Journal of King Saud University – Science 31 (2019) 398–411

Contents lists available at ScienceDirect

Journal of King Saud University – Science

journal homepage: www.sciencedirect.com

Review

Morphologies and functionalities of polymeric nanocarriers as chemical tools for drug delivery: A review

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ARTICLE INFO

Article history:
Received 31 July 2017
Accepted 30 October 2017
Available online 1 November 2017

Keywords:
Nanostructured polymers
Drug delivery systems
Dendrimers
polymeric micelles
Polymeric nanoparticles
Nanogels
Polymeric nanocapsules
Vesicles

ABSTRACT

In these years a variety of polymeric nanocarriers such as dendrimers, polymeric micelles, nanoparticles, nanogels, nanocapsules and vesicles are widely investigated as potential drug delivery systems. In addition to the different morphologies and sizes, these carriers may have on their surfaces specific functionalizations to improve the drug loading and controlled release and specific ligands for cell receptors, in order to achieve a precise targeting. This review focuses on recent functionalized polymeric nanomaterials used as drug delivery systems, with an emphasis on morphology and surface modifications of polymeric nanocarriers to improve controlled drug delivery. Moreover, this work offers a number of suggestions on how to achieve the systematization of data on the most relevant physico-chemical parameters, which govern and control the interaction between carrier and drug, with the aim to give the reader an overview of the most significant advances in this field.

Contents

1. Introduction

In the last decade the fabrication of nanostructures has allowed to obtain materials, organic, inorganic and composites, with better performance in huge range of different applications, such as sensors (Scognamiglio, 2013; Fratoddi et al., 2016; Potyrailo et al., 2011; Prosposito et al., 2016), optoelectronics (Zhao et al., 2010; Venditti et al., 2010a,b; Venditti, 2017; Beshkar et al., 2017a,b), catalysis (Safardoust-Hojaghan et al., 2017a,b; Valian et al., 2017) energy (Zhang et al., 2013; Persano et al., 2015; Venditti et al.,

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

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https://doi.org/10.1016/j.jksus.2017.10.004
1018-3647/

2014; Shi et al., 2015), biotechnology (Safardoust-Hojaghan et al., 2017a,b; Beshkar et al., 2017a,b; Fratoddi et al., 2012a,b), and medicine (Ho et al., 2015; Venkataraman et al., 2011; Fratoddi et al., 2015; Sangsefidi et al., 2017). In particular polymers can be used in the fabrication of several nanostructures, such as polymeric micelles, dendrimers, nanopartilces, nanogels, nanocapsules and vesicles, that are widely used as drug delivery systems. These nanostructures show the properties of the carries and often chosen polymers respond to a stimulus or their environment, such as changes in temperature, pH, light, redox potential, inducing dynamic and reversible changes useful to release the drugs (Sagadevan and Periasamy, 2014; Hruby et al., 2015; Rossi et al., 2016). Moreover, many scientific researchers are moving towards the realization of efficient vectors from the point of view of load and controlled release and, at the same time, aimed to a specific action site (Chithrani et al., 2006; Jiang et al., 2008; Bessar et al., 2016; Porcaro et al., 2016).

This review seeks to give a wide view of the recent developments in drug delivery systems based on nanostructured polymers, in particular on dendrimers, micelles, nanoparticles, nanogels, nanocapsules, vesicles, stressing that the surface chemistry and the introduction of specific functionalization likely to be crucial in drug delivery applications. Let us now see specifically the advantages and limitations of the various nanostructured polymeric systems.

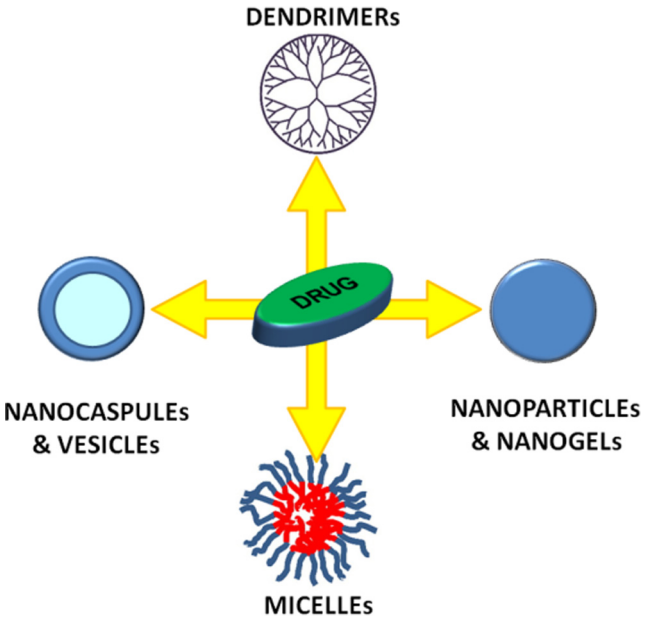

Fig. 1. Schematic structures of various representative polymeric drug delivery systems.

2. Polymeric nanocarries

Most polymeric materials have been adopted as a preferred method for drug delivery because they show a good potential for surface modification via chemical transformations, provide excellent pharmacokinetic control, and are suitable for the entrapment and delivery of a wide range of therapeutic agents (Couvreur, 2013; Jia et al., 2013). In particular, several morphologies, including dendrimers (Newkome and Shreiner, 2008; Kim et al., 2007; Murugan et al., 2014; Cong et al., 2016), micelles (Hong et al., 2017; Cho et al., 2012; Otsuka et al., 2003; Matsuno and Ishihara, 2011; Feng et al., 2006; Zhang et al., 2009; Yang et al., 2009), polymeric nanoparticles (Fratoddi et al., 2012a,b; Laganà et al., 2011; Kumari et al., 2010; Fratoddi et al., 2011) nanogels (Joung et al., 2013; Koehler et al., 2013), nanocapsules (El-Gogary et al., 2014; Chen et al., 2014; De Koker et al., 2012) and vesicles (Carafa et al., 2010; Coviello et al., 2015) schematized in Fig. 1, are used for their easy surface modulation in terms of charges and functionalities.

In fact, several properties can be achieved by opportune choice of superficial functionalization of polymeric nanomaterials, such as loading optimization, best bioavailability and controlled-targeted release to specific site. For this reason, research is focused on the introduction of specific surface functionalization, often amine and acid, on the nanostructured drug delivery systems.

In Table 1 common functionalities were reported with several morphologies that highlight the importance of surface chemistry in nanomaterials for biomedical application.

In fact, the polymer matrix prevents drug degradation and may provide management of drug release from these soft nanoparticles. Varying the drug-to-polymer ratio and molecular weight and composition of the polymer can modify the extent and level of drug release (Prabha and Labhasetwar, 2004). Surface properties of these materials are also the main component of their targeting characteristics: when the cellular membranes come into direct contact with soft nanoparticles surface and their properties, this can determine the mechanism of internalization and intracellular localization: the polymeric surface can be conjugated with peptides, aptamers, or antibodies to enable specific targeting (Ernsting et al., 2012; Gan and Feng, 2010; Kim et al., 2012).

2.1. Dendrimers

Dendrimers are highly branched nanostructures with an inner core. The drugs are incorporated both in the interior core both attached on the branched surface, covalently or by electrostatic mode, as schematically reported in Fig. 2.

