



An overview of nanoparticles in drug delivery: Properties and applications

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ABSTRACT

Today, in diverse medical and clinical fields, including cancer treatment, nanoscience has evolved and evolved. Cancer and its forms, on the other hand, have been rumored and inclusive, and many individuals suffer from this fatal and lethal condition. Actually, even with the medicinal effect, current therapeutic approaches, including chemotherapy, radiotherapy, etc., create symptoms that are inconvenient for patients. Scientists and scholars are also working to establish and, strengthen the options and methods of therapy to deal with this dangerous illness. Nanoscience and nanotechnology have been popular today, their different areas, including nanoparticles, are commonly used for a number of applications, especially for drug delivery and diagnostic products, and cases of imaging. Release mechanisms focused on nanotechnology have a profound effect on the release of cancer drugs. Biomaterials and bio-engineering developments are leading to novel approaches to nanoparticles that could offer a new way for cancer patients to improve. In the drug release method, Nano-technology has had a great effect on the selection of cancer cells, the release of a targeted drug, and the overcoming of traditional chemotherapy limitations. This article discusses the drug delivery to tumor tissue, a method that is more effective than traditional drug delivery methods, also many new nanoparticles have solved the problem of cell resistance to the drug, provided a new field in the treatment of cancer.

1. Introduction

Currently, cancer treatment includes invasive procedures such as using a catheter for chemotherapy, primary chemotherapy to shrink existing cancerous tumors, surgery to remove the tumor if possible, and radiation therapy (Brannon-Peppas and JO, 2004; Duncan et al., 2005).

The goal of chemotherapy and radiation therapy is to kill cancer cells that are more sensitive to chemotherapy drugs and radiation because of their much faster growth and division than healthy cells in the body. Existing research in the field of chemotherapy seeks to provide drug carriers with different drug entry routes, to find new therapeutic targets such as blood vessels that nourish tumor tissue, and to develop targeted

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and specific drug forms (Hanna et al., 2002). The effectiveness of a treatment directly depends on its ability to kill cancer cells so that healthy cells in the body are not affected (Gu et al., 2007). Currently, the limiting factor in cancer chemotherapy is the lack of drug selection against cells (Abou-Jawde et al., 2003). Moreover, most anticancer medications have a limited clinical index that induces side effects that are toxic. During chemotherapy, some cells become resistant to treatment, which either increases the dose of the drug during treatment or uses several drugs at the same time. But with these measures, the toxicity of the drug is even greater. To reduce these side effects and improve existing drugs, a variety of drug delivery systems have been developed that include soluble drug-polymer conjugates, polymer micelles, nanoparticles, liposomes, and micro particles (Nobs et al., 2004; Wilson and Szostak, 1999; Brissette et al., 2006). Among these, nanoparticles have received more attention because they have an easier production method and can be prepared through biocompatible polymers. Due to the fact that the vessels around the tumor tissue are more permeable than the vessels of normal tissues and also need more oxygen and nutrients due to their higher growth rate, as a result, they have better drug absorption, which increases this permeability and persistence (enhanced permeability and retention=EPR) (Brannon-Peppas and JO, 2004; Duncan et al., 2005).

2. Targeted drug delivery

Targeted drug delivery includes active and passive prototyping. In active targeting, the therapeutic agent or carrier binds to a specific tissue or cell, but in passive targeting, the drug agent inactively reaches the target cell and tissue together with the carrier (Sudimack and Lee, 2000; Benita, 2006; Haley and Frenkel, 2008). They are not able to pass, they can pass easily (Duncan et al., 2005). Studies have shown that nanoparticles cross the blood-brain barrier after strong bonds are opened by the effect of hyphemia Mannitol (Hanna et al., 2002; Gu et al., 2007).

2.1. Passive targeting

Nan systems are able to use the structural features of tumor tissue for Passive targeting (Fig. 1). When the tumor size reaches 2mm³ or more, it becomes permeable. This restriction affects the ability of cells to absorb food, waste and oxygen. Tumor tissue begins the process of angiogenesis to overcome this problem (Hu et al., 2010; Korting, 2010; Thassu et al., 2007). Characteristics of this phenomenon include abnormalities in the basement membrane, lack of endothelial lining prostheses, and as a result, the formation of leaking vessels containing pores and windows between 100 and 1200 nm in size. The size of the pores varies depending on the type of tumor (Abou-Jawde et al., 2003; Nobs et al., 2004). In addition, due to the lack of an efficient lymphatic system in the tumor tissue, the interstitial pressure at the center of the tumors is greater than the surrounding environment.

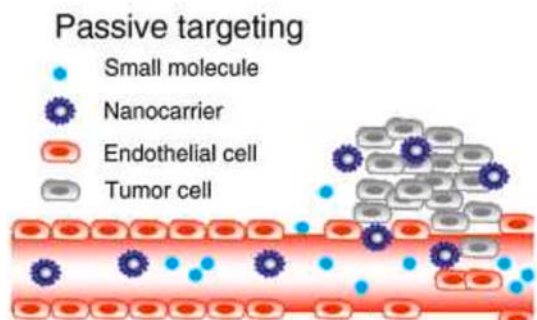


Fig. 1. Passive targeting of Nano carriers (Abou-Jawde et al., 2003).

2.1.1. Passive targeting using tumor permeability capillary network

Many drug delivery Nan systems use Enhanced Permeation Retention (EPR) of tumor tissue. This feature is based on two characteristics of tumor tissue: a) Capillary endothelial in malignant tissue is more irregular than healthy tissue and has higher permeability to macromolecules (Wilson and Szostak, 1999). This allows drug Nan carriers to leave the vessels in the endothelial tumor. B) Lack of lymphatic drainage in the tumor bed leads to drug entrapment in this area. As a result, by binding the chemotherapy drug to a suitable polymer or carrier, the Passive targeting using tumor permeability capillary network (Fig. 2) (Brissette et al., 2006).

2.1.2. Passive targeting using tumor tissue environment

2.1.2.1. Enzymatic targeting. Another type of passive targeting is based on the characteristics of the tumor tissue environment. The drug is injected into the patient in a Passive form and then turns into its active form under certain conditions (Sudimack and Lee, 2000; Benita, 2006). For example, the Passive and nontoxic form of the anticancer drug "lipid phospholipid choline ether" is converted to the active and toxic form of phospholipid choline ether lipid by phospholipase A2, which is abundant in the tumor environment (Gogotsi, 2006; Banerjee and Sengupta, 2011; Vlerken and Amiji, 2006). Now, if a liposome containing an anticancer drug is made using the Passive form of phospholipids, the liposomes will become active forms as they enter the tumor environment and be exposed to phospholipase A2, in addition to destroying and releasing the drug. As a result, they double-kill the tumor cells (Fig. 3) (Haley and Frenkel, 2008).

2.1.2.2. Passive targeting based on environmental acidity. The overgrowth and proliferation of cancer cells necessitates the use of other methods, such as glycolysis, in addition to natural methods of obtaining energy, which are unable to meet their metabolic and oxygen and energy needs (Hu et al., 2010; Korting, 2010; Thassu et al., 2007). This in turn creates a mildly acidic environment in the tumor environment. Scientists use this property of tumors by designing and manufacturing drug-containing polymer nanoparticles that change shape in an acidic environment (National Cancer Institute 2014; Ferlay et al., 2010; Vaughan et al., 2011; Burke and Morris, 1994). There are two problems with this method: a) Due to the distance of the acidic environment from the tumor, the drug is released before reaching the tumor and damages the tissues around the tumor (Gogotsi, 2006). B) Given that the acidity of the tumor is not much lower than the natural environment of the body (about 6.5), the design of nanoparticles that do not release the drug in the natural environment of the body and release in the tumor environment will be very difficult (Fig. 4) (Banerjee and Sengupta, 2011).

2.1.2.3. Targeting based on temperature changes. Due to its high activity, the temperature in the tumor environment is somewhat higher than the natural environment of the body, so this property can be best used by designing temperature-sensitive drug nanoparticles (Fig. 5) (Vlerken and Amiji, 2006).

2.2. Active targeting

Active targeting by connecting targeting molecules to drug delivery systems allows the drug to be delivered specifically to tumor tissue, within cancer cells, intracellular organs, or specific molecules in cancer cells (National Cancer Institute 2014; Ferlay et al., 2010; Naumann and Coleman, 2011; Armstrong et al., 2006; Chatelut et al., 2003). This method directs drug carriers to surface carbohydrates, receptors, and specific tissue-specific antigens, and is particularly important in the treatment of primary tumors that have not yet metastasized (Fig. 6) (Gu et al., 2007).

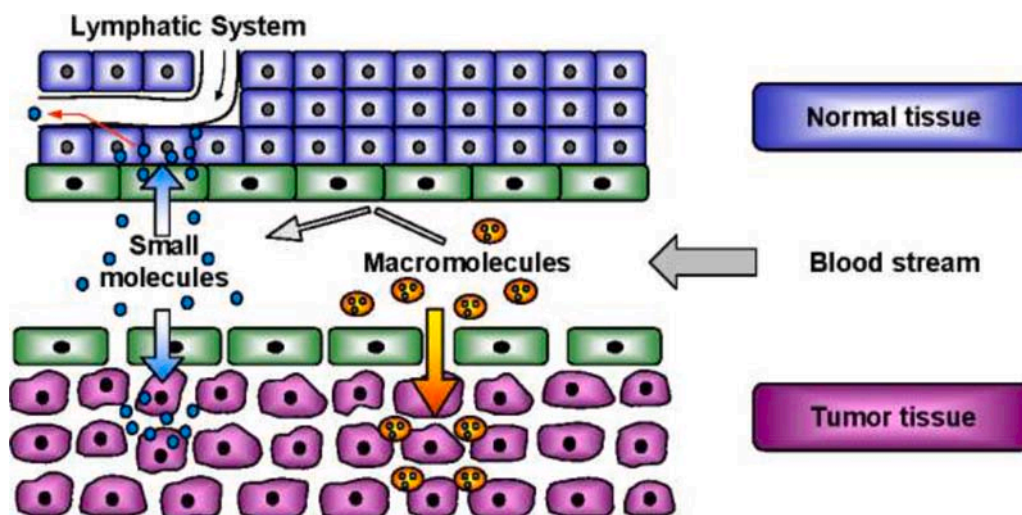


Fig. 2. Passive targeting using tumor permeability capillary network (Brissette et al., 2006).

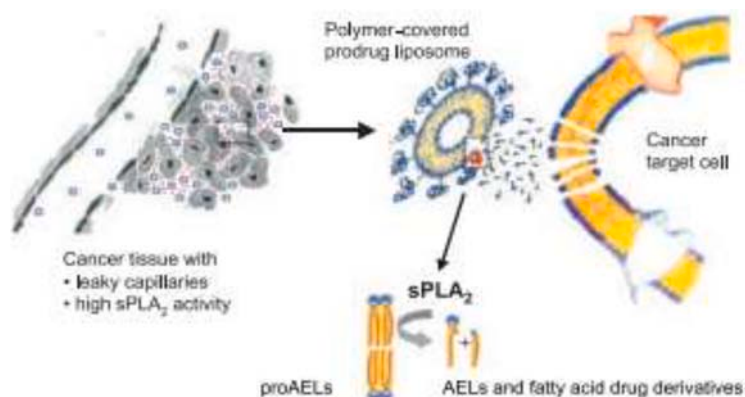


Fig. 3. Phospholipase A2 or (sPLA2), which is abundantly found at the tumor site, has the ability to convert the chemical structure of a Passive drug into an active form. After the liposomes enter the tumor site, this enzyme destroys the liposome and releases the drug from it (Haley and Frenkel, 2008).

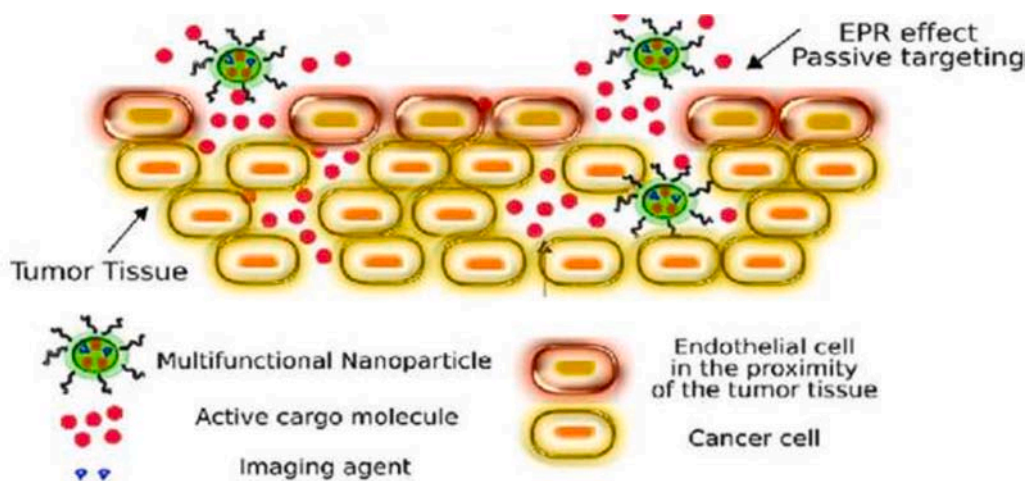


Fig. 4. Passive targeting based on environmental acidity (Banerjee and Sengupta, 2011).

2.2.1. Targeting against carbohydrates

An example of active targeting is the carbohydrate-lectin system (Fig. 7). The tumor cells' associations with healthy cells in the body as well as with the extracellular matrix are influenced by cell surface carbohydrates. These interactions are mediated by proteins called lectins,

which are capable of binding to carbohydrates (Carroll et al., 2011; Walters et al., 2013; Armstrong et al., 2013). Some lectins are able to detect a different carbohydrate pattern in cancer cells as an "alien" pattern, thereby triggering innate and acquired immune responses (National Cancer Institute 2014; Ferlay et al., 2010). Research has

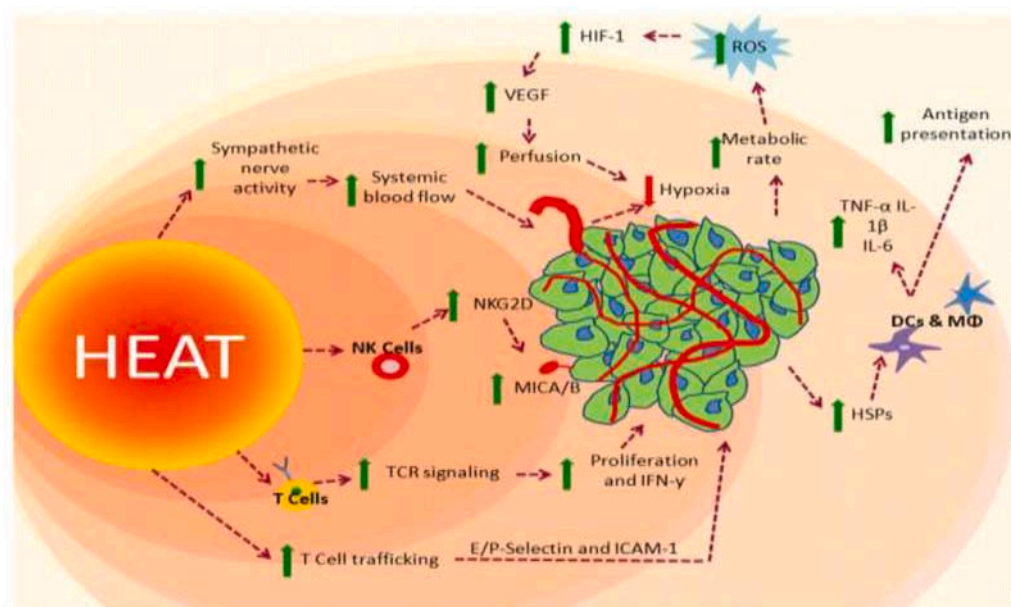


Fig. 5. Targeting based on temperature changes (Vlerken and Amiji, 2006).

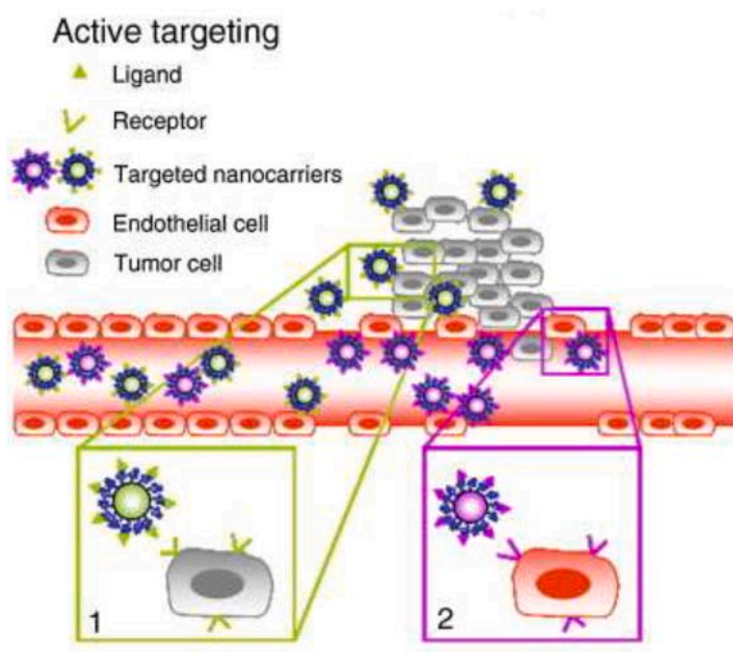


Fig. 6. Active targeting of Nano carriers (Gu et al., 2007).

shown that lectin plays an important role in the survival of tumor cells, their attachment to the endothelium and extracellular matrix, and tumor angiogenesis. These interactions can be used to provide a targeted drug delivery system by binding to carbohydrate ligands (direct lectin targeting) or by binding to lectins (reverse lectin targeting) (Vaughan et al., 2011).

