP) that can obstruct the movement of nanocarriers [50]. Moreover, nanoparticles' tissue penetration is limited by the ability of immune cells to endocytosis these structures and the present of the natural biological barriers. A good example can be the blood-brain barrier that remains a challenge in central nervous system therapy [51]. Besides, large endothelial fenestrations are naturally existing in liver and spleen (100 nm 5000 nm respectively). This allows the nanoparticles to penetrate these organs and thus, reducing the specificity of drug targeting. Therefore, targeting strategies that are more sophisticated to exploit the EPR effect of altering the size and charge of the particles are needed [52].

Active targeting

Active targeting is based on the idea that the carrier is not only responsible for the protection and solubility of the drug but is also a major player in delivering the drug to a specific site. Here, the carrier must have a specific affinity to certain organs or even to specific types of cells in a key and lock fashion. Different approaches can be found in the literature to increase the specificity of nanoparticles towards certain sites [53], [54]. **Figure 8** illustrates the targeting strategies that will be treated in this part.

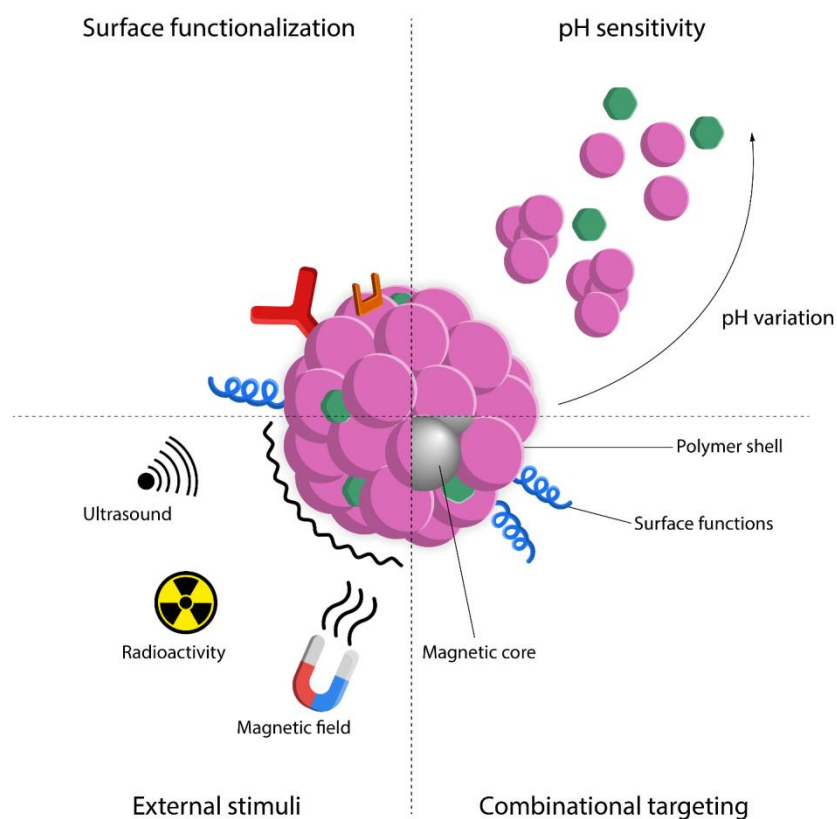


Figure 8 Active targeting strategies of nanoparticles

Surface functionalization

Probably one of the most known approaches for specific targeting is surface functionalization. Mostly, it is possible to functionalize nanoparticles via the introduction of functional groups into their surface or their surface alteration.

Polymeric and lipid carriers can be used for the treatment of liver disease. By decorating with galactose, these particles will be able to specifically target the hepatocytes since galactose possess a high affinity to the asialoglycoprotein receptor (ASGP-R), a receptor that is highly abundant on the plasma membrane of hepatocytes. This strategy will prevent other liver cells such as Kupffer cells from intaking these particles and thus increase specificity and effectiveness while reducing side effects [55]. Jeong et al. conducted *in vitro* studies on galactosylated PBLG/PEG polymeric nanoparticles loaded with paclitaxel. It was found that HepG2 cells possessing the ASGP-R receptor were more sensitive to loaded paclitaxel than the free form. While other cell lines that do not possess this receptor were more sensitive to the free paclitaxel. Confirming the specificity of the galactose coated nanoparticles [56].