In general the most used macromolecules in this field are produced from macromolecules such as polyamidoamine (PAMAM), polypropyleneimine and polyaryl ether (Zhao et al., 2009; Eichman et al., 2001; Newkome and Shreiner, 2008; Kim et al., 2007; Murugan et al., 2014; Ponnapati et al., 2011). The particle size range is between 1 and 100 nm although, in general, their sizes are mostly less than 10 nm (Tomalia et al., 2012; Sadekar and Ghandehari, 2012). The uniqueness of dendrimers is based on their series of branches, multivalency, well defined molecular weight and globular structure with controlled surface functionality, which enhances their potential as carriers for drug delivery (Imae, 2012; Gupta et al., 2006). Due to their versatility, both hydrophilic and hydrophobic drugs can be incorporated into dendrimers (Imae, 2012; Wolinsky and Grinstaff, 2008; Nowacek and Gendelman, 2009). Their advantages, which include increased half-life, increased solubility, stability, and permeability of drugs, the capability to deliver a variety of drugs, reduced macrophage uptake, targeting ability, facile passage across biological barriers, rapid cellular entry, improved de-livery efficiency, and reduced side effects by targeted delivery (Nowacek and Gendelman, 2009; Najlah et al., 2007; Najlah and D'Emanuele, 2006;Wong et al., 2012; Menjoge et al., 2010). However, dendrimers suffer from several limitations such as poor/unstable hydrophobic drug loadings, inefficient release of drug at targeting (Bugno et al., 2015). New class of molecules called dendronized polymers, which are linear polymers that bear dendrons at each repeat unit, are recent development to answer at this problem (Tomalia et al., 2012). Another approach is to use dendrimers incorporating a degradable link that can be further used to control the release of the drug. For example Chang et al. prepare drug release system based on folic acid (FA) conjugated to poly(ethylene glycol) (PEG)-modified dendrimers (PAMAM) with doxorubicin (DOX) and superparamagnetic iron oxide (Fe_3O_4) (FA-PEG-PAMAM-DOX@IONPs) (Chang et al., 2012).

Table 1
Monomers, functionalities, morphologies of selected nanostructured polymers used as drug delivery systems.

Monomer	Polymer Acronym	Functionality	Morphology	References
Amidoamine	PAMAM	$-RCONR_1-NH_2$	Dendrimers	Newkome and Shreiner (2008)
Propyleneimine	PPI	$-[N-(CH_2)_3-]_nNH_2$	Dendrimers	Newkome and Shreiner (2008), Kim et al. (2007), Murugan et al. (2014), Cong et al. (2016)
Ethylenglycol	PEG	-OH	Micelles	Hong et al. (2017), Cho et al. (2012), Otsuka et al. (2003)
2-methacryloyloxyethyl phosphorylcholine	pMPC	$-PO_3^-CH_2-N^+R_3$	Micelles	Matsuno and Ishihara (2011), Feng et al. (2006)
Carboxybetainemethacrylate	pCBMA	$RCOOR_1$	Micelles	Zhang et al. (2009), Yang et al. (2009)
Methylmethacrylate	PMMA	-COOMe	Spherical NPs	Fratoddi et al. (2012a,b), Laganà et al. (2011)
Lactic acid	PLA	-COOR	Spherical NPs	Kumari et al. (2010)
Dimethyl propargyl amine	PDMPA	$-N(Me)_2$	Core-shell NPs	Fratoddi et al. (2011)
Heparin-Pluronic nanogel	Hep-Pr	$-SO_3^-$ - COOH	Nanogel	Joung et al. (2013)
Ethylenglycol	PEG	-OH	Nanogel	Koehler et al. (2013)
Lactide-co-glycolide	PLGA	-OH	Capsules	El-Gogary et al. (2014), Chen et al. (2014)
Styrenesulfonate- allylamine	PSS-PAH	SO_3^- $-CH_2=CH-CH_2-NH_2$	Capsules	De Koker et al. (2012)
Alginate-N-isopropylacrylamide-N, N′-dimethylacrylamide	Alg-PNIPA- PDMAA	$-CONHCHMe_2$ $-CONMe_2$	Multilayer capsules	Zarket and Raghavan (2017)
Liposomes			Vesicles	Carafa et al. (2010)
Niosomes			Vesicles	Coviello et al. (2015)

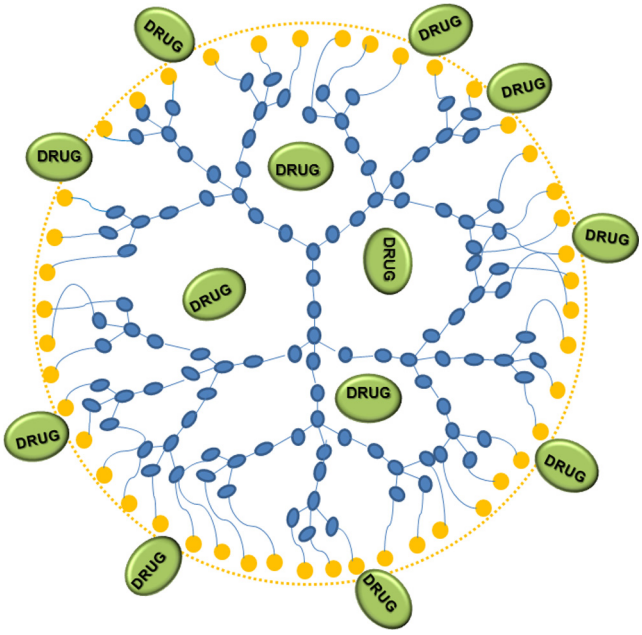

Fig. 2. Scheme of drug loading in dendrimeric structure.

This conjugates have pH-responsive drug release systems, which enabled pH-controlled activation of DOX in buffers that model the environment within endosomes/lysosomes of tumor cells. Further limitation of dendrimers is their toxicity due to their size and to the existence of positively charged surface functionalities, in case of cationic dendrimers, in particular amino groups. In fact, their characteristic size and functionalizations guide to non-specific interaction with biological entities, such as mitochondria, enzymes and cell membrane. Recent research has focused on the biocompatibility improvement of dendrimers: surface engineering masks the cationic charge of dendrimer surface either by neutralization of charge, for example PEGylation, acetylation, carbohydrate, peptide conjugation and complexation with DNA (Jain et al., 2010; Janaszewska et al., 2013; Caminade et al., 2015a,b; Kesharwani et al., 2015). Although the good outlook, dendrimers based drug delivery systems application in therapies with defined dosage regimen is still not acceptable, above all due to the difficulty of synthesizing the desired systems in large quantities at clinical grade purity, for clinical trials (Yeo, 2013). Recently, Cong et al. focused the study upon the bioconjugation of glycyrrhetinic acid (GA) onto PPI dendrimers to enhance their liver cell targeting capacity and minimize cytotoxicity: one step synthesis of GA-PPI dendrimers was developed through introduction of GA to the backbone of the PPI dendrimer by EDC chemistry with fine tuning substitution, that influenced particle size and zeta potentials and consequently the DNA binding and protection capability of GA-PPI carriers, as reported in Fig. 3 (Cong et al., 2016).

In this work it is demonstrated how to develop high-performance gene carriers based on PPI dendrimers via one step conjugation. Moreover authors the authors show how it is necessary to test in vitro and in vivo systems, thus opening the prospect of subsequent clinical trials.

2.2. Micelles

Amphiphilic polymeric molecules, associated in aqueous medium to form core-shell structures or vesicles, form polymeric micelles (see Fig. 4). Hydrophobic drugs or contrast agents can be encapsulated in the core of the polymeric micelle (Liang et al., 2006) and its multifunctionality should lead to more developments regarding biomedical applications.

In general polymeric micelles are formed from amphiphilic block copolymers and are more stable than surfactant micelles in physiological solutions: the inner core of a micelle is hydrophobic while the surface corona is hydrophilic as a result of conjugating with commonly utilized polymers such as polyethylene glycol (PEG) and oligo(ethylene glycol) (OEG) (Hong et al., 2017; Cho et al., 2012; Almgren et al., 1995). The hydrophilic shell and size (<100 nm) of polymeric micelle naturally gives a surface-smoothing effect, reducing its interaction with serum proteins and prolonging their circulation time in the blood (Jiang et al., 2011; Lai et al., 2012). Lipid moieties, such as cholesterol and fatty acyl carnitines, can also be employed to impart good stability to the polymeric micelles. Polymeric micelles have been extensively used for passive targeting, *i.e.* by exploiting the enhanced permeability and retention (EPR) effect of tumor tissues (Bae and Kataoka, 2009; Tyrrell et al., 2010). However, one of the significant disadvantages of normal self-assembled polymeric micelles is that micelles are not stable and they may dissociate upon dilution. Besides, sometimes, the targeting ability of polymeric micelles is limited due to low drug loading and low drug incorporation stability which cause the drug release before getting to the action site (Yamamoto et al., 2007; Seow et al., 2007). Cross-linking approaches have been shown to be an effective way to improve