2.2.2. Targeting against antigen and receptor

Antigens and receptors in cancer cells are a way for drug systems to enter through endocytosis. The drug bound to the polymer carriers enters the cell through receptor-ligand interactions (Burke and Morris, 1994). Separation of the drug from the polymer may occur in the extracellular space, at the cell surface, and most importantly in the lysosome, by lysosomal enzymes (Fig. 8) (Naumann and Coleman,

2011).

2.2.3. Monoclonal antibody

Monoclonal antibody is the first and most efficient group of target molecules that can bind to tumor-specific antigens (Fig. 9). The development of anti-cancer antibody depends on the identification of appropriate antigens. An appropriate antigen is expressed at the level of all cancer cells, but not at the level of healthy cells (Armstrong et al., 2006; Chatelut et al., 2003; Carroll et al., 2011; Kelemen et al., 2010; Choi and Mason, 2000; Stokstad, 1990). For the treatment of B lymphoma, Rituximab was approved by the FDA (FDA) in year 1997. Another antibody used to treat breast cancer is trastuzumab. The antibody binds to the Her₂ receptor and shows a high expression in about 20–30% of women with breast cancer. Rituximab and trastuzumab, for

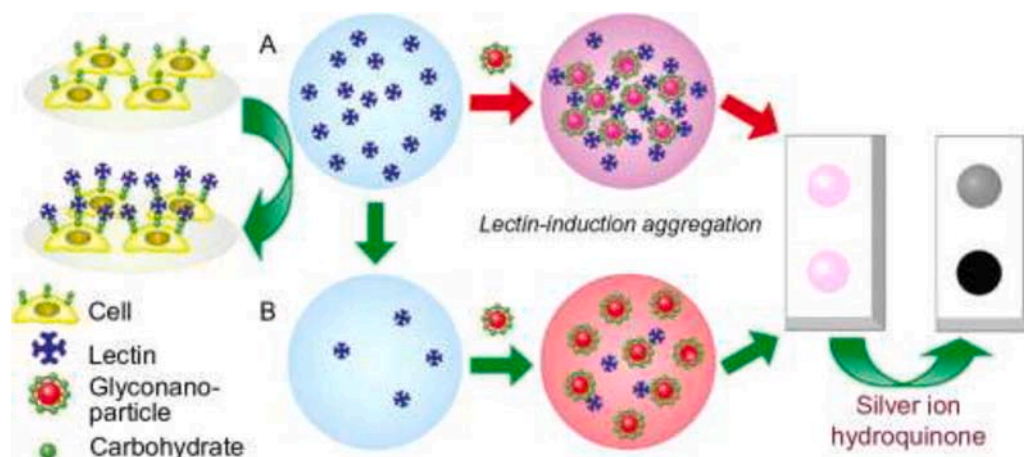


Fig. 7. Targeting against carbohydrates: (A) regulation solutions for lectin and (B) supernatants Gathered after cell incubation (BGC-823) with ConA (Vaughan et al., 2011).

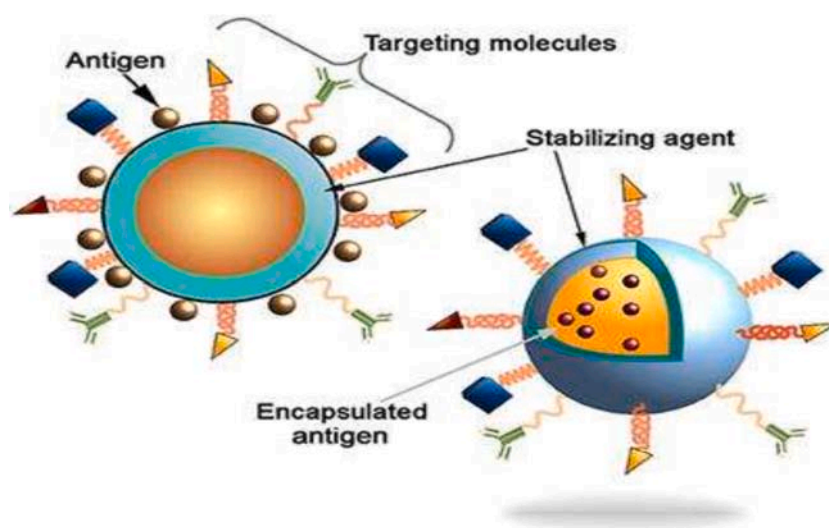


Fig. 8. Targeting against antigen and receptor (Naumann and Coleman, 2011).

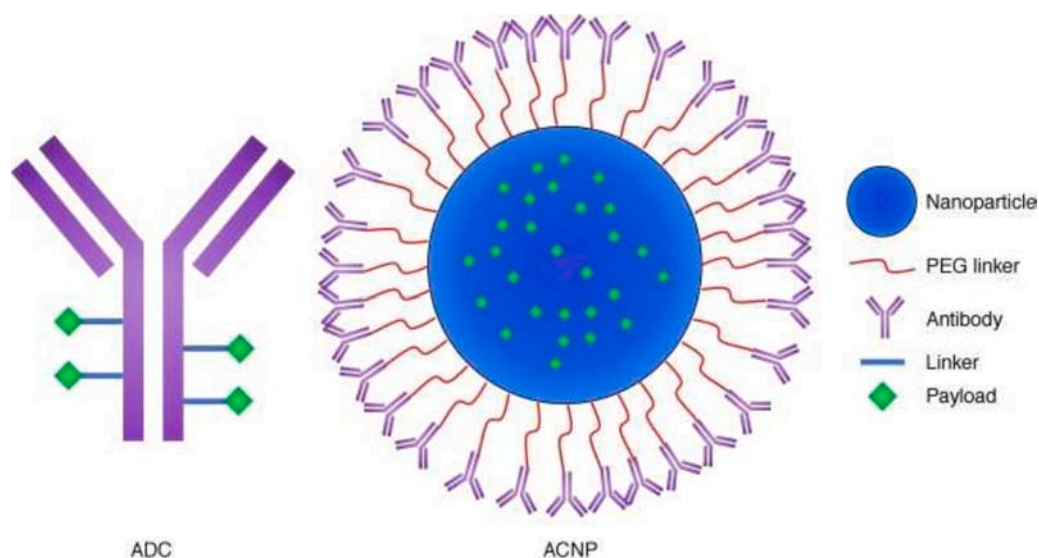


Fig. 9. Monoclonal antibody (Armstrong et al., 2006).

example, are attached to polylactic nanoparticles. This target increases the entry of nanoparticles into the cell by 6 equals (Fig. 10).

2.2.4. Aptamer

A new group of target molecules are aptamer receptors. Aptamers are RNA or DNA oligonucleotides that, as a result of intramolecular interactions, take on a specific spatial shape that gives them the ability to bind to ligands (Zhao et al., 2009; Gonen and Assaraf, 2012; Matherly et al., 2007; Whetstine et al., 2002). Aptamers can be prepared in such a way that, like antibodies, they bind specifically to the target antigens and are highly inclined. Such as aspirin, etc. are identified (Walters et al., 2013; Armstrong et al., 2013; Kelemen, 2006; Shen et al., 1997; Shen et al., 1994; Shen et al., 1995; Wang et al., 1998; Rijnboudt et al., 1996). Aptamers can even detect spatial antinomies of various molecules, such as caffeine and theophylline. Second, aptamers with a high affinity for a target molecule can be produced in the laboratory using a method called the evolution of the ligand system with exponential enrichment (Fig. 11) (Kelemen et al., 2010).

2.2.5. Oligopeptides

The use of peptides as target molecules has been considered in recent years (Fig. 12). The advantages of peptides over antibodies are: small size; Lower immunization; higher stability and easier production (Ramamoorthy et al., 2007; Yuan et al., 2009; Spiegelstein et al., 2000). Among these peptides can be referred to the tripeptide of arginine-glycine-aspartic acid (Choi and Mason, 2000; Stokstad, 1990).

2.2.6. Folate

Folic acid (folate) is one of the most important and widely used target molecules. Folate receptors are highly expressed in many types of cancer, including breast, uterine, lung, and brain and colon cancers (Ragoussis et al., 1992; Wang et al., 1992; Miotti et al., 1987). Folate binds specifically to the folate receptor (Kalofonos et al., 2001). This target molecule is attached to various types of drugs, including liposomes, polymer nanoparticles, and dendrites. But because the receptor is also present in normal epithelial cells of the intestine, lung, kidney, placenta and chorioidea networks (Fig. 13) (Zhao et al., 2009; Gonen and Assaraf, 2012; Matherly et al., 2007; Melani et al., 1998; Toffoli et al., 1997; Elnakat and Ratnam, 2004).

3. Types of nanoparticles and biophysical and chemical properties of nanoparticles

Nanoparticles used for drug delivery include a variety of structures with different sizes, shapes and materials, each with different drug

loading capacity, release, cell targeting and stability (Chancy et al., 2000; Weitman et al., 1994; Garin-Chesa et al., 1993; Toffoli et al., 1998). Biophysical and chemical properties of nanoparticles such as size, geometry / shape, surface charge, surface chemistry, hydrophobicity, roughness, hardness and degree of combinability can significantly affect the targeted drug delivery through these nanoparticles (Fig. 14) (Whetstine et al., 2002; Kelemen, 2006).

3.1. Particle size

The drug's loading and unloading is influenced by the distribution of the particle size. Nanoparticles have more intracellular penetration than micron-sized particles (Bellati et al., 2011; Hartmann et al., 2007; Kalli et al., 2008; Lorusso et al., 2012). Due to their small size and mobility, nanoparticles can achieve a wide range of biological purposes. Studies performed in the laboratory environment show that particle size can control the adsorption of nanoparticles (Brown Jones et al., 2008; Naumann et al., 2013; Ratnam et al., 1989; Wu et al., 1999). Smaller nanoparticles have a higher specific surface area, so most drugs that attach to the outer part are released faster. The large surface area causes the active substance to be located near the outer part, resulting in faster release of the active substance the non-solvent alternative (Ross et al., 1994; Salazar and Ratnam, 2007; Puig-Kröger et al., 2009). The mean particle size obviously depended on the type of non-solvent used and the water order was followed (Ross et al., 1999; Zhao et al., 2008). Fifty percent ethanol, 100% ethanol (Fig. 15A) (Shen et al., 1997; Shen et al., 1994; Shen et al., 1995; Wang et al., 1998). As compared to water, ethanol is potentially a "poorer" solvent for PLGA, and it facilitates the polymer's precipitation more aggressively. With the change in the non-solvent composition, where particles made with 100% ethanol display a small distribution profile, the size distribution has also changed dramatically (Fig. 15B). As the amount of DMSO remained unchanged, no substantial improvement in the performance of the trap was observed (Fig. 15A). The addition of a surfactant (VE-TPGS) was required for stabilization of AMB-NPs suspension as aggregation was observed without use of VE-TPGS. For the subsequent studies, 100% ethanol was used as a non-solvent, considering the lowest particle size and narrow size distribution (Rijnboudt et al., 1996; Sadasivan et al., 1987; Sadasivan et al., 1986; Wang et al., 2000). Fig. 16 highlights the above-mentioned methods to co-encapsulating various drugs into polymeric nanoparticles, and Table 1 summarizes the latest advancements in polymeric nanoparticle-assisted combination therapies for the treatment of cancer (Ramamoorthy et al., 2007; Yuan et al., 2009; Spiegelstein et al., 2000; Ragoussis et al., 1992).

3.2. Surface charge

Recent studies show that the Surface charge of nanoparticles can be one of the most important factors affecting the ability of nanoparticles to penetrate cells (Paulos et al., 2004; Pan et al., 2002; Morphotek, 2013d; Ebel et al., 2007). Research also shows that among the two structures of receptors and their counterparts in spheres, spherical nanoparticles penetrate the cell structure more easily and faster (Kamen and Smith, 2012; Armstrong, 2010; Konner et al., 2010; Coleman et al., 2009; Kim et al., 2012; Rustin, 2003). Demimonde and colleagues in 2011, with the synthesis of nanoparticles in various forms, they found that the cellular penetration of nanoparticles with a rod structure is faster than cylindrical nanoparticles (Fig. 17). In addition, the shape of nanoparticles is one of the important factors in their biological distribution and internal circulation (Markman et al., 2004; Morphotek, 2013c; PRNewswire 2013).

3.3. Surface load

Another important feature that can affect particles in drug delivery systems is its efficient penetration into the endosomes by the surface

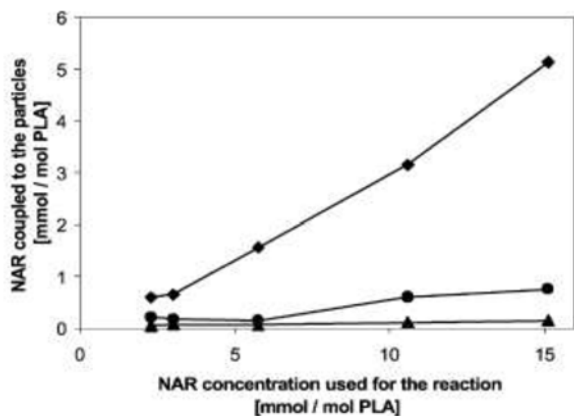


Fig. 10. Effect of NAR (2.3–15.1 mmol/mol PLA) concentration the sum of NAR coupled to the NAR used during the coupling reaction Nanoparticles (V, NAR, thiolated particles covalently bound; controls: O, simple nanoparticles; X, nanoparticles with thiolates) (Chatelut et al., 2003; Carroll et al., 2011).

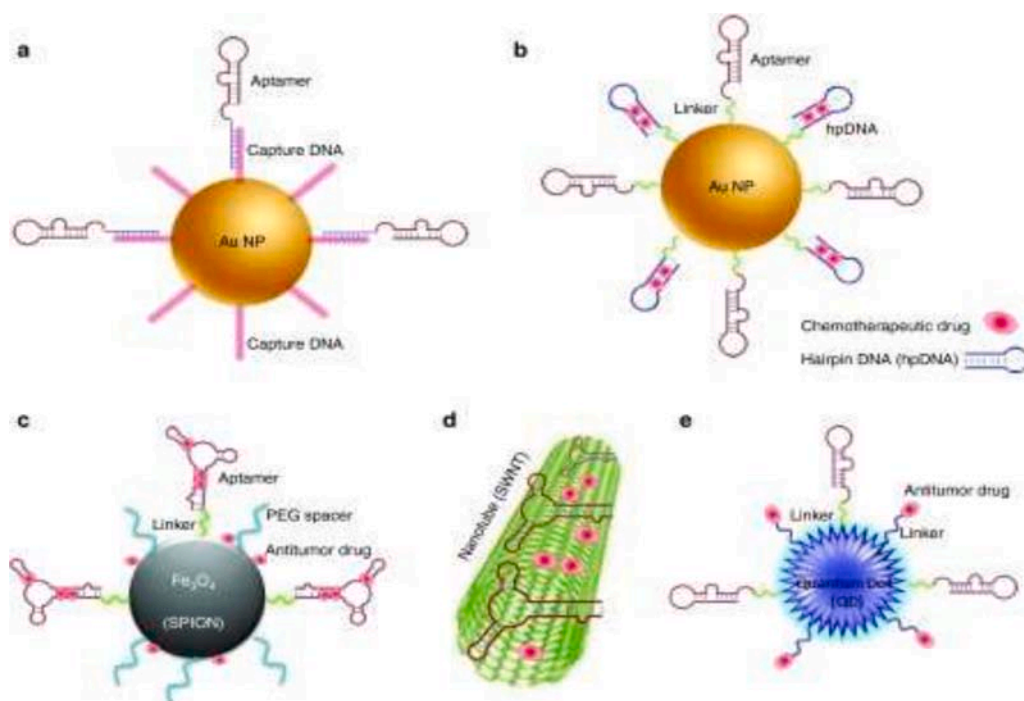


Fig. 11. Inorganic nanoparticles-functionalized by Aptamer. (a) An anti-EGFR aptamer-AuNP conjugate schematic created by a hybridization approach. AuNPs were first coated with brief (pink) DNA capture sequences and then hybridized with corresponding additional sequences attached to the 5' end of the antiEGFR RNA aptamer. (b) A sgs8c DNA aptamer/hpDNA-Dox/AuNPs diagram. The sgs8c DNA aptamer and hpDNA were assembled on the surface of AuNPs through standard gold-thiol chemistry. To load the chemotherapeutic drug Dox, the double-stranded region of the hpDNA was used. (c) Aptamer-functionalized SPION schematics. On the surface of an SPION, the PSMA RNA aptamer was covalently conjugated and then Dox was intercalated in the duplex region of the A10 aptamer and The SPION was also complicated by charging encounters. (d) Aptamer-functionalized diagram of single-walled carbon nanotubes (SWNTs). Through a π electron reaction, the sgc8c DNA aptamer and anthracycline agent (Dau) were loaded onto SWNTs. (e) Aptamer-functionalized QDs diagram. Via EDC/NHS chemistry, the mucin 1 DNA aptamer was covalently bound to the surface of QDs. Via a pH-

sensitive hydrazone bond, Dox was linked to QDs, which provided the complex with stabilization and allowed the release of drugs into the endosome (Kelemen et al., 2010).