Incorporating antibodies on the surface of particles is also a good example of surface functionalization. Pegylated liposomal doxorubicin conjugated with anti-CD22 antibody was designed against non-Hodgkin's lymphoma. *In vitro* studies showed that compared to non-conjugated particles, the immunoliposomes have greater cytotoxicity only in CD22-positive cells while preserving similar pharmacokinetics. In addition, doxorubicin accumulation in the tumor was created in the presence of conjugated antibody [57].

pH-sensitive nanocarriers

Drug delivery can exploit the pH changes that occur naturally or in tumor and inflamed tissues by developing pH-sensitive carriers. Due to the high glucose metabolism, insufficient blood supply and poor lymphatic drainage, tumor cells produce and accumulate lactic acid which decreases the pH at about 5.7. Griset et al. prepared polymer nanoparticles loaded with paclitaxel with a pH-sensitive 2,4,6-trimethoxybenzaldehyde linker. These particles were shown to have stability in neutral pH but cleaved in acidic pH. In their work, it was found that all paclitaxel was released within 24 hours due to the swelling of particles caused by the acidic pH. In addition, the pH-sensitive particles were able to inhibit the rapid growth of Lewis lung carcinoma in C57B1/6 mice. While non-pH sensitive nanoparticles show no significant reduction in tumor size [58].

pH-sensitive particles are also essential for intracellular drug delivery. During endocytosis, due to ATPase-mediated proton influx, the pH of early endosome drops below 6. This is where pH-sensitive nanoparticles can release their content in response to acidic pH. Yuba et al. build ovalbumin loaded liposomal formulation coupled with a pH-sensitive dextran derivative (MGlu-Dex). Cellular uptake by dendritic cells and ovalbumin delivery into the cytosol was more efficient in MGlu-Dex modified liposome, antigen-specific humoral and cellular immunity was higher and tumor growth suppression was significantly greater than non-modified liposomes [59].

External stimuli

Despite the efficacy of using a specific receptor or pH-dependent formulations, drawbacks can always be discovered. Receptors that may be overexpressed in some inflamed tissues, can also exist in a fewer amount in healthy sites giving rise to potential side effects. And pH-sensitive substances can sometimes disrupt cell membranes and lead to cytotoxicity [60]. Another approach is controlling the fate of nanoparticles by an outside manipulator, the behavior of nanoparticles can be altered by radiation, ultrasound, etc. probably the most studied factor, is the control of magnetic nanoparticles through a magnetic field.

Magnetic nanoparticles, as mentioned before, usually prepared by the co-precipitation method, have the ability to target a large variety of sites simply by applying an external magnetic field allowing accumulation within a specific area. The ability of magnetic targeting was previously demonstrated. Magnetic nanoparticles were injected intravenously in rats with orthotopic 9L-gliosarcomas and subjected to a magnetic field (0.4 T, 30 minutes). It was found that magnetic targeting was able to increase the total glioma exposure to magnetic nanoparticles by 5-fold, and enhance the target selectivity index of nanoparticle accumulation in glioma over the normal brain by 3.6-fold. This suggests that magnetic nanoparticles are promising vehicles for glioma targeted drug delivery and magnetic targeting of brain tumors [61].

Combinational targeting

Indeed, other approaches were suggested such as convection-enhanced delivery, ultrasound, enzyme-mediated targeting, the use of inflammatory mediators, etc. Moreover, a combination of two different approaches can also exist to overcome different difficulties. Liao et al. developed a complex nanosystem consisting of an iron oxide core, alginate shell and a cell-targeting ligand (D-galactosamine) on the outer surface. While the ligand assures the specific targeting, a magnetic field can induce hyperthermia and can lead to cancer cell death. It was found that the particles have an enhanced cellular uptake in a human hepatocellular carcinoma cell line (HepG2) and an excellent hyperthermic efficacy [62].

In another study, iron oxide nanoparticles and dendrimers were modified by coating with poly(ethylene glycol) (PEG) and incorporating a cancer-specific targeting moiety (LHRH peptide). PEG is known to preserve the stability of particles in circulation and released in the endosome, while LHRH peptide will assure the specific internalization. Undeniably, the siRNA loaded within these particles have an enhanced internalization into cancer cells and increased efficiency of targeted gene suppression *in vitro*. Moreover, these particles were able to enhance the antitumor activity of Cisplatin *in vivo* [63].

Conclusion

Nanotechnology has revolutionized the field of drug delivery. Recently, many studies were conducted to develop a wide range of suitable nanocarriers for all kinds of drugs. To this end, different preparation methods were suggested such as nanoprecipitation, salting out, emulsion polymerization, miniemulsion polymerization, ionic gelation, etc. Each method has its own advantages and drawbacks, which makes these techniques proper for special kinds of materials and drug molecules. Indeed, through the variety of nanoparticles and preparation methods, different drug targeting strategies can be designed. From surface modification to the exploit of environmental changes around diseased targets, different formulations were designed with high efficacy, minimal toxicity, and side effects. However, there is still room for improvement in formulation science and drug targeting strategies in order to overcome the current difficulties. Thanks to the nanoparticles capacity of accurate drug delivery to the target site such as cancer/tumor cells without disturbing normal cell physiology, nanomedicine is the trend that will be the future research and development area.

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