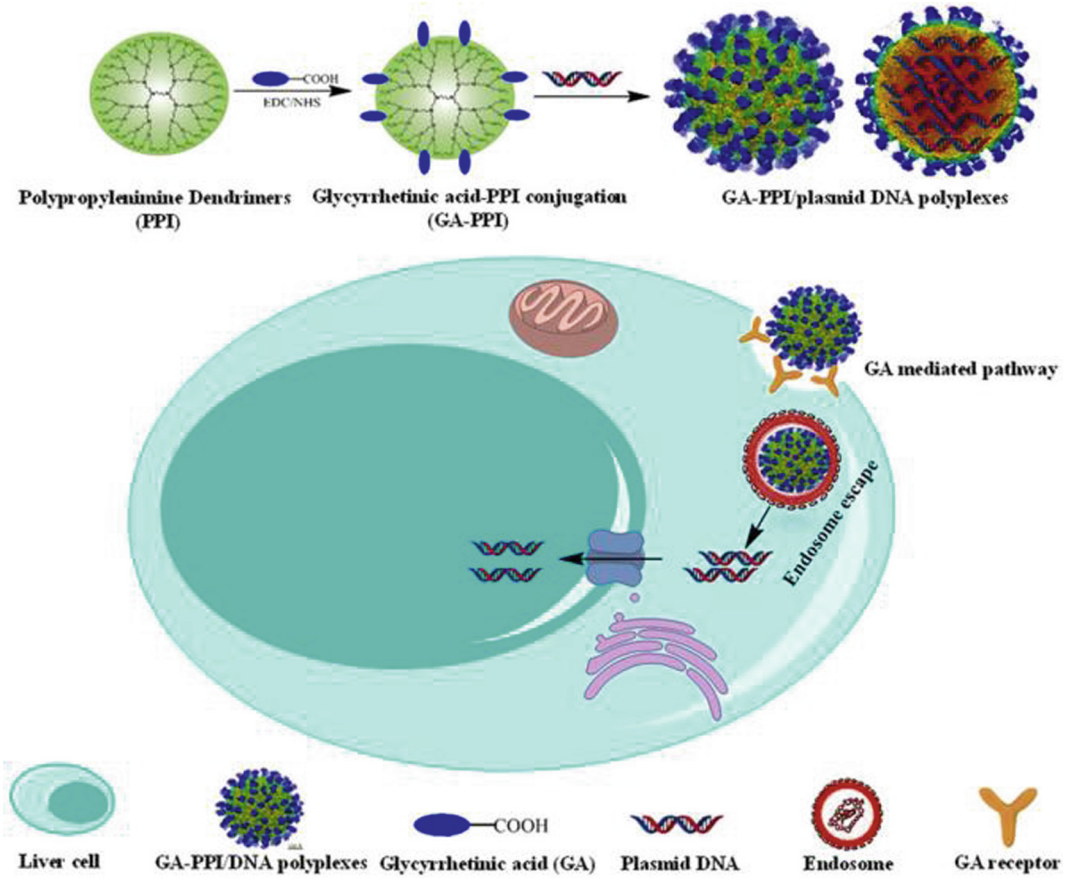

Fig. 3. Schematic illustration for the targeted gene delivery of GA equipped PPI dendrimers (GA-PPI) (Cong et al., 2016).

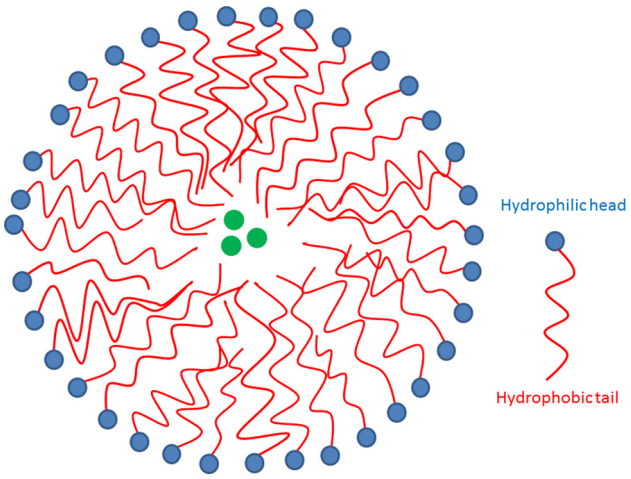

Fig. 4. Scheme of drug loaded micelle.

the stability of micelles (Read and Armes, 2007; Li et al., 2006), but most techniques resulted in overly stable micelles, which are not desirable due to the extremely slow drug release after the micelles arrive at the target sites. In this sense, the application of degradable linkages for cross-linking would facilitate the drug release. Stimuli responsive polymeric micelles are very promising because they can achieve sudden drug release with environmental stimulus such as temperature (Fujimori et al., 2005), pH (Chan et al., 2008), light (Patnaik et al., 2007; Dai et al., 2011), and redox (Song et al., 2011; Li et al., 2011). With the investigation on the mechanism of nonfouling materials, polyzwitterionic materials, such as poly(2-methacryloyloxyethyl phosphorylcholine) (pMPC) (Matsuno and Ishihara, 2011; Feng et al., 2006), poly(sulfobetaine methacrylate) (pSBMA) (Chien et al., 2013), poly(carboxybetaine methacrylate) (pCBMA) (Zhang et al., 2009; Yang et al., 2009), and simply mixed-charge materials (Tah and Bernards, 2012; Li et al., 2013) have been recognized as effective nonfouling materials which can maintain the stability of micelles in complex media such as serum. Therefore, polyzwitterionic materials might be good alternatives of PEGs for excellent stability in blood.

A promising approach to reverse multidrug resistance (MDR) is intracellular co-delivery of different MDR-modulating agents. Hong et al. report the synergistic MDR reversal effect induced by curcumin and the Pluronic L61 unimers that was evacuate using a system designed for intracellular co-delivery with pH-sensitive micelles: a micellar delivery system, including a copolymer of PHis-PLA-PEG-PLA-PHis and Pluronic F127, was partially conjugated with folate (see Fig. 5). Folate is used to ensure intracellular co-delivery via endosomal pH-triggered drug release, copolymer facilitates endosomal escape and both the Pluronic L61 unimers and curcumin were selectively accumulated in the mitochondria (Hong et al., 2017).

2.3. Polymeric nanoparticles and nanogels

Nanoparticles are known as hard/inorganic nanoparticles, referring those particles made by inorganic materials that keep their original shape and size, or soft/polymeric nanoparticles, made by organic materials that are subject to size and shape change in specific conditions of temperature, pH, pressure and ionic strength (Chen et al., 2016; Sangtani et al., 2017).

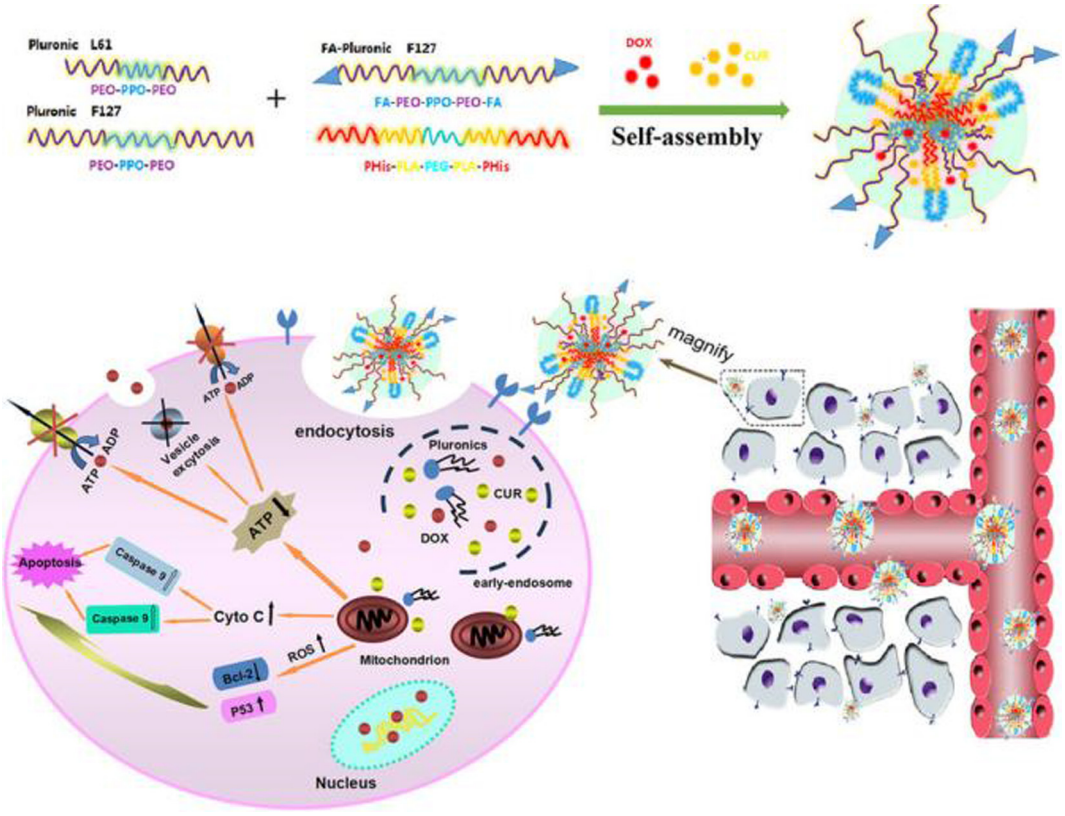

Fig. 5. Scheme of the design and proposed mechanism of F-pHSM-L61/CUR/DOX (Hong et al., 2017).