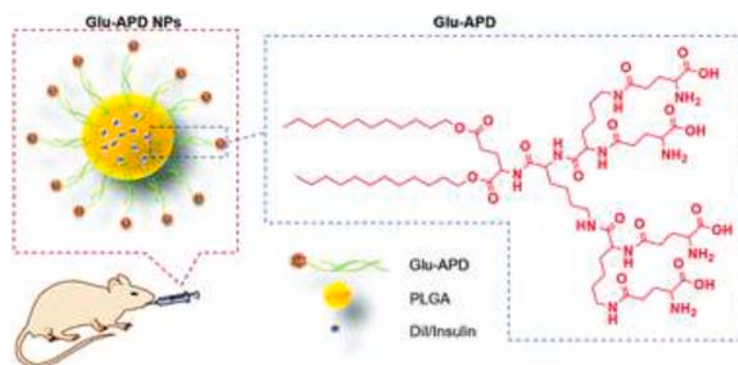


Fig. 12. As alternative oral drug delivery mechanisms, nanoparticles with surface features of dendritic oligopeptides (Choi and Mason, 2000, Stokstad, 1990).

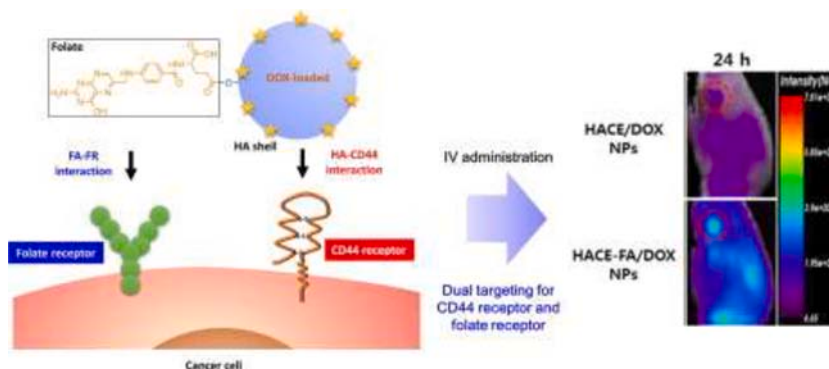


Fig. 13. For cancer detection and anticancer drug delivery, folate receptor-targeted nanoparticles (Zhao et al., 2009, Gonen and Assaraf, 2012, Matherly et al., 2007).

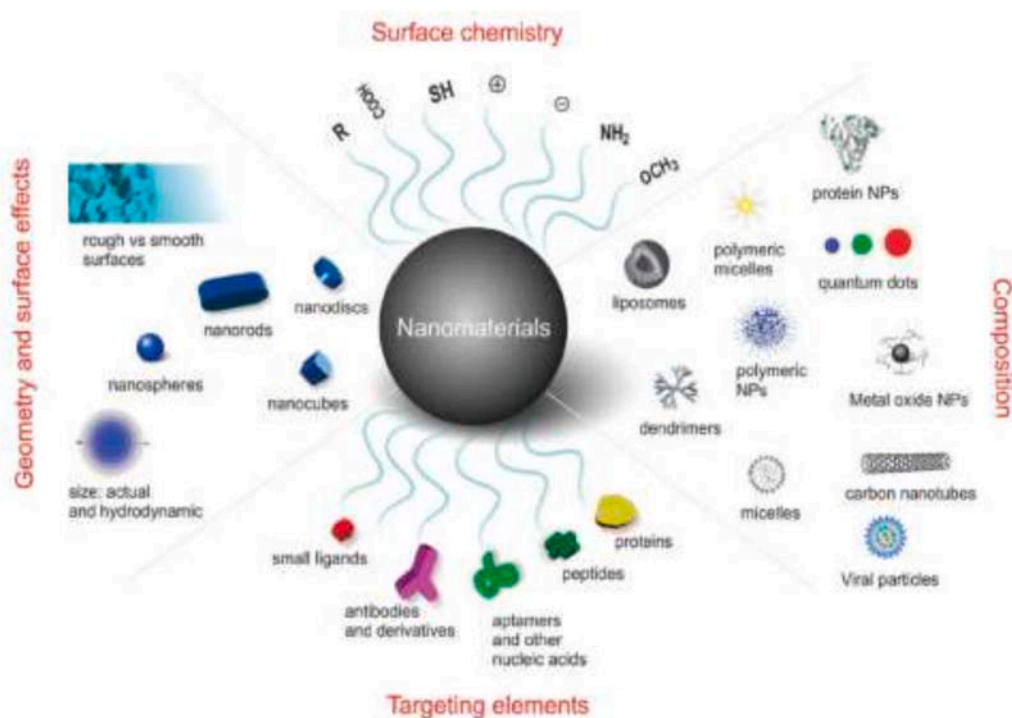


Fig. 14. Biophysical and chemical properties of nanoparticles, effective in their In-vitro in-vivo performance (Matherly et al., 2007, Whetstine et al., 2002).

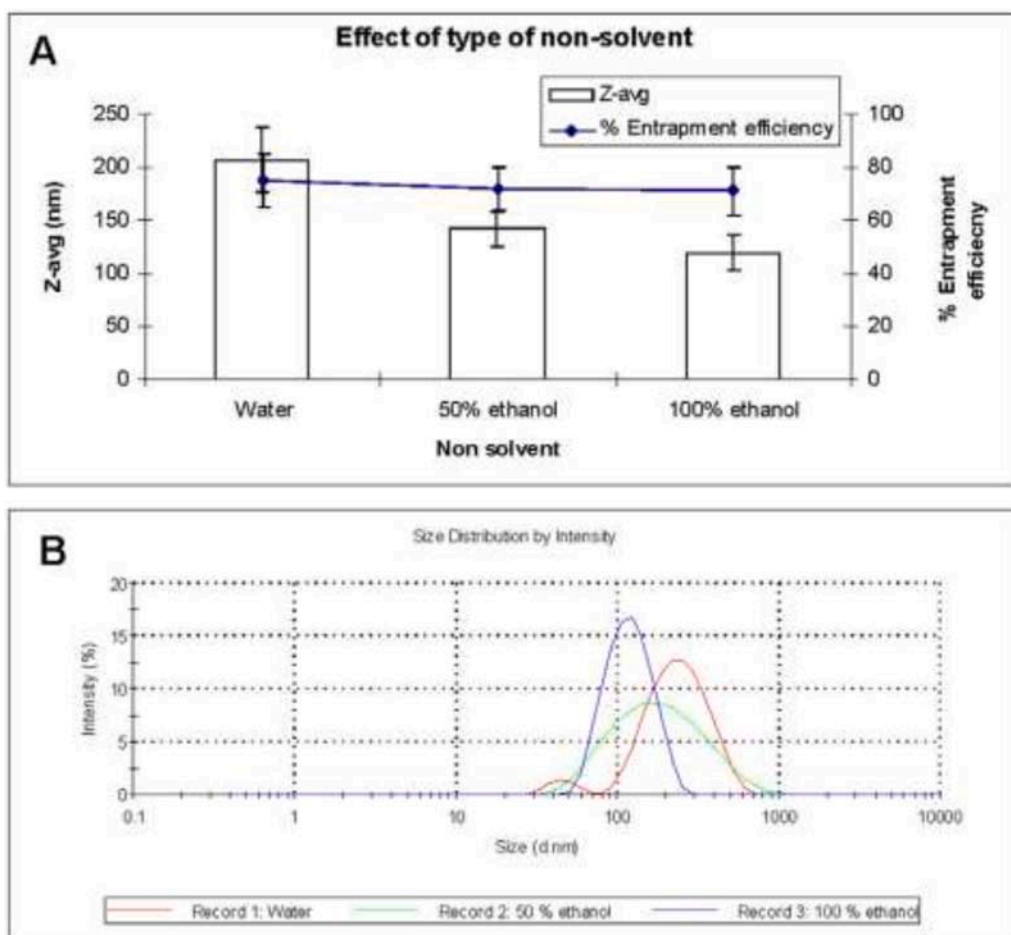


Fig. 15. The effect of non-solvent composition on particle size, efficiency of entrapment (A) and distribution of particle size (B). PDI, water: 0.360.1; ethanol 0.160.07 for 50 percent; ethanol 0.160.02 (Shen et al., 1997).

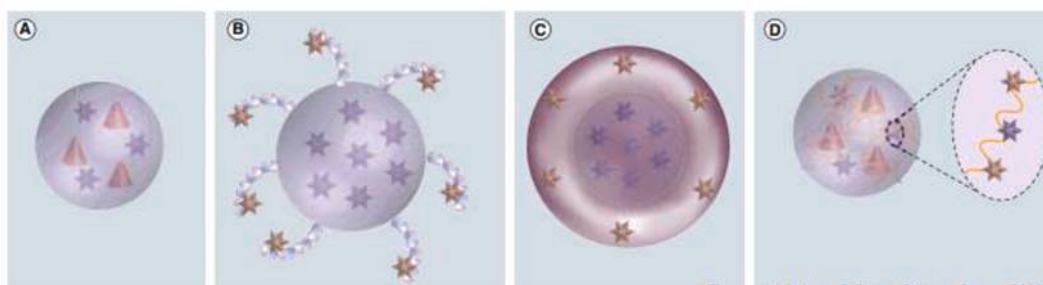


Fig. 16. For the co-delivery of several products, polymeric nanoparticle systems. (a) Bare polymeric nanoparticle for co-encapsulation of several hydrophobic agents (cones and stars); (b) modified polymeric nanoparticle oligonucleotides with hydrophobic agents (inner stars) embedded inside the particle and intercalated hydrophilic agents in the oligonucleotides (outer stars); (c) lipid-coated polymer nanoparticles containing drugs embedded in the polymer center (inner stars) and lipid envelopes (outer stars) respectively; and (d) polymer nanoparticles containing several drugs covalently bound to the polymer chains (cones and stars) (Shen et al., 1994, Shen et al., 1995, Wang et al., 1998).

Table 1

For integrated cancer treatment, polymeric nanoparticles and polymer-drug conjugates.

Formulation	Drugs	Indication	Status	Ref.
HPMA–Gem–Dox	Gemcitabine and doxorubicin	Prostate cancer and various cancer types	In vivo	(Wang et al., 1992)
PEG– p(Asp) block copolymers–Dox–WOR	Doxorubicin and phosphatidylinositol-3 kinase inhibitor (Wor)	Breast cancer and various cancer types	In vivo	(Chancy et al., 2000)
Combretastatin–doxorubicin nanocell	Combretastatin and doxorubicin	Lung carcinoma, melanoma and various cancer types	In vivo	(Ragoussis et al., 1992)
Cationic core-shell nanoparticles	Paclitaxel and Bcl-2-targeted siRNA	Breast cancer	In vivo	(Kamen and Smith, 2012)
PDMAEMA–PCL–PDMAEMA-based cationic micelles	Paclitaxel and VEGF siRNA	Prostate cancer and various cancer types	In vivo	(Armstrong, 2010)
Nanoparticle–aptamer bioconjugates	Doxorubicin and docetaxel	Prostate cancer and various cancer types	In vivo	(Shen et al., 1997)
Poly(lactic-co-glycolic acid) nanoparticle co-encapsulating vincristine and verapamil	Vincristine and verapamil	Breast cancer	In vivo	(Kalofonos et al., 2001)
Polyalkylcyanoacrylate nanoparticles co-encapsulating doxorubicin and cyclosporin A	Doxorubicin and cyclosporin A	Various cancer types	In vivo	(Melani et al., 1998)

charge (Vergote et al., 2013; Morphotek, 2013a, 2013b; Zwick et al., 2012). Surface loading of gold nanoparticles with polyethylene glycol and cytosol after entering the endometrium, the nanoparticles move away from the endometrium and enter the cytoplasm (Aronov et al., 2003; Liu et al., 2001; Majoros et al., 2006; Ladino et al., 1997). This event depends on the surface charge of the nanoparticles and changes it from negative to positive (Suzuki et al., 2007; Vlahov et al., 2006). Blood-brain barriers are electrostatic that act as a boundary when drugs penetrate the brain. Scientists have found that the surface charge of nanoparticles can alter the permeability of the blood-brain barrier (Kalofonos et al., 2001; Weitman et al., 1992; Vlahov and Leamon, 2012; Li et al., 2009). Hydrophobicity of temporal particles which are absorbed into the blood is related to the amount of components absorbed by the blood (Fig. 18).

3.4. Dendrimers

In fact, dendrimers are nanostructures that are being considered in many biomedical fields today. Dendrimers consist of a central nucleus from which many branches branch out like a Dendrites step by step (Melani et al., 1998; Toffoli et al., 1997; Elnakat and Ratnam, 2004; Chancy et al., 2000; Fisher et al., 2008; Matteson et al., 2009; Reddy et al., 2007; Sausville et al., 2007). Both indoor and outdoor buildings are very, very similar (Naumann et al., 2009; Merck Sharp and Dohme Corp, 2013; Merck Sharp and Dohme Corp, 2014). These particles have the ability to place different molecules between their branches and completely trap them and protect them against external factors or release them in a controlled environment (Amato et al., 2004; Endocyte, 2012b; Squibb Bristol-Myers, 2011a, 2011b). Also, by trapping drugs, the solubility of this They increase the materials (Garin-Chesa et al.,

1993; Toffoli et al., 1998; Lorusso et al., 2012; Endocyte 2012a; Zasadzinski et al., 2011; Bernard et al., 1947; Bangham, 1992). On the other hand, due to the presence of multiple functional groups on the surface, they are able to attach and carry a variety of molecules to their surface, on the other hand, their same property can be used to actively target a specific tissue (Bellati et al., 2011; Hartmann et al., 2007; Kalli et al., 2008; Koolman and Roehm, 2005; Suk et al., 2014; Kirby et al., 1980; Squibb http 2012). Dendrimers are usually three-dimensional Dendrimers-like structures with a central molecule (Fig. 19). Branches can be added to the central part by polymerizing the central molecule or by synthesis (Brown Jones et al., 2008; Wu et al., 1999; S. Wu et al., 2020; Caster et al., 2017; Jones, 1995; Vemuri and Rhodes, 1995; Gómez-Hens and Fernández-Romero, 2006). The branches are limited in size to eventually form a small but heavy circle. The drug molecule can be attached to functional groups on the surface of Dendrimers or placed between its branches (Reza Mozafari et al., 2008; Drug Delivery Analysis; Dua et al., 2012; Tao et al., 2012). Arborists can accommodate both hydrophilic and hydrophobic molecules. The hydrophobic center usually has a hole that can hold the hydrophobic drug. Although Dendrimers dealers are not very popular, research has been done on the loading of some hydrophobic drugs such as methotrexate and Doxorubicin inside the Dendrimers (Table 2). By attaching target functional groups to the surface of these macromolecules, their solubility and chemical behavior can be controlled (Fig. 20) (Salazar and Ratnam, 2007; Puig-Kröger et al., 2009; Ross et al., 1999).