In particular the polymeric nanoparticles are colloidal soft particles with a size range of 10 to 1000 nm (Yih and Al-Fandi, 2006; D'Amato et al., 2006; De Angelis et al., 2014; Pantalei et al., 2007) and they can be spherical, branched or shell structures (Venditti et al., 2011; Bearzotti et al., 2008; Fratoddi et al., 2011). They are developed from non-biodegradable and biodegradable polymers (Venditti et al., 2015; Venditti et al., 2007; Chronopoulou et al., 2009; Kumari et al., 2010; Venditti et al., 2010a,b). Their small sizes enable them to penetrate and to be taken up by cells, thereby increasing the accumulation of drugs at target sites. Several method can be used to incorporate drug into polymeric nanoparticles such as dissolution, precipitation, adsorption or attachment, as schematically shown in Fig. 6 (Kumari et al., 2010; Tang et al., 2012; Reis et al., 2006).

The polymeric nanoparticles can provide sustained release of the drugs for longer periods, e.g., days and weeks. (Arias et al., 2008; Fratoddi et al., 2012a,b) and they can enhance immunization by prevention of degradation of the vaccine and increased uptake by immune cells (Singh et al., 2006). To target drugs to site of action, the drug can be conjugated to a tissue or cell specific ligand or coupled to macromolecules that reach the target organs (Guicun et al., 2012; Laganà et al., 2011).

In general nanoparticles used for drug delivery have at least three components: the constituent material, the therapeutic molecules and the biological surface modifiers, which enhance the biodistribution and tumour targeting of the nanoparticles, as reported by M. Ferrari and schematically represented in Fig. 7 (Ferrari, 2005).

Some applications of polymeric nanoparticles include brain drug targeting for neurodegenerative disorders such as Alzheimer's disease(Mittal et al., 2011; Masserini, 2013), topical administration to enhance penetration and distribution in and across the skin barrier (Alvarez-Román et al., 2004; Schneider et al., 2009) and

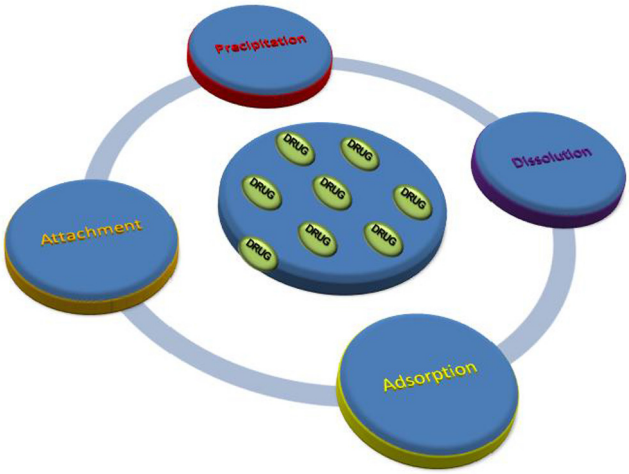

Fig. 6. Scheme of methods for drug loading in polymeric nanoparticles and nanogels.

pH-sensitive polymeric nanoparticles to improve oral bioavailability of drugs (Dai et al., 2004; Vijay and Wagh, 2014). Most of the polymers used in the fabrication of nanoparticles are biodegradable, such as chitosan, alginate, albumin, gelatin, polyacrylates, polycaprolactones, poly(D,L-lactide-co-glycolide) and poly (D,L-lactide) (Venditti et al., 2008; Venditti et al., 2011; Kumari et al., 2010). However, there are concerns about their scalability in biomedicine applications, due to some disadvantageous aspects such as: a) degradable polymers can exhibit substantial dose dumping at some point following implantations; b) "burst effect" or high initial drug release soon after administration is typical of most system; c) degradable systems which are administered by polymeric

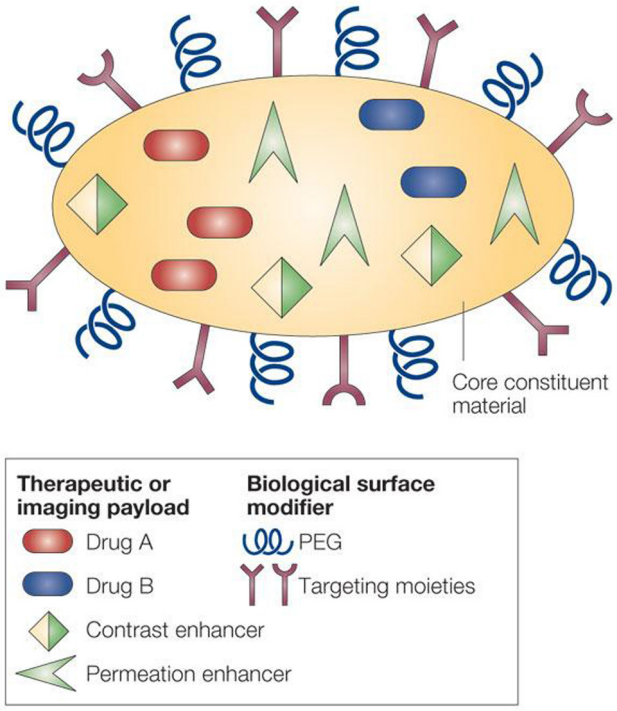

Fig. 7. Scheme of multifunctional nanoparticles (Ferrari, 2005).

nanoparticles injection are non-retrievable (Phale et al. 2013; Shen and Burges, 2012). A new class of polymeric nanocarriers showing amazing properties are the nanogels (Jiang et al., 2014). These materials show excellent biocompatibility, a fine structure with modificable porosity being flexible and feasible platform for targeted drug delivery (Joung et al., 2013; Hu et al., 2015). In the past decade, various physical and chemical cross-linking strategies have been developed Nanogels can be to fabricated by two main ways, the physical approach and the chemical approach. The physical approach produces thermosensitive, stereocomplexed, and ionically crosslinked hydrogels, under particularly mild conditions, but these materials show poor long-term stability in tissues (Hoare and Kohane, 2008). On the other hand, chemical approach forms nanogels generally characterized by better stability, durability, and mechanical properties (Censi et al., 2010), but they can bring in potential toxicity concerns, such as the presence of copper catalyst in some cases. In recent years, a new strategy based on the click reactions is emerging to produce nanogels for biomedical applications. This approach allow to obtain materials with high coupling efficiency and specificity, bioorthogonality, compatible with live cells, proteins and therapeutics. Thiol-ene click reaction, DielseAlder and inverse electron demand Diels-Alder reaction, oxime reaction, and tetrazole-alkene photo-click reaction are used as click reaction to produces nanogels. As example, Diels Alder click reaction to produce hydrogels could be reversed at high temperature through the retro-DA reaction, which opens a way to controller drug release (Koehler et al., 2013).

2.4. Nanocapsules and vesicles

Nanocapsules are spherical hollow structures in which the drug is confined in the cavity and is surrounded by a polymer membrane (Landfester et al., 2010; Couvreur, 2013). Biodegradable polymers are used for preparing nanocapsules, which include both natural polymers and synthetic polymers. The main preparation methods are: nanoprecipitation, emulsion-diffusion, double emulsification, emulsion-coacervation, layer-by-layer assembly (Mora-Huertas et al., 2010) The selection of appropriate components for nanocapsule preparation is crucial for achieving a long term stability and biocompatibility of the functional cargo as well as its improved internalization by target tumor cells: the crucial requisite to construction of long-term container is formation of stable interfacial complex between an appropriate ionic surfactant and the first layer of oppositely charged PE. Bazylińska et al. report two types of multifunctional core-shell nanocarriers obtainable by self assembly approaches (Fig. 8) (Bazylińska, et al., 2016). The strategy applied for fabrication of the $NaYF_4$:Tm^{3+},Yb^{3+} NPs-loaded nanocapsules via a two-step process is presented in Fig. 5: first evaporation method (Stage I), followed by layer-by-layer (LbL) saturation technique (Stage II). Furthermore, LbL assembly allows for engineering their shells on the nano-level, leading to the construction of biocompatible nanocontainers with desired biospecific properties including (i) improved biodistribution via pegylation process; (ii) tumor targeting via functionalization of the top PE layer with ligand of a specific cell receptor overexpressed on tumor cells; (iii) reduced immunogenicity via application of protein- or polysaccharide-based materials (del Mercato et al., 2014).

Nanocapsules use in drug delivery systems involves targeting drug delivery, controlled/sustained release drug delivery systems, transdermal drug delivery systems and improving stability and bioavailability of drugs (Rong et al., 2011; El-Gogary et al., 2014). Sizes between 50 and 400 nm are preferred for drug delivery and they can be employed as confined reaction vessels, protective shell for cells or enzymes, transfection vectors in gene therapy, dye dispersants, carriers in heterogeneous catalysis, imaging and drug carriers (Baier et al., 2012; Chen et al., 2014). Indiscriminate drug distribution and severe toxicity of systemic administration of chemotherapeutic agents can be overcome through encapsulation (MacDiarmid et al., 2007; Hervella et al., 2008). An interesting example of a new smart materials for drug delivery are the polymeric multilayer capsules (PMLCs), that are generated by sequential deposition of polymer layers from aqueous solutions onto a sacrificial template (De Koker et al., 2012; Peyratout and Dahne, 2004) or by a strategy involving successive free-radical polymerizations around an initial gel core (Zarket and Raghavan, 2017) (see Fig. 9). This latest approach allows to modulate both thickness and composition of each layer and in particular, the polymeric layers can be responsive to different stimuli, such as temperature and pH. PMLCs have attracted attention for drug-delivery applications because they are now being engineered to encapsulate various classes of drug molecules, by using polymers that are biodegradable (Sukhorukov et al., 2007; De Geest et al., 2009) and because they can respond and release their payload in response to well-defined stimuli following step-like profiles.

The major benefit of PMLCs is their flexibility: they can be fabricated using various templates, with sizes varying from a few nanometers to hundreds of micrometers, and their chemical and mechanical properties can be precisely tailored by modulating the thickness and constitution of the shell (Parakhonskiy et al., 2014).

Among other Cyclodextrins (CDs) have been studied and widely used as pharmaceutical excipient for being capable to incorporate or adsorb the guest molecules into their central cavity. The arrangement of D-glucopyranose monomers in chair confirmation gives cyclodextrin a specific truncated cone shape structure with hydrophobic inner cavity and hydrophilic outer surface. The inner central cavity is lined by skeletal C H groups and ethereal oxygen of the glucose residue imparting lipophilic property. The hydroxyl functions of sugar moieties of CDs are oriented to the exterior of the cone where the secondary hydroxyl group are located at the wider edge and the primary ones are positioned on the narrow

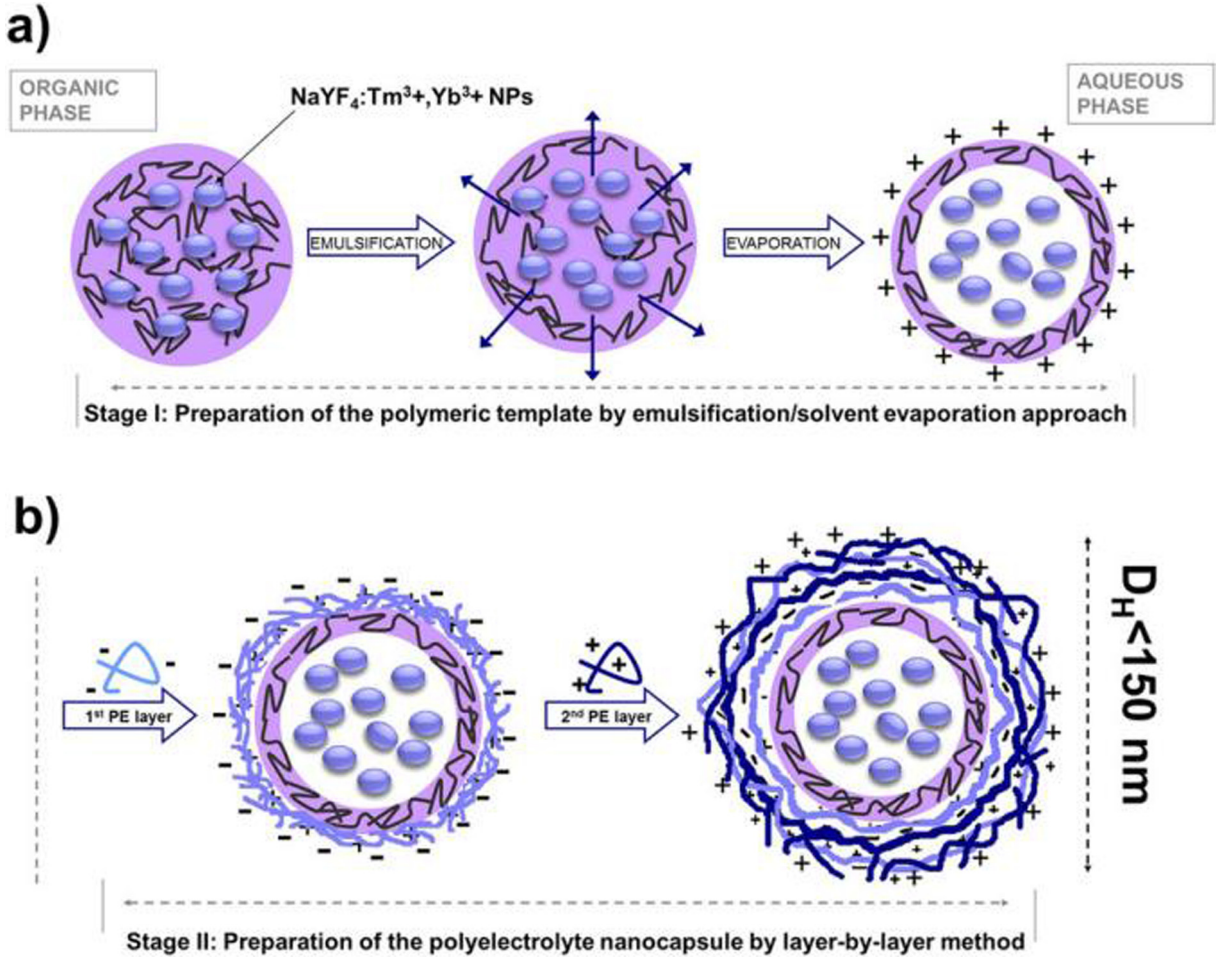

Fig. 8. $NaYF_4$:Tm^{3+},Yb^{3+}NPs loaded oil-core polyelectrolyte nanocapsules preparation by two-steps: emulsification/solvent evaporation (a) and LbL (b) approach (Bazylińska, et al., 2016).

edges, which make the outside surface hydrophilic. Cavity is used for encapsulation of hydrophobic drug of suitable size. Recently, new CDs based nanomaterials were proposed, such as cyclodextrin nanosponges: drug is loaded into nanocavities of cyclodextrin by suspending nanosponges within drug dispersion followed by freeze drying with drug. Solvent evaporation is another technique to load the drug into nanosponges in which suitable organic solvent is used to dissolve drug. Nanosponges are added to this drug dispersion and triturated till the solvent gets evaporated (Gurusalkar et al., 2013). Moreover, to control drug release in response to exogenous or endogenous stimulations, stimuli sensitive nanosponges were developed. Other class of these materials are the molecularly imprinted nanoponges, in which the drug could be included in the cross-linked structure during the synthesis, thereby leading to an increased payload and much slower drug release (Swaminathan et al., 2016; Caldera et al., 2017).