3.4.1. PAMAM and PPI dendrimers

The most prevalent class of dendrimers suitable for many material science and biotechnology applications are polyamidoamine (PAMAM) dendrimers. PAMAM dendrimers consist of the central and tertiary

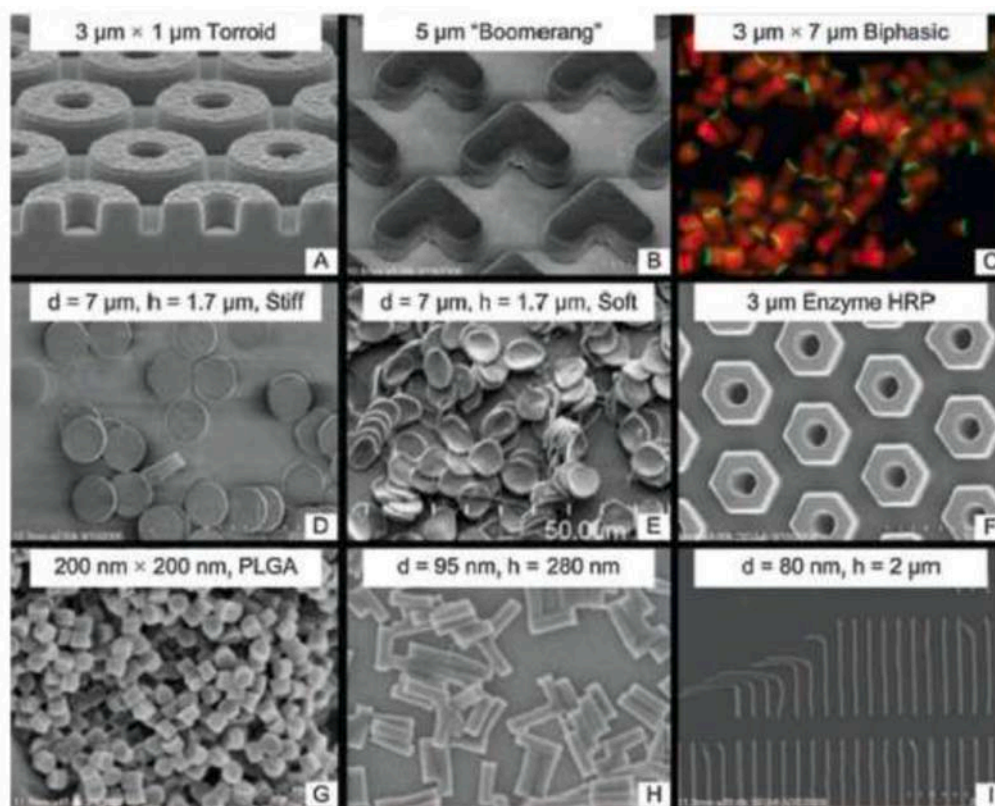


Fig. 17. Different shapes of nanoparticles and micro particles (Wang et al., 1992).

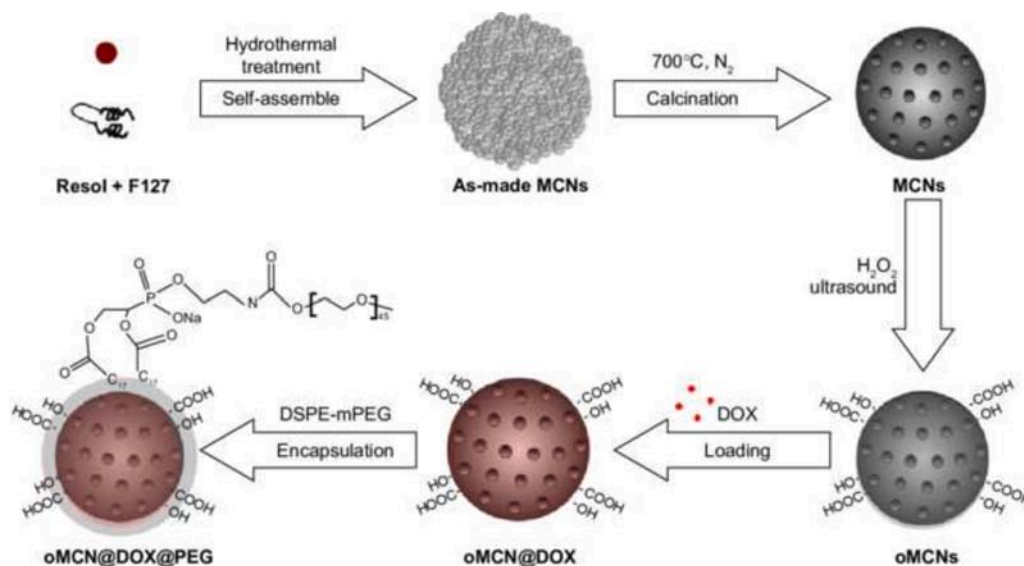


Fig. 18. A schematic diagram of nanoparticles for synthesis, drug loading, and surface modification. Abbreviations: MCNs, nanospheres of mesoporous carbon; oMCN@DOX@PEG, oxidized mesoporous carbon nanospheres of polyethylene glycol-modified doxorubicin; DSPE-mPEG, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-(methoxy[polyethylene glycol]-2000); oMCN@DOX, oxidized doxorubicin-loaded nanospheres of mesoporous carbon; DOX, doxorubicin; oMCNs, oxidized nanospheres of mesoporous carbon (Miotti et al., 1987).

amine branches of alkyl-diamine (Zhao et al., 2008; Sadasivan et al., 1986, 1987; Wang et al., 2000; Chen et al., 2011; Hale et al., 1980; ElBayoumi and Torchilin, 2009; Bogdanov et al., 1989; Francis et al., 1992; Zhang et al., 2005). With 5 distinct core forms and 10 usable surface classes, they are available in generations G 0 - 10. Most PAMAM dendrimers are supplied as methanol solutions for enhanced long-term improvement (Paulos et al., 2004; Pan et al., 2002; Morphotek, 2013d; Yoshino et al., 2012; Haywood and Boyer, 1986; Shichijo and Alving, 1986; McDaniel et al., 1986; Crook et al., 1986). In other application-specific solvents, they can be dried and reconstituted (Fig. 21). SyMO—Chem acquired Poly (propylene imine)-dendrimers

(PPI-dendrimers) and sells these dendrimers in analysis sample quantities to consumers (Goodwin et al., 1982; Sarkar and Blumenthal, 1987; Pinnaduwa and Huang, 1989; Ho et al., 1992; Wilschut, 2009). It is possible to buy the amine terminated PPI-dendrimers of generations 1, 2 and 3. Above, the second generation (G2) molecular form of the amine terminated PPI-dendrimer (or DAB-Am-8). Astramol dendrimers have also been called poly (propylene imine) dendrimers, or have literally been abbreviated as PPI-dendrimers, or DAB-Am-x dendrimers (Ho et al., 1986; Feng et al., 2009, 2010; Manjappa et al., 2011). DAB stands for the center of diaminobutane and $x = 4, 8, \text{ or } 16$ for the number of end groups of primary amines identified with generations 1, 2, or 3,

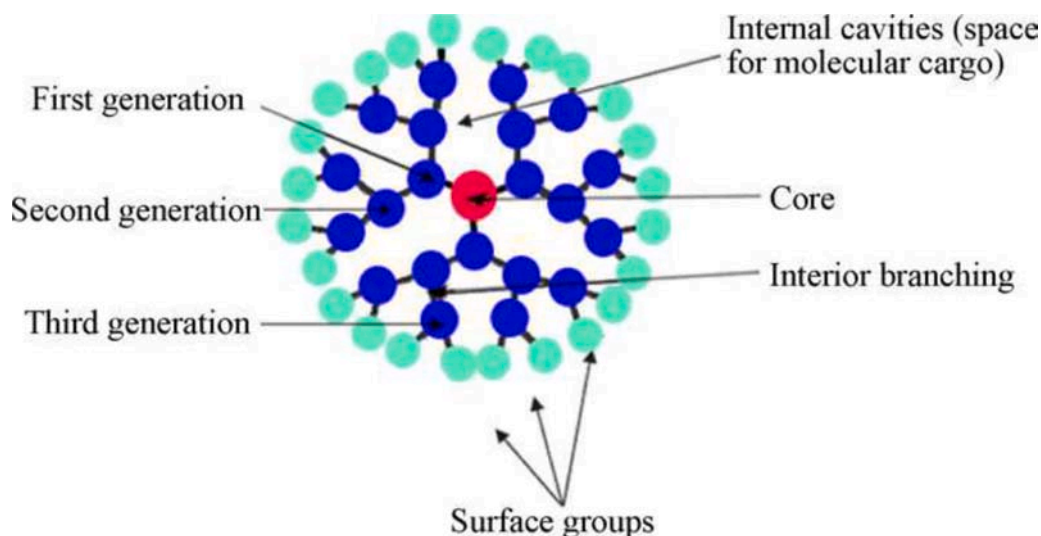


Fig. 19. Structures Dendrimers.

Table 2

Dendrimers and other hybrid cancer treatment nanoparticles.

Formulation	Drugs	Indication	Status	Ref.
Generation-3 poly(l-lysine) octa(3-aminopropyl)silsesquioxane dendrimer	Doxorubicin	Glioblastoma	In vitro	(Bellati et al., 2011)
Generation-5 poly(propyleneimine) dendrimer with ethylenediamine core	Methotrexate	Leukemia	In vitro	(Konner et al., 2010)
Generation-4 polyamidoamine dendrimers	Methotrexate	Leukemia	In vitro	(Lorusso et al., 2012)

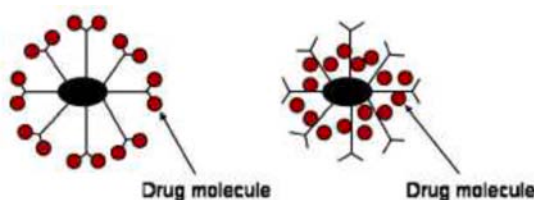


Fig. 20. Drug delivery systems with dendrimers (Salazar and Ratnam, 2007).

respectively (Fig. 22).

3.4.2. Nanospheres

Nanospheres or matrix-type nanodevices (Fig. 23) are polymeric NPs composed of spherical polymeric matrices that have been extensively observed as carriers of therapeutic molecules where the entire mass is solid (Rustin, 2003; Markman et al., 2004; PRNewswire 2013; Vergote et al., 2013; Morphotek, 2013b,2013c). The biological active agents are normally spread uniformly across the polymeric core and the primed active compound is released by the diffusion mechanism into the atmosphere. Besides, medicines can be adsorbed on the surface of Nano spheres (Morphotek, 2013a; Zwicke et al., 2012; Fukui and Fujimoto, 2011; Fan et al., 2012; Gao et al., 2012; Fukui and Fujimoto, 2009; Machová and Bystrický, 2012; Zalipsky, 1993). These nanostructures have maintained and controllable drug-release profiles and high loading capability for poorly water-soluble drugs because at concentrations greater than their inherent water solubility, they have the potential to

integrate hydrophobic drugs (Aronov et al., 2003; Liu et al., 2001; Biswas et al., 2012; Riaz, 1996; Mishra et al., 2011). The time required to release the substance from the Nano spheres depends on the structure and capacity of the polymer matrix to contain fluid. Critical factors affecting drug release from these types of nanostructures are drug-loading performance and Nano sphere size (Majoros et al., 2006; Ladino et al., 1997; Suzuki et al., 2007; Vlahov et al., 2006; Weitman et al., 1992; Vlahov and Leamon, 2012; Li et al., 2009; Fisher et al., 2008; Christensen et al., 2011; Peer et al., 2007; Wu et al., 2009; Anderson et al., 2010; Liu et al., 2007). Different methodologies, such as emulsification-evaporation and Nano precipitation, will prepare Nano spheres (Désormeaux and Bergeron, 1998; Steger and Desnick, 1977; Finkelstein and Weissmann, 1978). The first procedure may be carried out by single or double emulsification (Matteson et al., 2009; Reddy et al., 2007; Sausville et al., 2007; Naumann et al., 2009; Kubo et al., 2000; Minko et al., 2006; Anaissie et al., 1991). The single method of emulsification consists of preparing an oil-in-water emulsion which, in the oil phase, contains the drug and polymer and, in the aqueous phase, a surfactant. For hydrophobic medicines, this approach is ideal for encapsulation (Merck Sharp and Dohme Corp 2013; Date et al., 2007; Alving, 1986; Alving et al., 1978; Drulis-Kawa and Dorotkiewicz-Jach, 2010). A (water-in-liquid)-in-water emulsion is obtained with the drug and the surfactant in the internal aqueous phase, the polymer in the oil phase and another surfactant in the external aqueous phase in the double emulsification step. In general, this procedure is used for hydrophilic drug encapsulation. In both cases, solvent evaporation is required after the emulsification phase for the Nano spheres to be obtained (Merck Sharp and Dohme Corp 2014; Kilian et al., 2011; Barani et al., 2010; Malcher et al., 2008).

3.4.3. Nano capsules

A Nano capsule consists of a shell and a room where it is possible to position the desired substances (Li et al., 2005; Gilbert and Knight, 1996; Koff and Fidler, 1985). Antibodies or cell surface receptors that bind to cancer or different cells and release their biological compound upon interaction with that particular tissue can be covered with drug-filled Nano capsules (Pollock et al., 2008; Logue et al., 2010; Mannino and Gould-Fogerite, 1988; Straubinger and Papahadjopoulos, 1983). Relevant sizes and shapes can now be developed for polymeric Nano capsules (Amato et al., 2004; Endocyte, 2012b; Nicolau et al., 1987; Madeira et al., 2010; Lee et al., 2004). These can then be functionalized by injecting molecules into the shell of Nano capsules with a special property. In reaction to a specific biomolecule, which will be the initiating mechanism in a targeted drug delivery system, these molecules

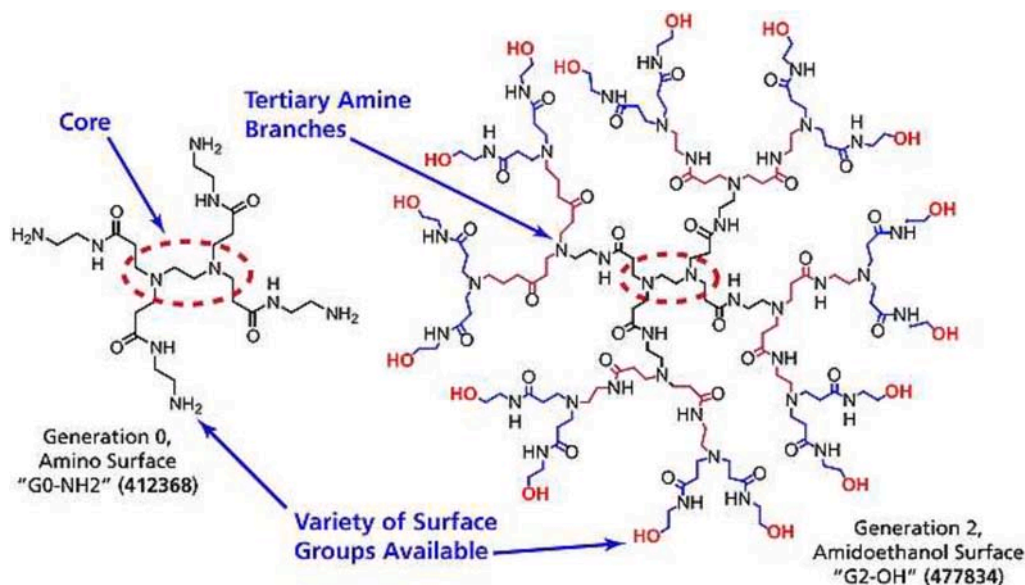


Fig. 21. PAMAM Dendrimer Structures (Puig-Kröger et al., 2009).

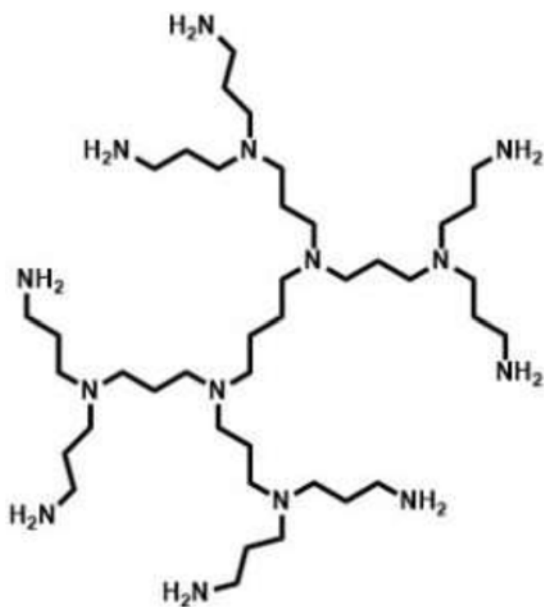


Fig. 22. PPI Dendrimer Structures or DAB-Am-8 (Ross et al., 1999, Zhao et al., 2008).

induce the release of the contents of the Nano capsule (Fujii et al., 2010; Malone et al., 1989; Kinet et al., 2009). Nano capsules are carriers of biocatalysts and drugs for enzymes and for vector delivery to malignant cells (Squibb Bristol-Myers, 2011b; Williams et al., 1984; Presant et al., 1988; Dong et al., 2012). They are circular in shape; in the hollow core, medicines are put and jacketed with a polymeric membrane (Bernstein et al., 2009; Christensen et al., 2009; Tiwari et al., 2009). They range in size from 50 to 300 nm. With the aid of Nano capsules, both hydrophilic and lipophilic drugs can be administered (Fig. 24) (Squibb Bristol-Myers, 2011a; Endocyte, 2012a)

3.4.4. Liposomes

A liposome is a microscopic vesicle covering a fluid space containing a phospholipid bilayer (Christensen et al., 2011; Niesman, 1992). Typically, the thickness of this bilayer lipid is between 3 and 6 nm, but