In these years, vesicles are extensively studied as drug nanocarrier, due to their chemico-physico properties useful to obtain a multi-functional devices. In fact, these materials have amazing properties such as nanoscale size, high surface-to-volume ratio, and they have the potential to modulate both the pharmacokinetic and pharmacodynamic profiles of loaded drug (Marianecci et al., 2016). Among others liposomes and niosomes have attracted great attention (Tavano and Muzzalupo, 2016). Liposomes are nanovesicles that contain amphipathic phospholipids arranged in one or more concentric bilayers, which enclose an equal number of aqueous compartments. Niosomes are vesicles composed mainly of hydrated non-ionic surfactants in addition to, in many cases, cholesterol (CHOL) or its derivatives: this tructures make niosomes capable of encapsulating both hydrophilic and lipophilic substances. The main advantages of these nanomaterials are the ability to respond to external stimuli, prolonged blood circulation, the capability to penetrate across peptide channels inside the cell (Carafa, et al., 2010; Coviello et al., 2015).The drawback of liposomes and niosomes is a physical instability because during dispersion there is possibility of aggregation, fusion, drug leakage, or hydrolysis of encapsulated drugs (Moghassemi and Hadjizadeh, 2014). Moreover the challenge is open regarding the understanding of the mechanisms by which these nanocarrier reach the target site and exercise drug action at cellular level.

3. Critical properties of nanostructured polymers

Currently materials science is promoting the study and development of stimuli-responsive materials, not only in the construction of model systems to understand the response of biological materials to trigger, but also in designing and implementing new "smart" materials with stimuli-responsive structures and functionalities (Girard et al., 2007; Mitragotri and Lahann, 2009; O'Reilly et al., 2006; Moughton and O'Reilly, 2008). Polymer-based systems are promising in this field because it can be produced with a variety of chemical functionalities, post synthetically modified easily, in large scale and processed in different forms such as films,

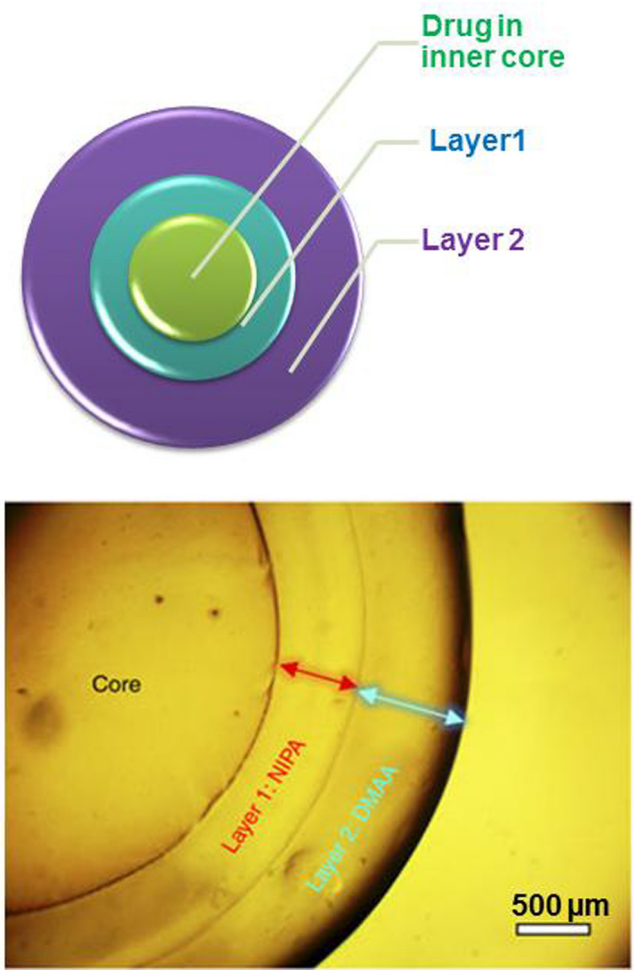

Fig. 9. a) Scheme of drug loaded polymeric multilayer capsules (PLMCs); b) Example of real PLMCs: optical micrograph of a capsule with an alginate (Alg) core, a layer 1 of N-isopropylacrylamide (NIPA) and layer 2 of N,N′-dimethylacrylamide (DMAA). (Zarket and Raghavan, 2017).

solutions, solids. In fact, external stimuli such as pH, temperature, redox potential, light and magnetic field, can induce variation of density, transparency and conductivity, volume (or degree of swelling), or solvent absorption capacity of the polymeric materials (Hirst et al., 2008; Esser-Kahn et al., 2011).

The preparation of polymeric nanostructured materials, with controlled dimensions, morphology and surface features, properties that directly affect the "smart" behavior, require specific methods of preparation. Synthesis of dendrimers include the use of Tomalia's divergent growth approach, convergent growth approach, and orthogonal coupling strategy, while methods of preparing polymeric micelles include dialysis, solution-casting, direct dissolution (Gilles and Fréchet, 2005; Gaucher et al., 2005; Chen et al., 2018). The polymeric nanoparticles can be prepared by ionic gelation, coacervation, solvent evaporation, spontaneous emulsification/solvent diffusion, salting out/emulsification-diffusion, supercritical fluid technology and emulsion polymerization, and nanocapsules are produced by microemulsion, miniemulsion polymerization and interfacial polymerization (D'Amato et al., 2003; Vauthier and Bouchemal, 2009).

When a NP enters a biological environment its surface is rapidly covered by various biomolecules (typically proteins), leading to the formation of a 'corona': these adsorption of proteins alters the particle size, stability and surface properties and, more importantly, provides the NPs with a biological identity and NP–protein interactions are dependent on the NP physicochemical properties, exposure time as well as protein source and concentration (Fig. 10) (Shi et al., 2017). While ligand-functionalized NPs might lose targeting capability when a protein corona forms on their surface, decoration of NPs with some particular plasma proteins could improve delivery to specific organs. In contrast, NP–protein interactions in clinical settings can also trigger hypersensitivity reactions in patients by activating the complement system (Karczewski et al., 2012; Fytianos et al., 2016).

The size of the nanoparticle carrier, which also can be used as passive targeting mechanism, alters the biological distribution profile. The small nanomaterials, 1–20 nm, have long circulatory residence times and slower extravasation from the vasculature into interstitial spaces (Winter et al., 2003). Local injections require an engineering of polymeric nanoparticles of slightly larger sizes, 30–100 nm, sufficient to avoid leakage into capillaries, but also small enough to avoid reticulo endothelial clearance (Moghimi et al., 2001). Polymeric nanoparticles greater than approximately 100–150 nm in diameter will tend to accumulate in tumors due to their poor extravasation from normal vasculature (Kohane, 2007).

The presence of disturbed, porous vascular beds at the tumor allows for selective targeting by this passive mechanism. In general, the cancer drug delivery process can be divided into three steps, as reported by Sun et al. (2012)). A) Initially, the drug-loaded nanocarriers circulate in the blood compartments, including the liver and the spleen. When passing through tumor blood vessels, some carriers may fall into the pores in the blood vessel wall and diffuse into the tumor tissue (EPR effect) (Torchilin, 2000; Maeda et al., 2000). B) Next, they may further penetrate the tumor tissue, which is non-trivial because of the high cell density and high interstitial osmotic pressure (Wong et al., 2011). C) Upon sticking to the surrounding cancer cell membrane the carrier is expected to enter the cells via one or several possible pathways, and finally traverse the crowded intracellular structures and viscous cytosol to the targeted subcellular sites and release the carried drug cargo.