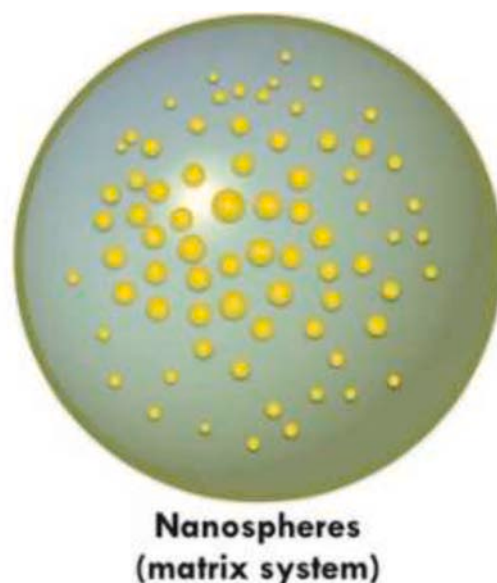


Fig. 23. Nano spheres Structures (Rustin, 2003).

the liposomes formed from it can be between 50 nm and 50 μ m in diameter (Singh and Mezei, 1984; Singh and Mezei, 1983; Ebrahim et al., 2005). Liposomes facilitate the delivery of hydrophilic hemophilic drugs due to the amphipathic (dual-friendly) properties of their constituent elements (L. Zhang et al., 2007; Lindman et al., 1980). Features such as low intrinsic toxicity, biodegradability and lack of immunogenicity have made liposomes a very suitable carrier in modern drug delivery systems. These tiny, sac-like structures are like packets or capsules that can be used to carry drugs to different parts of the body by encapsulating drugs inside them. As a consequence, one of the major uses of liposomes is drug delivery (Uskoković and Drofenik, 2007; Squibb http 2012; W. Zhang et al., 2007; Harada and Kataoka, 2006; La et al., 1996). As high-potential drug carriers, liposomes - microscopic phospholipid bubbles with a bilayer membrane structure - have gained a lot of interest over the past 30 years. New discoveries have recently been made in the area of liposomal medicines. This ranges from new advances, from clinically proven products to new experimental

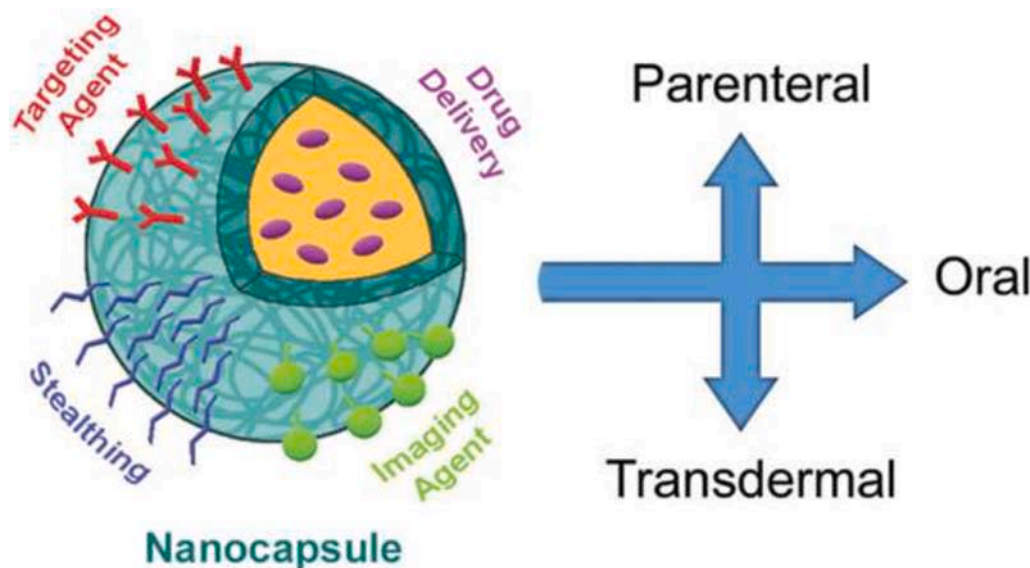


Fig. 24. Nano capsule Structures (Squibb Bristol-Myers, 2011).

applications in gene delivery and cancer treatment (Zasadzinski et al., 2011; Bernard et al., 1947). The biocompatibility and portability of hydrophilic and lipophilic drugs in the Novel Drug Delivery System has made liposomes one of the most attractive carriers. Scientific uses have been seen today in novel anticancer medications such as daunorubicin and doxorubicin, which use liposomes as drug carriers (Benahmed et al., 2001; Weissig et al., 1998; Yokoyama et al., 1998). Phospholipid vesicles, or liposomes, are colloidal particles with two or more phospholipid membrane membranes that, due to their high importance as drug carriers in modern drug delivery systems, can now be engineered to a wide range of different sizes, phospholipid composition, and surface properties. There are many different methods for preparing liposomes, and two general methods for preparing liposomes based on drug loading are: 1- Passive loading techniques 2- Active loading techniques (Shin et al., 1998; Lukyanov and Torchilin, 2004; Torchilin, 2001). Depending on the different application purposes, the surface of liposomes can be modified with different molecules and polymers to create a special feature. There are a variety of applications for liposomes today. In the Novel Drug Delivery System, the biocompatibility and portability of both hydrophilic and lipophilic medicines have made them one of the most attractive carriers (Trubetskoy, 1999; Torchilin, 2007; Jones and Leroux, 1999). Scientific uses have been seen today in novel anticancer medications such as daunorubicin and doxorubicin, which use liposomes as drug carriers. It is hoped that in the not-too-distant future, these new liposome-based liposuction systems will untangle the treatment of many patients whose disease is currently incurable (Oerlemans and Fau - Bult, 2010; Tuzar and Kratochvil, 1993; Zhang et al., 1996; Lazzari et al., 2007). Liposomes are colloidal particles with a membrane of two or more layers of phospholipids that have been the focus of intensive study for more than 45 years by researchers involved in this field (Bangham, 1992). Due to this feature, liposomes are most used in the fabrication of nanoparticles (Fig. 25).

3.4.4.1. Structural characteristics of liposomes. In drug distribution, the arrangement of liposomes reflects some of their special properties (Adams et al., 2003; Zhao et al., 1990; Wilhelm et al., 1991). Therefore, studying the liposome structure allows to better understand the liposome mechanism of action as well as the limitations and strengths of this emerging method of drug delivery. Liposomes are sacs of artificially formed bilayer lipids (Bader et al., 1984; Collett and Tobin, 1979; Lin and Kawashima, 1985; Kwon et al., 1995; Kazunori et al., 1993). The liposome structure is made up of amphipathic molecules which have a

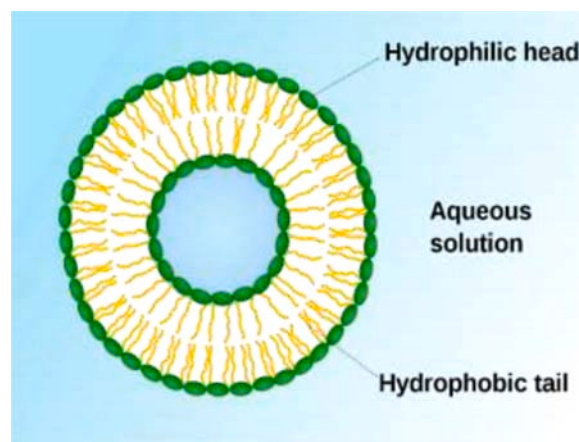
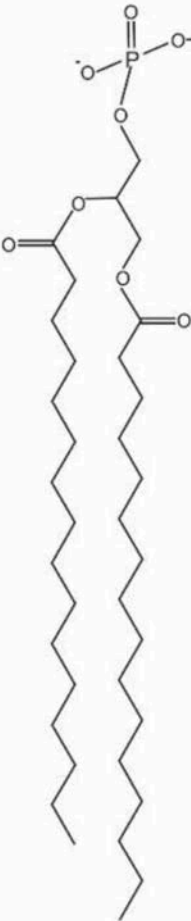
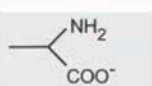
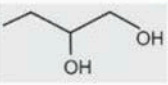
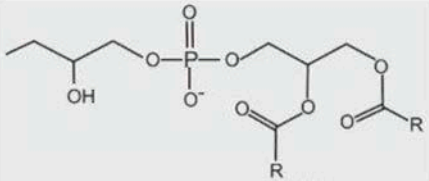
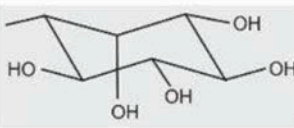


Fig. 25. The structure of a liposome that loads both hydrophilic and lipophilic drugs simultaneously (Bangham, 1992).

hydrophilic head and a hydrophobic head. We research the structure of phospholipids since most of the synthesized liposomes are comprised of amphipathic lipid molecules called phospholipids. The phospholipid composition comprises of an acidic group called the skeleton of phospholipids (which is either glycerol or sphingosine), two molecules of fatty acids, the phosphate group and the groups connected to phosphate (Koolman and Roehm, 2005; Yokoyama, 1992; Yokoyama et al., 1991; Kwon et al., 1993, 1994; Kwon and Okano, 1996). Fig. 26 shows a schematic view of phospholipids. Phospholipids have amphipathic properties. One end of them has a phosphate group (hydrophilic) and the other end has a fatty acid (it is hydrophobic due to its hydrocarbon structure). Phospholipid vesicles or liposomes arise from the community of these phospholipids in the surrounding environment. However, cholesterol is often added to control the fluidity of the membrane and make synthetic liposomes more stable. Fig. 27 shows a schematic view of the liposome (Suk et al., 2014; Maeda et al., 1992; Gabizon et al., 1994; Gangadharam et al., 1995; Kreuter, 1994).

3.4.4.2. Types of synthesis methods. Two important goals are considered in the synthesis of drugs in liposomal drug delivery systems, one is the synthesis of the target liposomes and the other is the efficacy of trapping the drug within them or the so-called packing of the drug within the

Basic phospholipid structure	Substituent (X)		Phospholipid/Characteristic	
		hydrogen	PA	anionic
		ethanolamine	PE	zwitterionic
		choline	PC	zwitterionic
		serine	PS	anionic
		glycerol	PG	anionic
	 phosphatidylglycerol		CL	anionic
		inositol	PI	anionic

Phospholipids

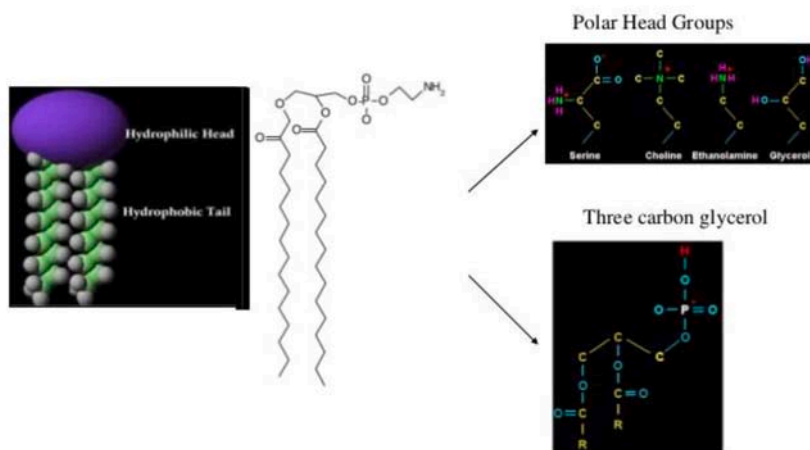


Fig. 26. Schematic view of the structure of phospholipids (Koolman and Roehm, 2005, Suk et al., 2014).

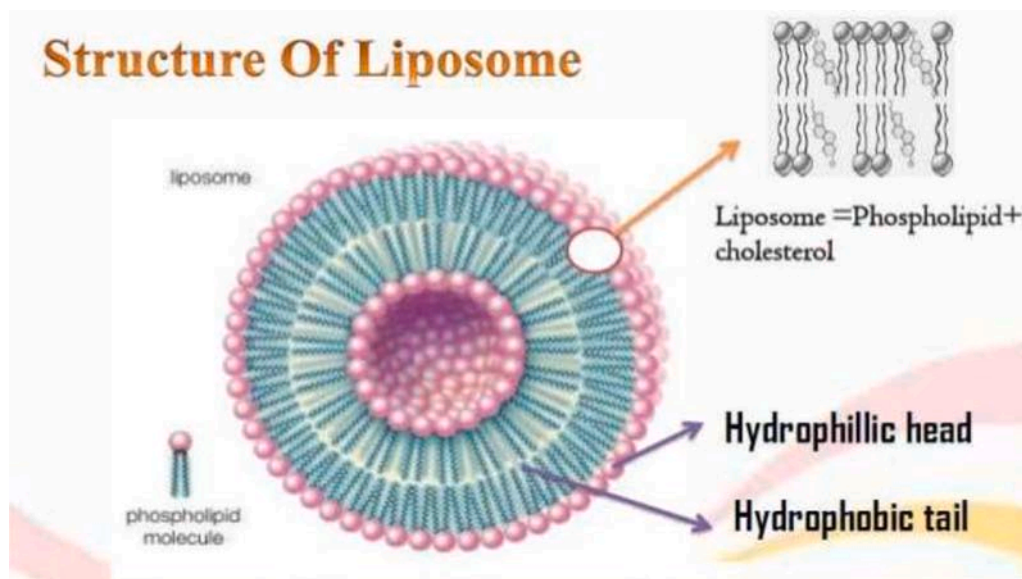


Fig. 27. Schematic view of the structure of liposome (Koolman and Roehm, 2005, Suk et al., 2014).

liposomes (Mahmud et al., 2007; Kabanov et al., 1989; Bae et al., 2005; Torchilin, 2008). A wide range of methods of liposome preparation have been developed and developed, but only a small number of water-soluble drugs are capable of trapping significant quantities. The right choice of preparation method for liposomes depends on the following parameters (Kirby et al., 1980; Lindman and Wennerström, 1980; Mukerjee and Yang, 1976; McBain, 1913; Patra et al., 2018; E. Kianfar, 2021; van der Meel et al., 2019; Dalby et al., 2019):

- 1 Physical and chemical properties of substances trapped within the liposome and those that are liposomal components.
- 2 The nature of the environment in which lipid vesicles are dispersed.
- 3 Effective concentration of trapped substances and their potential toxicity
- 4 Additional processes involved during the application of vesicles or delivery of vesicles
- 5 Optimal size, polydispersity and shelf-life of vesicles for functional purposes
- 6 Batch-to-batch reproducibility and the possibility of producing healthy and efficient large-scale liposomal products.

Now, depending on the purpose and type of administration, as well

as the condition of the target tissues or cells, as well as how the drug is released, it is time to choose the method of synthesizing liposomes. The general method of synthesizing liposomes can be seen in 3 or 4 steps according to Fig. 28.

3.4.4.3. Passive loading techniques. In this method, drugs are trapped before or during liposome production (Hauschild et al., 2020; L. Wu et al., 2020; Yin et al., 2017). This method is divided into three categories, each of which includes different techniques (Yin et al., 2014; Abderrahmane et al., 2023; Wang et al., 2022). Fig. 29 shows the division of this method. In these techniques, hydrophilic drugs are encapsulated in liposomes in aqueous medium, and hydrophobic drugs (lipophilic) are enclosed between two phospholipid layers. Water-soluble substances (eg drugs) are added to solutions that are trapped between the mass and the accumulation of hydrophobic heads, and the fat-soluble substances are placed between the phospholipid bilayers. Fig. 30 shows the encapsulation of the drug within liposomes. When water-soluble drugs are encapsulated in liposomes, they do not alter the physical properties of the liposome and there is no drug-liposome interaction; But when lipophilic drugs are placed in the liposome membrane, their physical properties are the same, they cause significant changes in temperature (TC). The temperature at which the

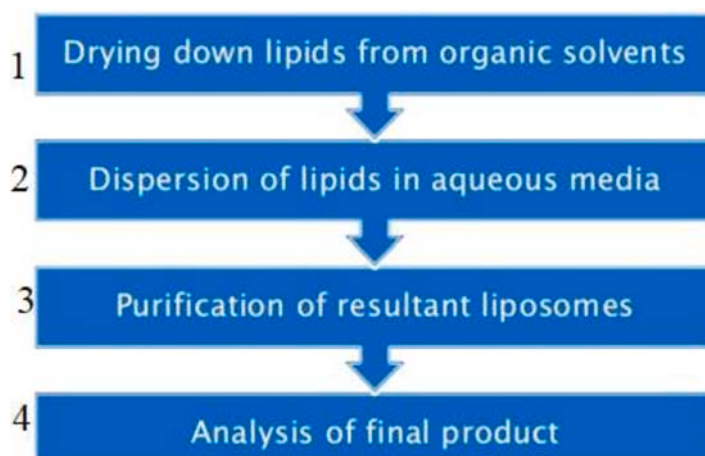


Fig. 28. General steps in the synthesis of liposomes (Kirby et al., 1980).

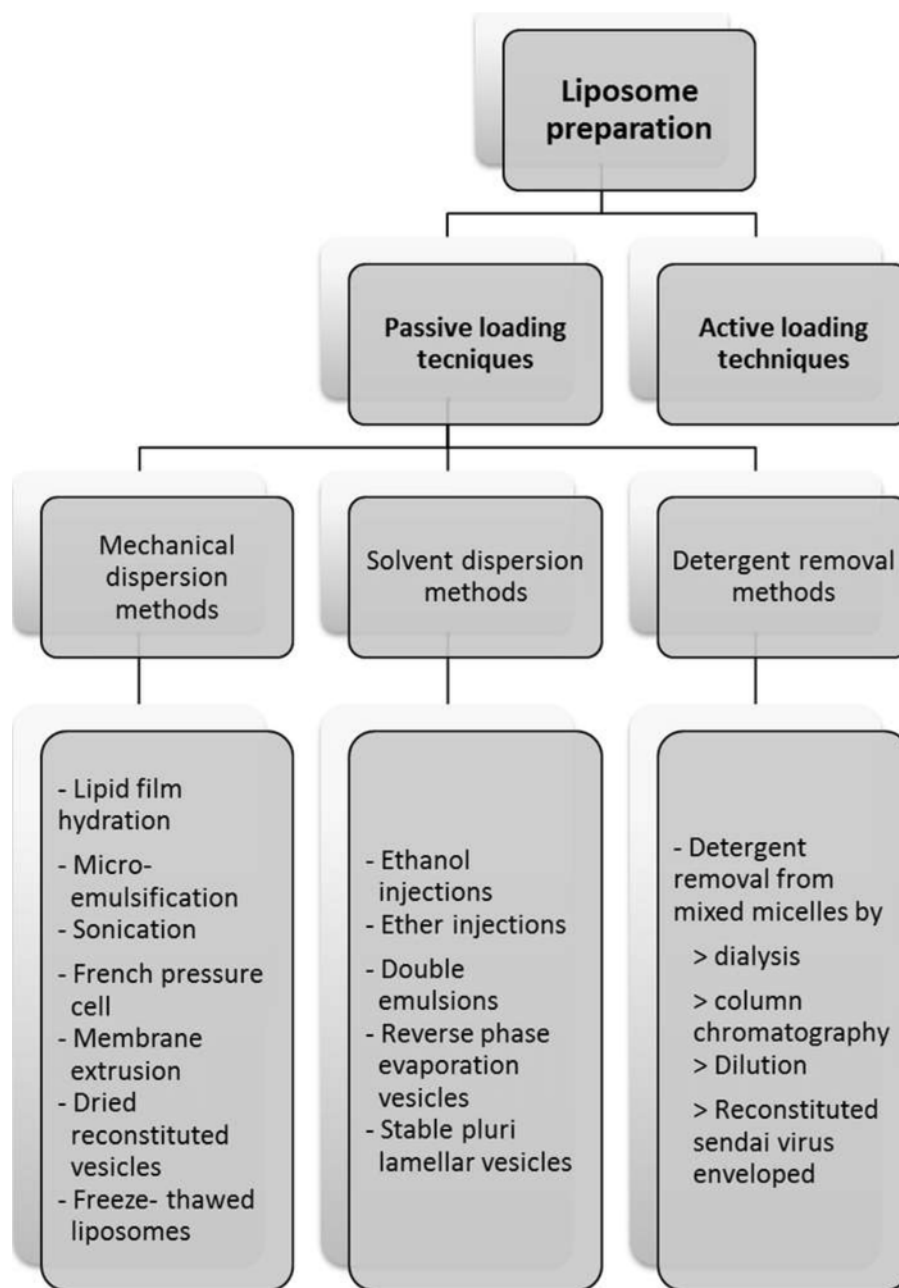


Fig. 29. Types of methods of Passive loading of liposomes (Squibb <http> 2012).

liposome chains change from a regular solid to an irregular liquid crystal is called the phase change temperature (TC) (Squibb <http> 2012; S. Wu et al., 2020; Xiao and Smaism, 2022; Mourad et al., 2022; G.F. Smaism et al., 2022; Abderrahmane et al., 2022).

3.4.4.4. Active loading techniques. It refers to a specific type of compound with ionizing groups or compounds that are soluble in both water and fat and can penetrate into liposomes after their formation stage (Tan et al., 2023; Mir et al., 2022; Ruhani et al., 2022). For example, drugs that are dual-friendly can easily penetrate and load into liposomes once they are formed. It should be noted that in passive loading techniques, drugs are trapped inside the liposomes before or during their formation and cannot penetrate them after the liposomes have formed. As a result, active loading techniques are limited to a limited number of drugs (Cai et al., 2022; Moarrefzadeh et al., 2022; Hai et al., 2022; Fadhil Smaism et al., 2022; G.F. Smaism et al., 2022). Fig. 31 Types of methods of Active loading of liposomes (Caster et al., 2017; Jones, 1995).

3.4.4.5. Surface modifications of liposomes. For different applications, liposomes with different properties are needed. In order to produce liposomes with distinct and suitable properties, this purpose can be accomplished to some degree by altering them superficially (Jiang et al., 2022; M.W. Tian et al., 2022a, 2022b; Alharbi et al., 2022; Wu et al., 2022). The number of applications of liposomes as carriers in advanced drug delivery systems has vastly extended with surface modification and the acquisition of new features. Fig. 32 the division of liposomes and the techniques for surface alteration applied in each group. The binding of polymers or macromolecules to the liposome surface is the form of chemical bond (covalent bonding) or the type of physical bond (van der Waals or hydrophobic or hydrophobic or hydrophobic or hydrophobic) that depends on the type of polymers or macromolecules, as well as on their surface or final functional groups (Ferlay et al., 2010; Reza Mozafari et al., 2008; Brontowiyono et al., 2022; Y. Tian et al., 2022; G. F. Smaism et al., 2022).

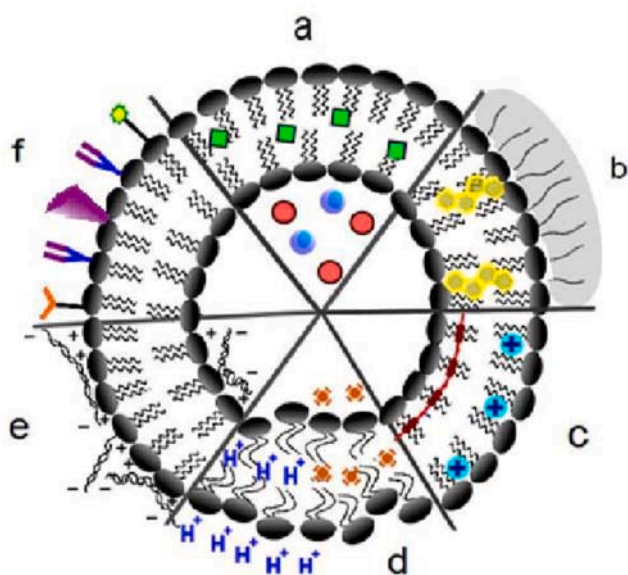


Fig. 30. A view of the encapsulation of lipophilic and hydrophilic drugs: (a) Hydrophilic drug encapsulation (red) and gas bubbles (blue) in the aqueous center and lipophilic drug encapsulation (green) within the bilayer; (b) Cholesterol lipid bilayer stability (yellow) and hydrophilic polymer layer attachment on the bilayer surface; (c) Bilayer lipid liposomes are reinforced and stabilized by polymerization (red) or multivalent cation incorporation (blue), (d) bio-responsive lipid bilayer destabilization at acidic pH (blue) or elevated temperature achieved by magnetic agents (blue), (e) binding of negatively charged DNA molecules to positively charged lipid molecules, (f) binding on the liposome surface of immunogenic or targeting ligands (S. Wu et al., 2020).

3.4.4.6. Classification of liposomes based on different methods. It should be noted that based on different synthesis methods and also with surface modifications of liposomes, liposomes with different properties can be obtained, each of which is suitable for a specific application (Fig. 33). Accordingly, before choosing the type of liposome, one should have a complete knowledge of their types and characteristics in order to choose the best possible option. For example, for intravenous drug delivery, GUL liposomes (Gaint Unilamellar Vesicle) ($\sim 1.0 \mu\text{m}$) in size cannot be used. Since the large size of these liposomes obstructs the capillaries, the use of SUL liposomes (Small Unilamellar Vesicles), which are approximately 20–100 nm in size (Drug Delivery Analysis; G.F. Smaism et al., 2022d, 2022c, 2022f) or pH-sensitive smart liposomes, is naturally a better option to deliver drugs to tumors that release drugs loaded into them near tumors with different pHs than other tissues. Liposomes modified by synthetic polymers such as polyethylene glycol (PEG) can also be used by the blood endothelial system to escape phagocytosis (Mozafarifar et al., 2022; Sharba et al., 2022; G.F. Smaism et al., 2022i; AbdulHussein et al., 2022; Ahamad et al., 2022; Doss et al., 2022; Lefteh et al., 2022). We must therefore choose the best liposomal carrier type. For this reason, based on different variables, we will introduce different types of liposomes so that we can select the best option from them according to our goal. Based on various variables, liposomes are classified into different classes (Dua et al., 2012; Perforated; Al-Madh-hachi and Smaism, 2021; Smaism, 2018; G.F. Smaism, 2017a, 2017b).

3.4.4.6.1. Segmentation based on structural parameters. It should be remembered that the number of layers (Tao et al., 2012; Chen et al., 2011; Hale et al., 1980) is the difference between Multilamellar and Oligolamellar liposomes. More layers are seen by Multilamellar liposomes. Based on their size, single-walled liposomes are often classified into four groups: thin, medium, huge, and giant. But MVV liposomes with many vesicles inside are large liposomes. More layers are seen by Multilamellar liposomes (G. Smaism et al., 2016a, 2016b). Based on their size, single-walled liposomes are often classified into four groups: thin, medium, huge, and giant. But MVV liposomes with many vesicles inside are large liposomes (Farahani et al., 2023; Mir et al., 2023; F.

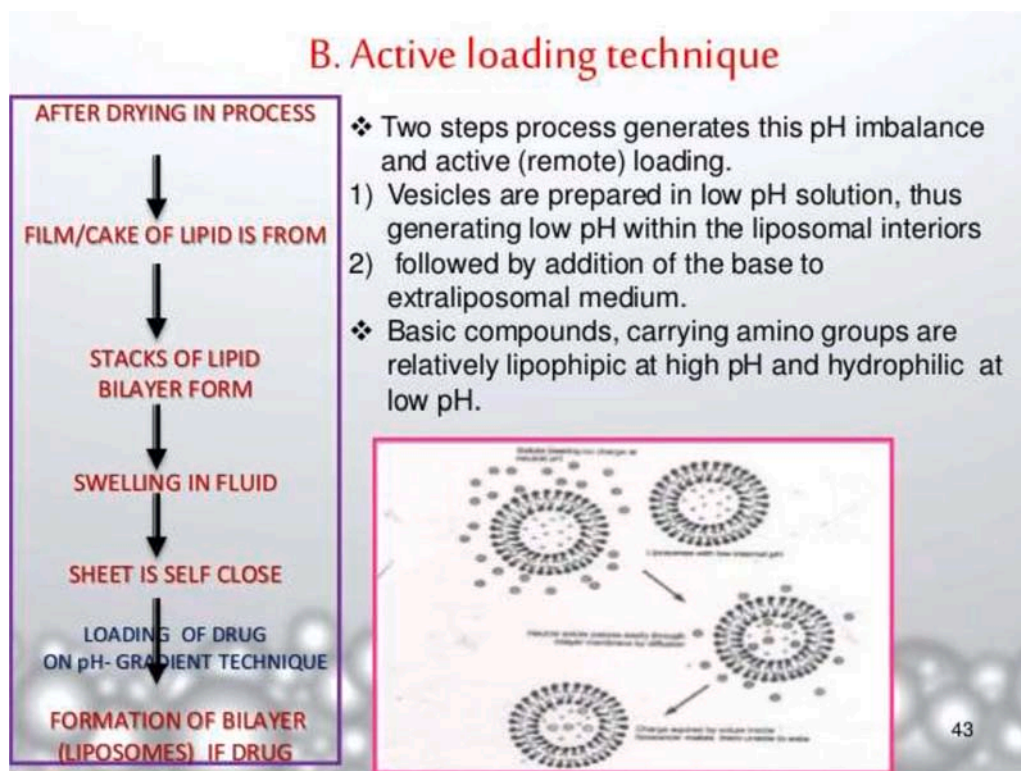


Fig. 31. Types of methods of Active loading of liposomes (Caster et al., 2017).

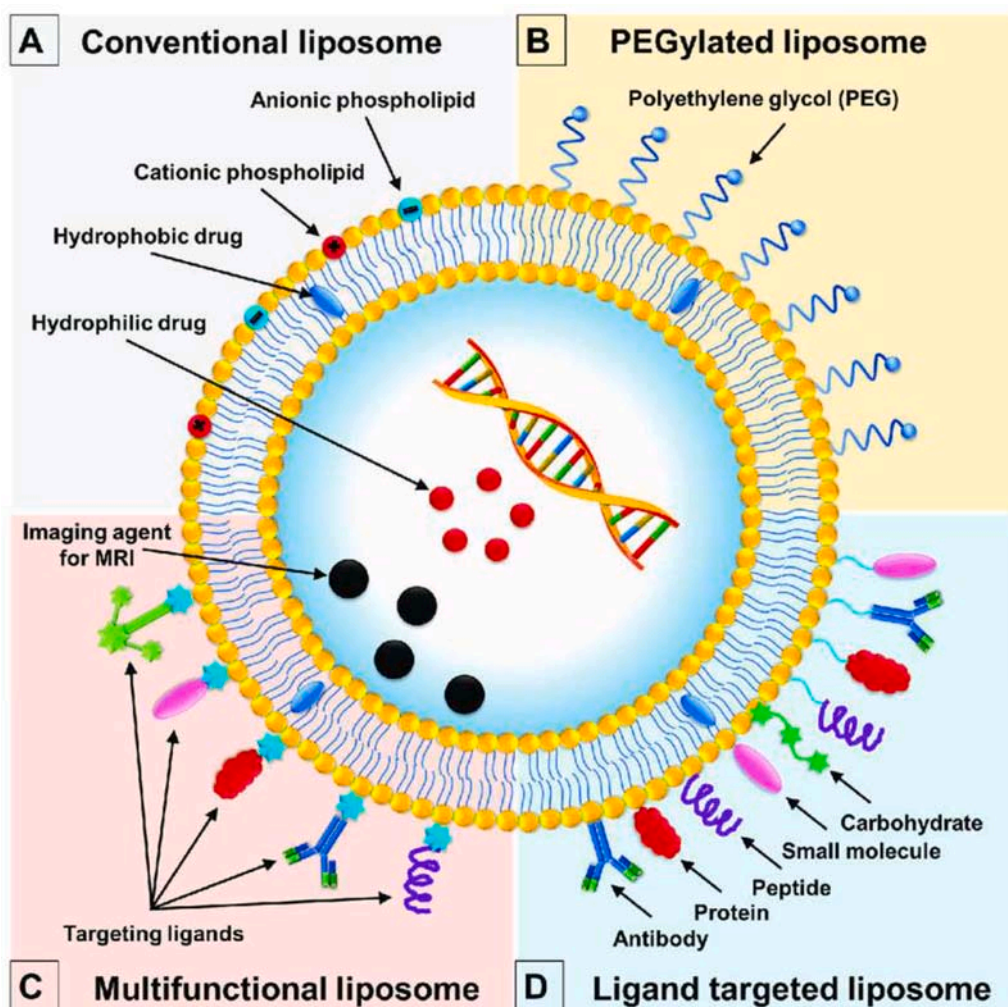


Fig. 32. Types of surface modifications of liposomes (Reza Mozafari et al., 2008).

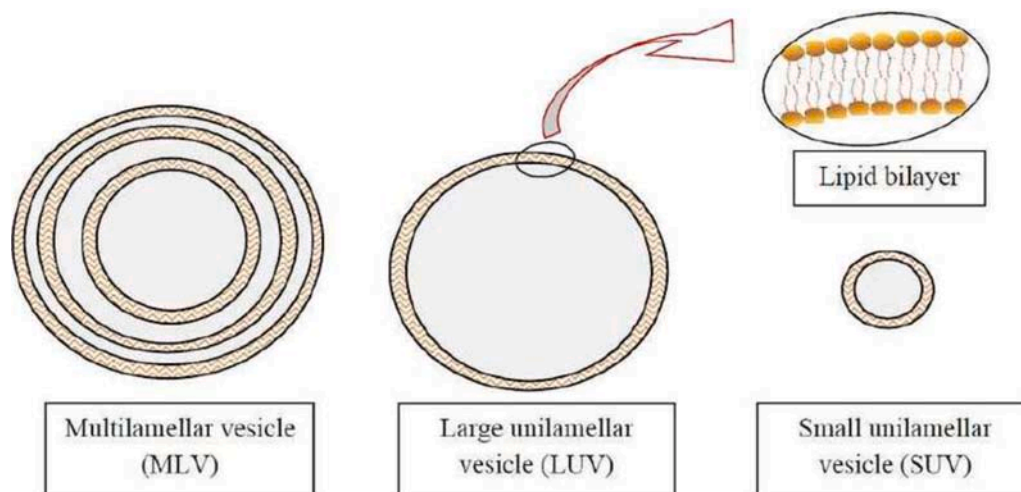


Fig. 33. Classification of liposomes based on different methods (Dua et al., 2012).

Wang et al., 2023). A schematic view of various forms of liposomes based on structural parameters is seen in Figs. 34, 35 for a clearer understanding of the subject (ElBayoumi and Torchilin, 2009).