Thus, to achieve efficient drug delivery from the injection site to the target in the tumor cells, the nanocarrier must simultaneously meet two pairs of challenges: (a) the nanocarrier retain the drug very tightly, but it must be able to efficiently release the drug once reaching the intracellular target to exert its pharmaceutical action; (b) the nanocarrier must evade the reticulo endothelial system (RES) screening, particularly the capture by liver and spleen, for a long blood circulation time: with the blood circulation time of the nanocarrier increases so does its opportunity passing the hyperpermeable tumor blood vessel and extravasation into the tumor. Only a nanocarrier capable of simultaneously satisfying the opposite 2R2S requirements at the right places, that is, "drug Retention in blood circulation versus Release in tumor cells (2R)" and "Stealthy in blood versus Sticky in tumor (2S)" will deliver the drug specifically to the tumor, giving rise to high therapeutic efficacy and few side effects.

Other important aspects are the clearance and the excretion. In fact, following systemic administration, the body allocate nutrients, clears waste, and deliver drugs via the vascular and lymphatic systems. Intravenously injected particles are scavenged and cleared from circulation by the reticulo endothelial system with a process that involves the deposition of opsonic factors and complement proteins on the nanoparticles themselves (Singh et al., 2011). Both clearance and opsonization are influenced by the size and surface characteristics of injected nanoparticles: particles greater than 200 nm in diameter activate the complement system more efficiently and are cleared more rapidly than very small nanoparticles. This may be a result of the geometry, charge, and functional groups on the surface of these particles that mediate

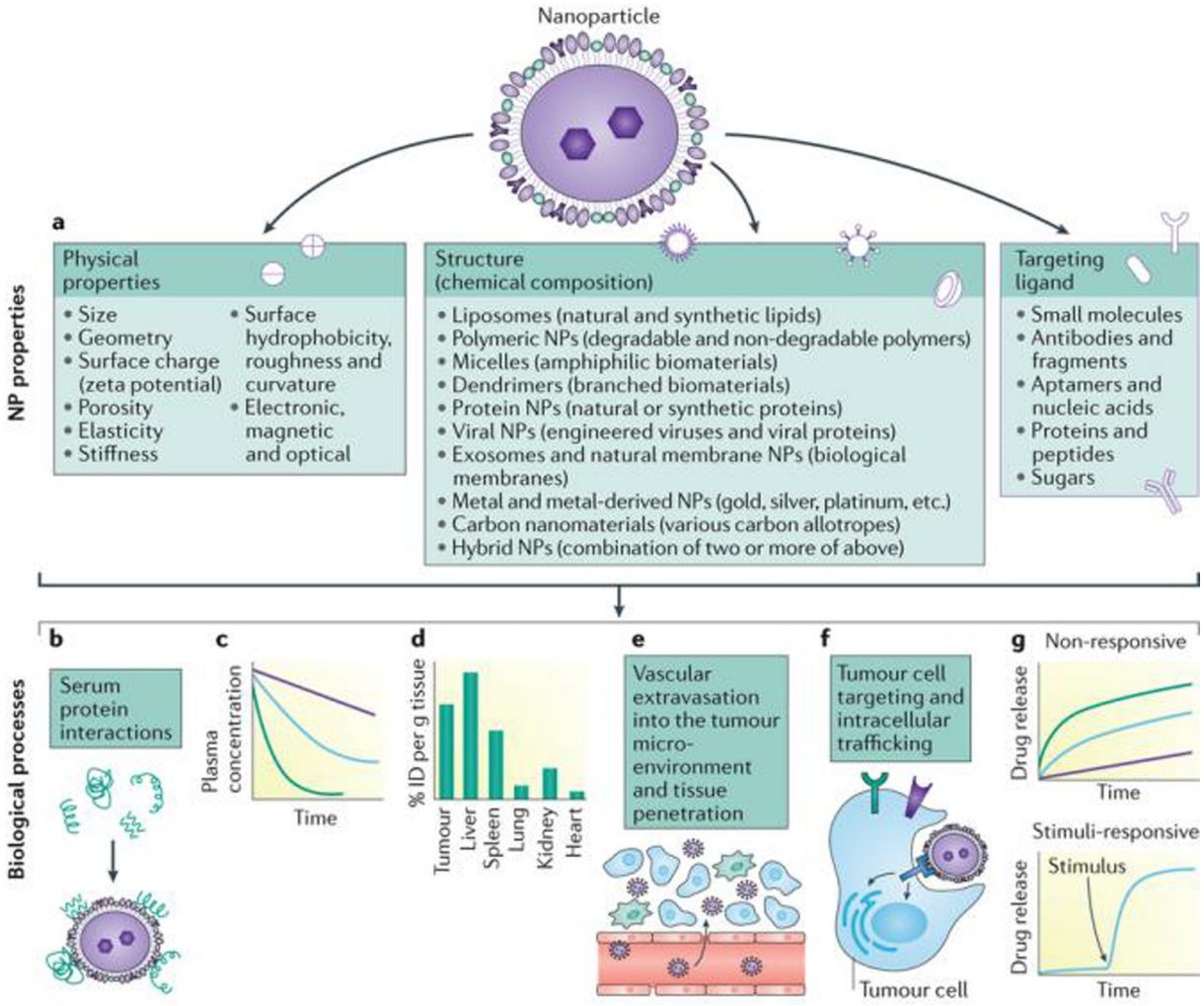

Fig. 10. Nanoparticles (NPs) from different materials can have different physicochemical properties and can be modified with ligands of different surface density (part a). NP properties affect the biological processes involved in the delivery to tumour tissues, including interactions with serum proteins (part b), blood circulation (part c), biodistribution (part d), extravasation to perivascular tumour microenvironment through the leaky tumour vessels and penetration within the tumour tissue (part e), and tumour cell targeting and intracellular trafficking (part f). NPs can also be designed to control the release profile of payloads (part g). ID, injected dose (Shi et al., 2017) .

binding to proteins and blood opsonins (Emerich and Thanos, 2007).

4. Strategies for drug loading and release

The interaction between nanocarrier and drug molecules has attracted great interest during these years. Different interaction mechanisms have been explored, and they can be broadly subdivided into three types: electrostatic interaction, covalent conjugation, encapsulations.

Electrostatic Interaction. The high density of functional groups (such as amine groups and carboxyl groups) on nanocarrier surface have potential applications in enhancing the solubility of hydrophobic drugs by electrostatic interaction: nonsteroidal anti-inflammatory drugs with carboxyl groups, including ibuprofen, ketoprofen, diflunisal, naproxen, and indomethacin, have been widely been complexed with dendrimers by electrostatic interactions (Imae, 2012; Gupta et al., 2006). Studies on many drug delivery systems based on electrostatic interaction between nanocarrier and other drugs, such as some anti-cancer drugs and anti-bacterial drugs, have also been reported. Often a common property of these drug molecules is that they are weakly acidic drugs with carboxyl groups in the molecules, such as for example, the well know drugs, aspirin, methotrexate and furosemide (Manallack et al., 2013).

Covalent Conjugation. The presence of large numbers of functional groups on carrier surface allows covalent conjugation with drugs using relevant functional groups (Chang et al., 2012). In this case, the drug is covalently bound to carrier, and its release occurs via chemical or enzymatic cleavage of hydrolytically labile bonds. Moreover covalent conjugation allows tissue targeting and controlled delivery as the drug–carrier conjugates diffuse slower than the free drug in the body and might be absorbed in specific interfaces (Alvarez-Román et al., 2004).

Encapsulation. The ellipsoidal or spheroidal shape, empty internal cavities, and open nature of the architecture of dendrimers and nanocapsules make it possible to directly encapsulate guest molecules into the macromolecule interior (Arpicco et al., 2015; Patil et al., 2016; El-Gogary et al., 2014; Tomalia et al., 2012; Rong et al., 2011). These empty internal cavities usually have hydrophobic properties, which make it suitable to interact with poorly-soluble drugs through hydrophobic interactions: in view of these specific properties, the relationship between the internal cavities of carrier and drug molecules may involve physical encapsulation, hydrophobic interaction, or hydrogen bonding.

The strategies for release involving the use of designed carriers to bond, encapsulate, or mask the therapeutic agent. The delivery of the drug to a tissue whereby penetration and distribution may not otherwise occur is possible with these 'Trojan Horse' strategies. In fact, during the course of evolution, cells have developed various mechanisms to prevent the entry of xenobiotics. Some of these mechanisms include the presence of a lipophilic cell membrane; existence of P-glycoproteins which efflux the drugs out; the occurrence of degradative enzymes and the development of endosomes which are highly acidic and these degrade xenobiotics which are endocytised into the cells. A succession of several membrane layers provides an obstacle for therapeutic agents attempting to target intracellular structures. During this process, the compound is lost due to ineffective partitioning across biological membranes. The extent of partition across a membrane is related directly to the polarity of a molecule; nonpolar or lipophilic molecules easily bypass this obstacle with greater membrane penetration, generally via diffusion. However, the situation is much more complicated, as a myriad of other cellular processes directly affect the intracellular concentrations and effectiveness of the therapeutic agent. In fact, as reported by Faraji and Wipf (2009) variable efficiencies of endocytosis mechanisms, intracellular trafficking, release of the therapeutic agent into the cytoplasm, diffusion and translocation of the therapeutic agent to its susceptible target, and partition into the nucleus or other organelles alter the actual activity of the therapeutic agent.

Polymeric nanoparticles present an interesting opportunity for eliminating much of this 'waste' due to masking of the therapeutic agent from its biological environment; this effectively limits the influence of a compound's physical properties on intracellular drug concentrations. Instead, the properties and surface characteristics of the nanoparticle play a greater role in compound delivery and resulting intracellular drug concentrations. Nanoparticles may be ingested by endocytosis process that includes three subtypes: phagocytosis, pinocytosis, and receptor mediated endocytosis. Phagocytosis involves the ingestion of materials up to 10 μm in diameter and can be accomplished by few cell types of the reticulo endothelial system, such as macrophages, neutrophils, and dendritic cells. Pinocytosis is an uptake mechanism that can be conducted by virtually all cell types, and normally involves ingestion of sub-micron material and substances in solution. Larger microparticles provide selective access to phagocytic cells, while smaller nanoparticles provide access to virtually all cell types. This distinct capability of nanoparticles may be utilized for the delivery of therapeutic agents to a wide array of cellular types and targets.

Cross-linking of receptors by ligands attached to the polymeric nanoparticles results in a more pronounced crater leading to membrane enfolding and reunification of the cell membrane to form an endosome: the size of the nanoparticles between 25 and 50 nm is a requirement for optimal endocytosis and intracellular localization (Chithrani et al., 2006; Jiang et al., 2008). In addition, the selective active targeting of polymeric nanoparticles to specific tissues can take advantage of the differential receptor expression between cell types. For example, the attachment of multiple herceptin molecules on the surface of the nanoparticles induced higher cross-linking of the receptors over expressed on human breast cancer cells as ErbB2, with variable internalization depending on size of the nanoparticles (Jiang et al., 2008). Switchable polymeric nanoparticles can be classified based on the type of stimulus as internally and externally controllable materials. Internal stimuli (e.g. activation by pH, redox potential, enzymes) might be controlled by a molecular mechanism highly specific for a disease and therefore excel in targeting properties (Lee et al., 2008; Yoo et al., 2011). However, absolutely disease-specific internal molecular triggers are difficult to find for certain diseases. External stimuli like light, ultrasound, electromagnetic fields or ionizing radiation have the advantage of being focusable on certain body areas (Sun et al., 2011; Fomina et al., 2011). This may be a significant advantage where a target cell is strongly involved in pathogenesis at one location (e.g., cancer stem cells in a cancer tissue), but of vital importance in other locations (e.g., stem cells in the bone marrow). A schematic overview of a cancer cell, presenting internal (glutathione) and external stimuli (e.g. magnetic field, ultrasound, light, radiation) used for imaging, drug release and therapeutical treatment is reported by Lehner et al. (2012).

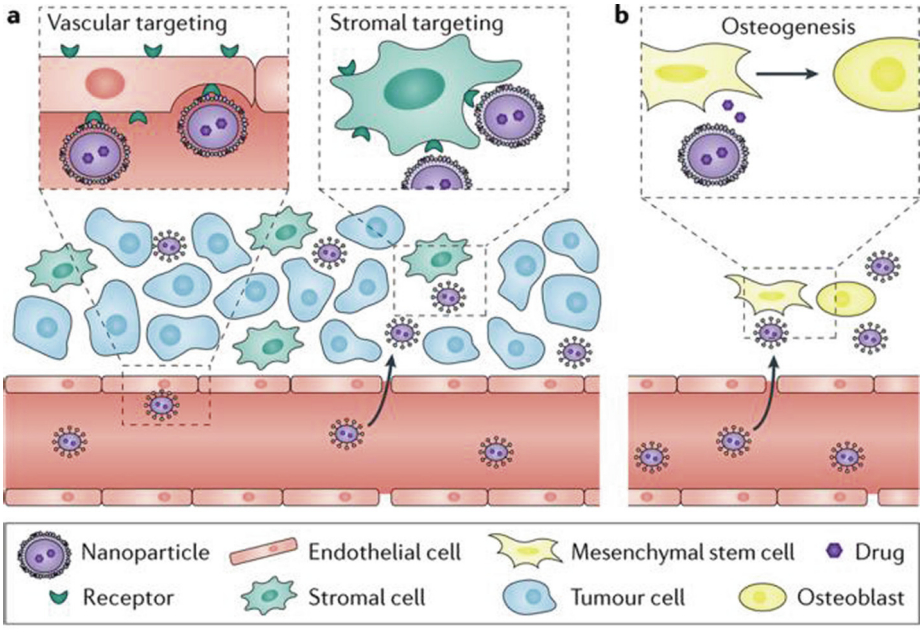

Fig. 11. Targeting of the tumour vasculature or stromal cells in the tumour microenvironment (part a) and the premetastatic microenvironments such as the bone marrow niche, where induction of the osteogenic differentiation of mesenchymal stem cells enhances bone strength and volume (part b). Modification of NPs by ligands that bind to specific receptors allows Cell-specific targeting (Shi et al., 2017).

Other interesting results are presented by Li et al. (2014). They demonstrated that DOX-loaded, dextran-based reversible crosslinked micellar nanoparticles can efficiently deliver DOX into cancer cells in vitro, and reduce A549 xenograft tumor size in vivo. Importantly, in situ crosslinking of the DOX-loaded polysaccharide nanoparticles by introducing a small amount of cisplatin as the crosslinker, could significantly increase the surface charge and stability, which would further improve the tolerability, in vivo pharmacokinetics, biodistribution, and antitumor efficacy, and reduce drug-related multiorgan toxicity side-effect. This study demonstrated that pH responsive polysaccharide-based cisplatin crosslinked nanoparticles held great potential for achieving an optimal therapeutic effect of the transported drugs in cancer therapy.

Much effort has focused on NP-mediated selective drug delivery to the tumor vasculature (Fig. 11), which is crucial to tumor growth and metastasis (Shi et al., 2017). This is commonly achieved by coating NPs with ligands that bind specifically to overexpressed receptors such as αvβ3 integrin on the surface of tumor endothelial cells. Targeting stromal cells such as tumor-associated fibroblasts and macrophages has also been proposed for cancer treatment. Comparatively little effort has been devoted to exploiting nanotechnology to modify the premetastatic microenvironmental niche and suppress tumors growth. In a recent study, a bone-homing polymeric NP platform was engineered for spatiotemporally controlled delivery of therapeutic agents (Fig. 11b) (Shi et al., 2017).

5. Conclusions

Polymer based nanostructures used as drug delivery systems hold great potential to efficiently target drugs to several cell types, overcoming some of the main problems, such as problems of drug resistance and to facilitate the movement of drugs across barriers. The challenge, however, remains open and regards the precise characterization of molecular targets and ensuring that these molecules only affect on targeted organs. In fact, one of the major problems that contribute to a low efficiency in drug delivery, we can mention the low drug concentrations to the active site and the very short drug residence time in the cellular and anatomical sites. The challenges associated with the optimization of drug therapy require research in the field of novel delivery systems. In recent years, smart polymeric nanodelivery systems have shown remarkable ability to overcome many of the anatomical and physiological barriers and deliver drugs locally to sites of interest thus improving therapy. The most successful approaches have used a combination of passive and active targeting. The current focus in the pharmaceutical industry is moving towards a 'smart drug', which increases the effectiveness and decreases the toxicity.

Acknowledgement

The author gratefully acknowledges the Sapienza University of Rome (Ateneo Sapienza 2016 projects) for financial support.

Conflict of interest

Author declare no conflict of interest.

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