3.4.4.6.2. *Segmentation based on liposome preparation methods.* The liposomes were manufactured and extruded using the dry film process

through a membrane with a pore size of 200 nm. This approach gives a homogeneous unilamellar liposomes solution (Fig. 36A). The scale and morphology of liposomes studied by transmission electron microscopy (TEM) (Chen et al., 2023; M.P. Narayanasamy et al., 2023; Y. Wang et al., 2023; Farahani et al., 2023; Mir et al., 2023). The liposomes are

Types of liposomes based on Structural parameters	Size (μm)
Multilamellar liposome (MLV)	0.1–0.5 μm
Unilamellar liposome	
Small Unilamellar liposome (SUV)	0.02–0.05 μm
Large Unilamellar liposome (LUV)	more than 0.06 μm
Multivesicular liposome (MVV)	2–40 μm
Oligolamellar liposome	0.1–10 μm in size
GL	10–1000 μm

MLV: Multilamellar vesicle, MVV: Multivesicular vesicle, SUV: Small Unilamellar vesicles, GL: Giant liposome, LUV: Large unilamellar vesicle

Fig. 34. Classification of liposomes on the basis of layer number and layer size (Hale et al., 1980).

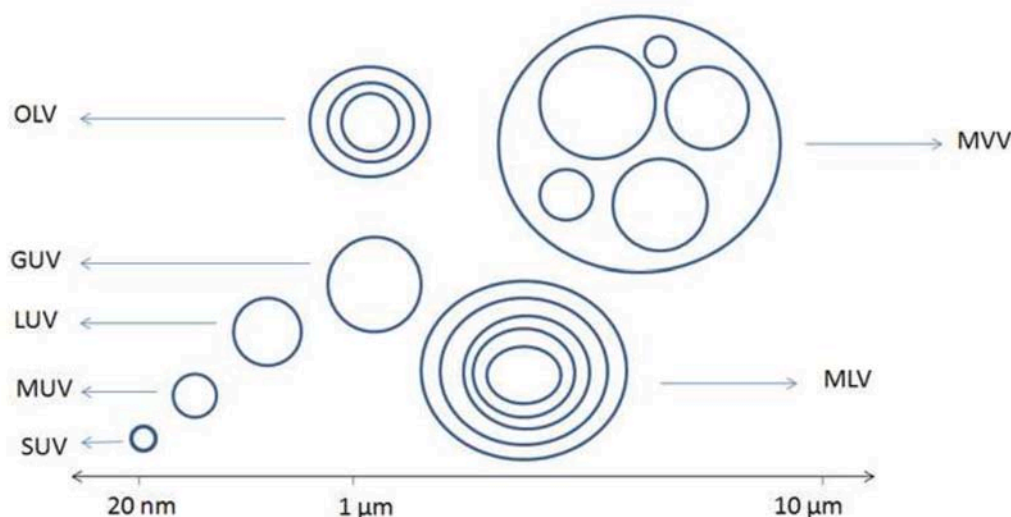


Fig. 35. Schematic view of the classification of liposomes based on structural parameters (ElBayoumi and Torchilin, 2009).

spherical and measure 181.8 ± 39.95 nm in shape (Fig. 36B). Furthermore, the potency of encapsulation of liposomes was measured and compared with Lipofectamine 2000. The samples were then incubated with fluorescence dye that was RNA-binding, and a standard curve was used to determine the volume of free mRNA (Abderrahmane et al., 2023; F. Wang et al., 2023). It has been shown that liposomes have an equal capacity to encapsulate mRNA, including the commercially available Lipofectamine 2000. After complexation of mRNA with liposomes, only 16.19 percent $\pm$ 3.58 percent of free mRNA was found (Chen et al., 2023, M.P. Narayanasamy et al., 2023, Elmasry et al., 2023). This is similar to the mRNA complexation of Lipofectamine 2000, where 17.88 percent $\pm$ 1.07 percent of free mRNA was observed (Fig. 36C) (Bogdanov et al., 1989; Francis et al., 1992; Zhang et al., 2005; Yoshino et al., 2012).

3.4.4.6.3. Classification liposomes based on compounds and applications. In this type of classification, which is the most important type of liposome classification in terms of functionality, we introduce liposomes in terms of functionality as well as their constituents. Table 3 describes the types of divisions based on composition and application (Haywood and Boyer, 1986; Shichijo and Alving, 1986; McDaniel et al., 1986; Crook et al., 1986).

3.4.4.6.4. Methods for identifying the characteristics of synthesized liposomes. The general properties of the drugs must be studied in order to obtain their features and properties after the drug is synthesized and stuck within the liposomes. Because of the flexibility and precision of the body's physiological environment and the method of drug administration, obtaining synthetic liposomal drug characteristics and requirements, such as distribution of size and size, number of layers, surface load, quality of yield and trapping, volume and ability of drug

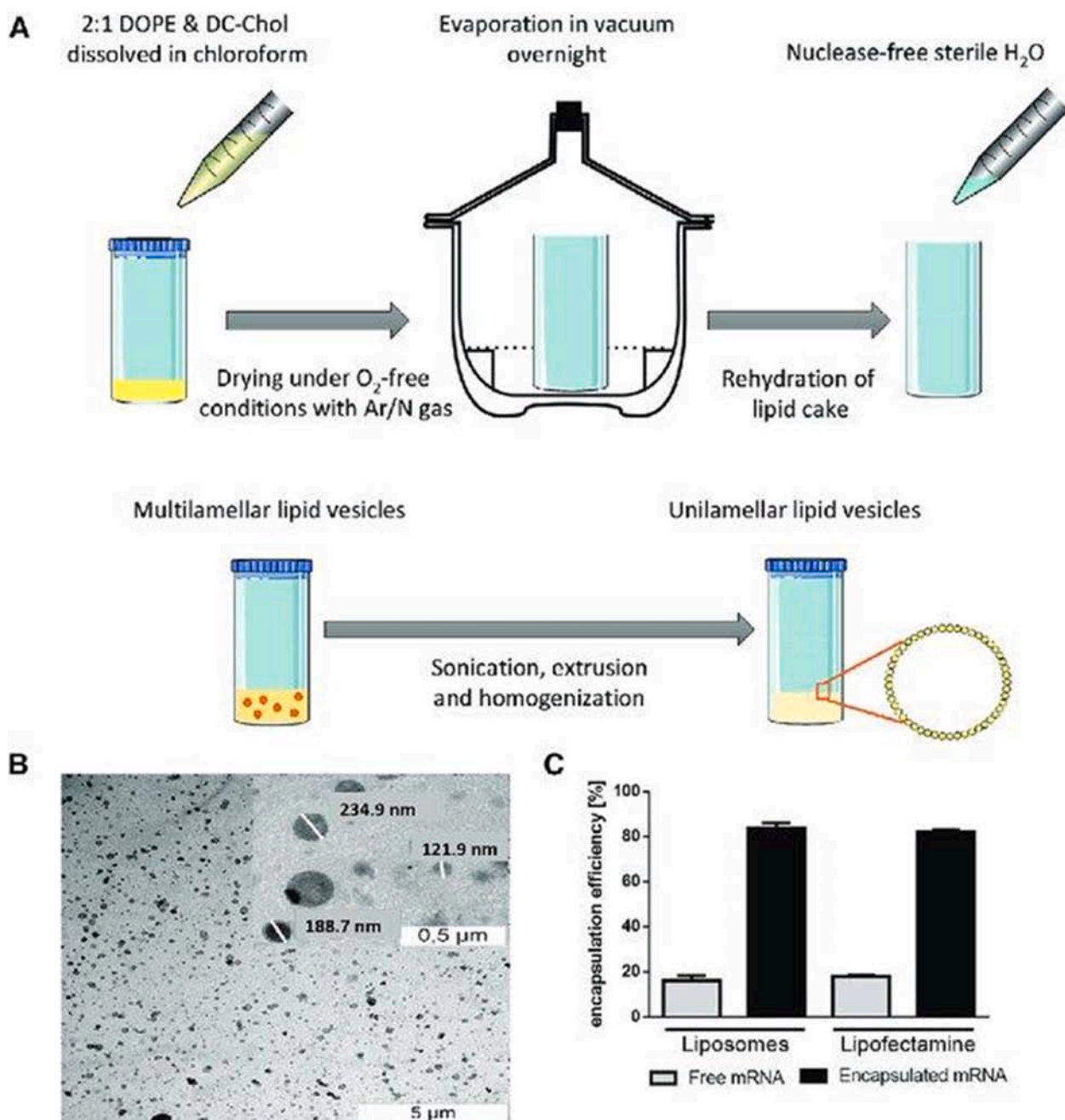


Fig. 36. Liposome preparation and classification (A) Graphical overview of the liposome manufacturing process, including lipid preparation and mixing, O₂ free drying and overnight vacuum evaporation. The developed lipid cake was rehydrated with water, followed by sonification, extrusion, and homogenization, to obtain unilamellar lipid vesicles. (B) Visualization of the liposome using TEM after negative staining. (C) Analysis of the mRNA encapsulation ability of liposomes according to Lipofectamine 2000. The data is seen as $\pm$ SEM mean ($n = 5$) (Bogdanov et al., 1989).

capture, the rate of drug release by synthetic liposomal carriers is very critical and should be calculated carefully (Goodwin et al., 1982; Sarkar and Blumenthal, 1987; Pinnaduwa and Huang, 1989; Mahdi et al., 2023; Pallathadka et al., 2023; Z.H. Mahmoud et al., 2023; Z.H. Mahmoud et al., 2023; Siswanto et al., 2023). The bigger the liposome scale, the simpler it is to cross the membrane, but less drug is stuck within the liposomes, resulting in decreased trapping ability, on the other hand. In the other hand, their surface energy increases and their stability declines as the size of liposomes decreases, and finally, they aggregate and form a mass to minimize surface energy, which significantly decreases their performance. The wider the distribution of particle size, the more uniform the size of the liposomes and the more similar the overall product characteristics are. Another critical element in liposome architecture is

the drug release rate (Ho et al., 1992; Wilschut, 2009; Z.H. Mahmoud et al., 2023e, 2023d, 2023a, S.A. Jasim et al., 2023a). The pace of the release of drugs can be regulated by speeding them up. The rate of drug release should be high in areas where we want the drug to be released immediately, and where we want the drug to be released slowly, drug release should be low (Al-Obaidi et al., 2023; S.A. Jasim et al., 2023b, 2022b, 2022a, Bokov et al., 2022). It should be remembered that even the slightest improvements in the properties of synthetic liposomes in clinical applications will demonstrate distinct clinical variations. Liposomes with a large size distribution, for example, should not be inserted intravenously and if the size of the liposomes is not standardized, they would be hindered by liposomes greater than a certain size by collecting within the capillaries (Ho et al., 1986; Feng et al., 2009; Mansoor Al

Table 3

Centered on substances liposomes based on applications and classification (Haywood and Boyer, 1986, Shichijo and Alving, 1986, McDaniel et al., 1986, Crook et al., 1986).

liposomes	compounds and applications
LV	Multilamellar large vesicles >0.5μ
OLV	Oligolamellar vesicles 0.1–1μ
UV	Unilamellar vesicles (all size range)
SUV	Small Unilamellar vesicles 20–100 nm
LUV	Large Unilamellar vesicles >100 nm
MV	Multivesicular vesicles
REV	Single or Oligolamellar vesicle made by reverse phase evaporation method
MLV-REV	Multilamellar vesicles made by reverse phase evaporation method
SPLV	Stable plurilamellar vesicles
FATMLV	Frozen and thawed vesicles MLV
VET	Vesicles prepared by extrusion techniques
DRV	Dehydration-rehydration method
Conventional liposomes (CL)	Neutral or negatively charge phospholipids and cholesterol
Fusogenic liposomes O(RSVE)	Reconstituted Sendai Virus envelopes
pH sensitive liposomes	Phospholipids such as PE or DOPE with either CHEMS or OA
Cationic liposomes	Cationic lipids with DOPE
Long circulatory (stealth) liposomes (LCL)	Neutral Tc, cholesterol and 5–10% of PEG-DSPE or GM1

Sarraf et al., 2022, Hameed Mahmood et al., 2022, Z.H. Mahmoud et al., 2022). The types of methods and devices to classify the characteristics of liposomes are listed in Table 4.

3.4.4.6.5. Applications of liposomes in medicine and their importance in drug delivery. In medicine, liposomes have a broad range of applications. Yet in advanced drug delivery systems, their most relevant uses are as drug carriers.

The following are some of the key reasons which laid the foundations

Table 4

Types of methods and devices for identifying the characteristics of liposomes (Feng et al., 2010, Manjappa et al., 2011, Fukui and Fujimoto, 2011).

Characteristic type of liposomes	Identification methods and devices
Phospholipids concentration	Lipid phosphorous content using Barlett assay Stewart assay, HPLC
Cholesterol concentration	Cholesterol oxidase assay and HPLC
Drug concentration	As per monograph
Phospholipids peroxidation	UV absorbance, TBA (for endoperoxidase), GLC
Phospholipids hydrolysis	HPLC, TLC, fatty acid concentration
Antioxidant degradation	HPLC, TLC
Residual organic solvents and heavy metals	As per the monograph
Shape and surface morphology	TEM, SEM, Freeze fracture electron microscopy
Size and Size distribution	Dynamic light scattering
Surface charge	Zetasizer
pH	pH sensitive probes
Lamellarity	Small angle X-ray scattering, Freeze fracture electron microscopy, P NMR
Bilayer fluidity	Fluorescence polarization, ESR
Phase behavior	Freeze fracture electron microscopy, DSC
% capture,% free drug	Fluorescence polarization, ESR Phase behavior Freeze fracture electron microscopy, DSC% capture, % free drug Minicolumn centrifugation, gel exclusion, ion exchange chromatography, protamine aggregation to separate the free drug followed by HPLC analysis or by radiolabelling and counting the activity of isotope Drug release Diffusion cell dialysis Osmolarity Osmome
Drug release	Diffusion cell dialysis
Osmolarity	Osmometer
Sterility	Aerobic or anaerobic cultures
Pyrogenicity	Rabbit fever response test, LAL test
Animal toxicity	Monitoring survival rates, histology and pathology

for the widespread use of liposomes in biological and therapeutic research (Fan et al., 2012; Gao et al., 2012; Fukui and Fujimoto, 2009; Machová and Bystrický, 2012; Zalipsky, 1993):

- 1) The similarity of the bilayer structures of cell-gardening liposomes and their ability to limit hydrophobic and hydrophilic materials.
- 2) Liposomes can deliver drugs to the body's target area and prevent them from reaching sensitive areas of the body where the drug is toxic (such as the liver and kidneys).
- 3) Liposomes can serve as a source of storage, slowly and at particular times releasing the trapped material inside them, thereby regulating the dosage of the drug in the bloodstream at regular intervals.
- 4) Drugs found in liposomes are shielded from the harmful factors present in the host body, in particular those ingested in the internal aqueous humor; this allows the patient to be shielded from the adverse effects of treatment.
- 5) By communicating in various ways with the target cells, liposomes can assist in the entrance of drugs that are unable to enter the cell in a free state.
- 6) Liposomes improve the drug's effects.
- 7) Ability to carry hydrophilic drugs as well as hydrophobic drugs.
- 8) Good biocompatibility with them and biodegradability.

There are a number of uses today for liposomes as carriers of medicines. They have been one of the most desirable opioid carriers due to the cases listed above. Along the two layers of liposome lipid membranes, drugs and hydrophobic substances are contained, and hydrophilic drugs and substances are encapsulated within the liposomes. There is also, of course, the risk of liposome adsorption on the surface of drugs and hydrophilic compounds. Liposomes are used to deliver vaccines, enzymes, or medicines (such as nosulin and anticancer drugs) to the body in drug delivery systems. When liposomes are used for drug delivery, good cells are protected from drug toxicity and drug doses are prevented in sensitive tissues (such as the liver and kidneys) (Biswas et al., 2012; Riaz, 1996). During chemotherapy sessions, using this procedure prevents or removes harmful side effects such as nausea, fatigue, and bruising and hair loss to kill cancer cells. But the sluggish release of the drug is one of the drawbacks of anticancer medications. Chemotherapy can fail due to the slow release of the drug encapsulated into the liposomes due to a lower than lethal dose hitting the tumor cells, which results in the cancer cells' drug stability (I. Raya et al., 2022; Mahmood et al., 2022; Bahadoran et al., 2022; Z.H. Mahmoud et al., 2022). Drug stabilization has a complex function which can be associated with improved MDR transporter expression (a universal membrane protein). These transducers of MDR effectively pump chemotherapy drugs out of the cell, taking the concentration of these drugs below the lethal threshold within cancer cells. At this stage, only drug-sensitive cells that do not express MDR will die if the release of the drug is too late. As a consequence, the release rate of anticancer drugs determines the stabilization of the drug produced in the population of cancer cells (Z.H. Mahmoud et al., 2022c, 2022b, 2022a; I. Raya et al., 2022; Rheima and Al-Salman, 2022). The larger the release of the drug, the lower the safety of the product. As a consequence, controlling the release rate of encapsulated drugs with temporal and spatial control (Mishra et al., 2011; Christensen et al., 2011; Peer et al., 2007) is one of the challenges of drug delivery by liposomes as well as other nanocarriers. Liposomes are particularly effective in treating diseases which damage the immune system's phagocytes. This is because of phagocytes that have been marked as foreign invaders (Wu et al., 2009), liposomes appear to accumulate. For instance, common liposomes are used to distribute medicine to people living with HIV (these types of liposomes are listed in Table 2). These liposomes bear human T cells with anti-HIV medications (such as siRNA). These typical liposomes are recognised by the blood endothelial system as foreign invaders and are phagocytated (such as T cells) by phagocytic cells and release internally encapsulated drugs into these phagocytic cells. In gene therapy, liposomes are therefore of

special interest and have been used experimentally to carry intact genes into cells to repair abnormal, defective and pathogenic genes; therefore, 'DNA' can be passed almost entirely by liposomes to a specific body tissue (Anderson et al., 2010).

Applications of liposomes as drug carriers, including delivery (Liu et al., 2007; Désormeaux and Bergeron, 1998; Steger and Desnick, 1977; Finkelstein and Weissmann, 1978; Chupradit et al., 2021; Mahmoud et al., 2021; G.F. Smaism et al., 2022):

- 1- Enzymes
- 2- Anti-cancer drugs
- 3- Fungicides (fungicides)
- 4- Antiparasitic drugs
- 5- Antibacterial drugs
- 6- Antiviral drugs
- 7- Types of nucleic acids in genetic manipulation.

Other uses for liposomes include:

- 1- In diagnostic imaging of tumors.
- 2- Vaccine additives.
- 3- Hygienic cosmetics to deliver moisture and anti-inflammatory agents to the skin.
- 4- Drug carriers in ophthalmology.

So far, 11 drugs have been approved by the liposomal drug delivery system and 6 drugs are in clinical trials. Recently, the Iranian drug Sina Dosome has been designed based on this drug delivery method and is in the final stages of clinical studies (Kubo et al., 2000; Minko et al.,

2006; Anaissie et al., 1991). This drug is an anti-cancer compound that is produced and used for the treatment of ovarian, breast, multiple myeloma (leukemia), Kaposi's sarcoma (a type of soft tissue cancer) for the first time in the Middle East at Mashhad University of Medical Sciences. Fig. 37 shows some of the drugs combined with liposomes. These drugs are encapsulated in liposomes and with the use of this new liposomal drug delivery system, the efficiency of the drugs has increased (Date et al., 2007; Alving, 1986; Alving et al., 1978; Drulis-Kawa and Dorotkiewicz-Jach, 2010).

3.4.4.6.6. Mechanism of action of liposomes. You have been acquainted with different methods of synthesizing and loading liposomes as well as their surface modification up to this stage. This segment deals with the liposome transport process as well as with how the drug is released (Li et al., 2005; Gilbert and Knight, 1996; Koff and Fidler, 1985; Pollock et al., 2008; Mahmoud et al., 2021; G.F. Smaism et al., 2022; Kianfar, 2023; Kianfar and Sayadi, 2022; Fattah et al., 2023). The desired substance (e.g. medicine) is placed inside liposomes and these liposomes are prescribed to tissue or organs. Depending on the therapeutic plan (Logue et al., 2010; Mannino and Gould-Fogerite, 1988; Straubinger and Papahadjopoulos, 1983; Nicolau et al., 1987; Bokov et al., 2021; Chupradit et al., 2022; Aldeen et al., 2022; Suryatna et al., 2022), they meet the target and enter it, releasing drugs into the extracellular or intracellular environment. For example, in gene therapy, in cells in which a certain gene is either not expressed or poorly expressed for a number of reasons, using cationic liposomes, and gene copies can be transmitted to target cells (Madeira et al., 2010; Lee et al., 2004; Abdelbasset et al., 2022; S.A. Jasim et al., 2022c; E. Kianfar et al., 2022a, 2022b; Ansari et al., 2022). There are also many directions for the medication to be released (Fujii et al., 2010; Malone et al., 1989;

List of Some clinically approved liposomal drugs			
Name	Trade name	Company	Indication
Liposomal amphotericin B	Abelcet	Enzon	Fungal infections
Liposomal amphotericin B	Ambisome	Gilead Sciences	Fungal and protozoal infections
Liposomal cytarabine	Depocyt	Pacira (formerly SkyePharma)	Malignant lymphomatous meningitis
Liposomal daunorubicin	DaunoXome	Gilead Sciences	HIV-related Kaposi's sarcoma
Liposomal doxorubicin	Myocet	Zenues	Combination therapy with cyclophosphamide in metastatic breast cancer
Liposomal IRIV vaccine	Epaxal	Berna Biotech	Hepatitis A
Liposomal IRIV vaccine	Inflexal V	Berna Biotech	Influenza
Liposomal morphine	DepoDur	SkyePharma , Endo	Postsurgical analgesia
Liposomal verteporfin	Visudyne	Novartis	Age-related macular degeneration, pathologic myopia, ocular histoplasmosis
Liposome-PEG doxorubicin	Doxil/Caelyx	Ortho Biotech , Schering-Plough	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer
Micellular estradiol	Estrasorb	Novavax	Menopausal therapy

Fig. 37. List of some approved liposomal drugs (Kilian et al., 2011, Barani et al., 2010, Malcher et al., 2008).

Kinet et al., 2009; Williams et al., 1984). Fig. 38 shows the mechanisms of intracellular gene delivery using cationic liposomes (Presant et al., 1988; Dong et al., 2012; Bernstein et al., 2009; Christensen et al., 2009; Tiwari et al., 2009).

4. Micelles

Micelles are tools that take a long time to discover. But today these biological structures have found an important role in modern drug delivery systems. In this article, we define micelles, the reasons for micelle formation, the definition of surfactants and polymers that are the building blocks of micelles, and the importance of CMC and the factors that affect it in micelle formation. In addition, types of micelles, especially widely used polymeric micelles, various methods of drug delivery with these micelles and also due to the importance of micelles in storage and transport of drugs and finally among the types of micelles, due to the increasing use of polymeric micelles in modern drug delivery systems. And their regulatory properties as well as the ease of synthesis of this type of micelles compared to other micelle carriers, we will focus on this type of micelle carriers and describe their physicochemical properties (Lindman et al., 1980; Uskoković and Drofenik, 2007; Squibb http 2012; W. Zhang et al., 2007; Harada and Kataoka, 2006; La et al., 1996).

4.1. Definition of micelles and how it is formed

Micelles are densities of surfactant molecules released in a colloidal liquid in which these ionic surfactants have an electrostatic attraction to the ions that surround them in solution (later known as cross-ions). The process of micelle formation is known as micellation. Fig. 39 shows a schematic view of the surfactant community around it and the formation of micelles. In a typical micelles in an aqueous solvent, the hydrophilic head region of its constituent elements in contact with the surrounding solvent and at the same time its single hydrophobic tail region in the center of the micelle forms a mass (Benahmed et al., 2001; Weissig et al., 1998; Yokoyama et al., 1998; Hachem et al., 2022; G.F. Smaism et al., 2022; Kianfar, 2022). Micelles are formed only when the surfactant concentration exceeds the critical micelle formation concentration (CMC) and the system temperature exceeds the critical micelle temperature (critical micelle temperature) or kraft temperature. Michelle formation can be explained by the laws of thermodynamics: Micelles can form spontaneously due to the balance between entropy and enthalpy (Shin et al., 1998; Lukyanov and Torchilin, 2004; Torchilin, 2001). In water, the hydrophobic effect exerts a force to form micelles, despite the fact that the accumulation of surfactant molecules around each other

reduces entropy. At very low lipid concentrations, only monomers are present in true solution. As the lipid concentration increases, it reaches a point where the unfavorable entropy contribution derived from the hydrophobic end of the molecule prevails. At this point the hydrocarbon chains of the lipids must be removed from contact with water (Yue et al., 2012; Trubetskoy, 1999). Thus lipids begin to form micelles. In general, above the CMC value, the final entropy of the assembly of surfactant molecules is less than the final entropy of trapping surfactant monomers by water molecules. The enthalpy contribution is also important, as is the electrostatic interaction that occurs between the charged parts of the surfactants. In general, for a reaction to occur spontaneously, the final enthalpy must be positive and the entropy negative (Torchilin, 2007; Jones and Leroux, 1999; Oerlemans and Fau - Bult, 2010; Salahdin et al., 2022; Isola et al., 2022; Al-Awsi et al., 2023; Alabada et al., 2023).

4.2. Surfactant

The term surfactant is a combination of the term “Surface active agents”. They are usually organic compounds that are amphiphilic, meaning that they have both a hydrophobic group (tail) and a hydrophilic group (head) (Fig. 39). Therefore, surfactants contain both water-insoluble (oil-soluble) compounds and water-soluble compounds (Tuzar and Kratochvil, 1993; Zhang et al., 1996; Lazzari et al., 2007; Adams et al., 2003). Many of the remarkable physicochemical properties of liquid surfactant systems, as well as their many special applications, can be related to the simultaneous tendency of non-polar groups to avoid contact with water and polar parts that have a strong tendency to hydrate. Different types of larger masses called micelles (from the Latin word micelle meaning small bit) or liquid crystal phase. Insoluble hydrophobic groups may enter outside the aqueous phase (into air or oil phase), while the heads of their water-soluble (hydrophilic) groups remain within the aqueous phase (Zhao et al., 1990; Wilhelm et al., 1991; Bader et al., 1984; Collett and Tobin, 1979). The accumulation of these surfactants and the formation of micelles are highly cooperative and similar to the diffusion phase. The concentration at which these micelles begin to form is called the Critical Micellization Concentrations (CMC) (Lin and Kawashima, 1985; Kwon et al., 1995; Kazunori et al., 1993; Yokoyama, 1992; Kwon et al., 1994). As the micelles begin to form, their tails form a nucleus and their ionic heads form an outer shell that improves contact with water (Fig. 39, 40) other factors, such as the spatial arrangement of atoms, are decisive for the compaction process. Extensive cooperative aggregation has been observed only for long-chain amphibious amphibians, while compounds with bulky non-polar groups such as dipalmitoyl lecithin and Aerosol OT have not

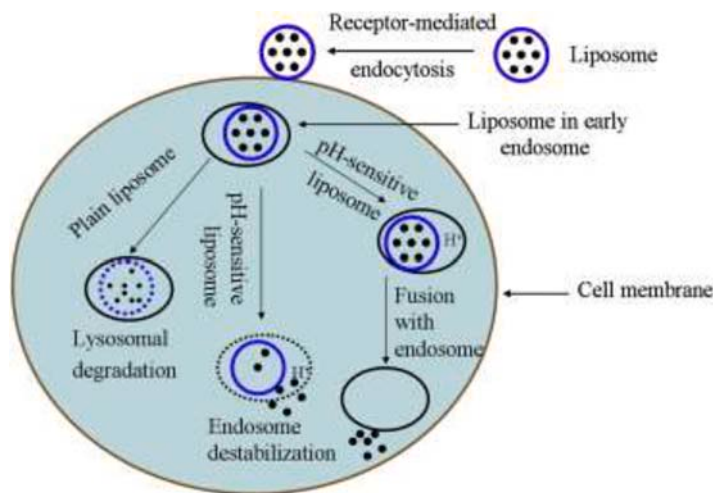


Fig. 38. Schematic view of various intracellular gene delivery mechanisms (Niesman, 1992; Singh and Mezei, 1984; Singh and Mezei, 1983; Ebrahim et al., 2005; L. Zhang et al., 2007).

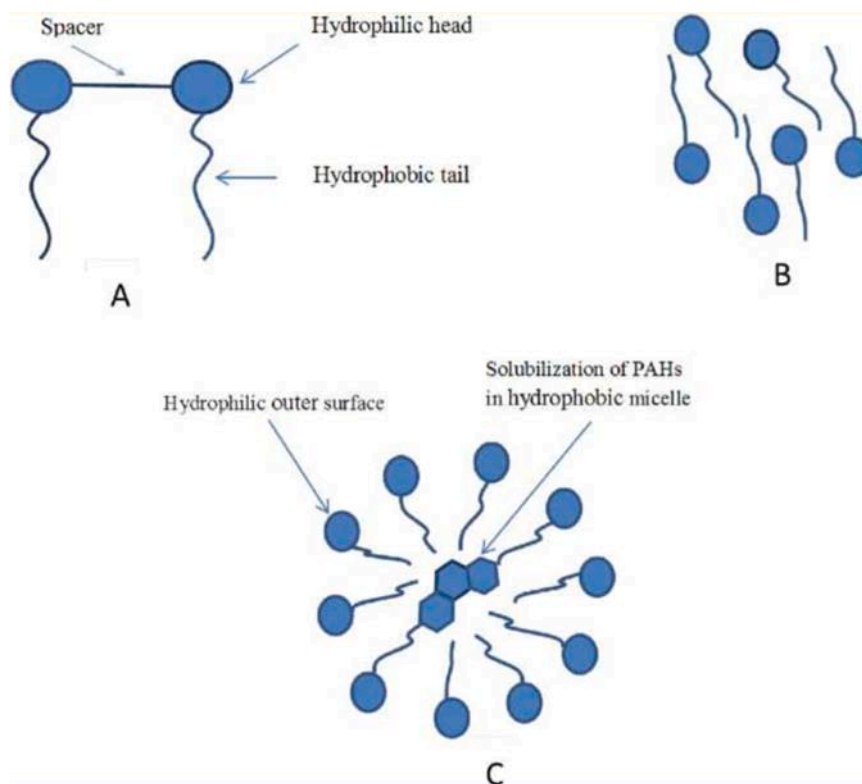


Fig. 39. Schematic illustration of monomers of surfactants and micelles of surfactants. (a) Gemini Surfactant (b) Monomers of surfactant (c) Micelles of surfactant (La et al., 1996).

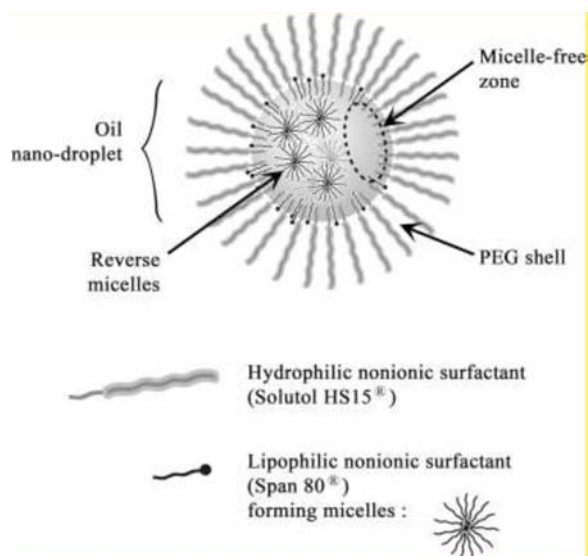


Fig. 40. Schematic of drug loading in reverse micelles (Yokoyama et al., 1991).

been shown to micellate in aqueous solution. Such compounds are often referred to as swollen amphiphiles as opposed to the micelle-forming surfactants they are called nonswelling. There is no obvious distinction between the two, and conditions may change considerably with temperature. Another useful classification of amphibious materials is related to polar groups, which are divided into ionic (cationic or anionic) and non-ionic (bipolar) (Yokoyama et al., 1991; Kwon et al., 1993; Kwon and Okano, 1996; Maeda et al., 1992; Younus et al., 2023; Smaisim et al., 2023; Mohammed et al., 2023).

4.3. Critical Michelle concentration (CMC)

Critical Micelle Concentration (CMC) Due to the importance of the CMC factor in the formation of micelles by dual-friendly molecules, it is necessary to become familiar with this factor and the factors affecting it. At low concentrations many physicochemical properties such as self-diffusion coefficients, activity, turbidity, conductivity, surface tension and spectral properties of NMR (nuclear magnetic resonance) indicate that there is no significant accumulation of surfactant. More than CMC, the change in these characteristics indicates that aggregation has begun to form larger masses. The concept of CMC is the exact meaning of the fuzzy separation model of micelle formation. Micelles are formed rapidly in surfactants with lower CMC, which is not the case with surfactants with high CMC (sabri Abbas et al., 2023; Abdul-Reda Hussein et al., 2023; Z.H. Mahmoud et al., 2023; Kadhim et al., 2023). In this section, due to the importance of CMC in the formation of micelles, we will focus on the factors affecting it. The graphical depiction of this description is seen in Fig. 41 (Gabizon et al., 1994).

4.4. Solvation

The monomers are considered single surfactant molecules that are in the environment but are not part of the micelle. Lipid micelles reflect a molecular group where individual components in their system are thermodynamically balanced with the same monomers. The hydrophilic heads of the surfactant molecules are still in contact with the solvent in water (regardless of whether the surfactants are monomers or part of the micelles) (Gangadharam et al., 1995). But the hydrophobic tails of surfactant molecules have fewer interaction with water molecules as they are part of a micelle, in order to gain greater stability. This is the base for the development of micelles through energetic stimulus. By comparison, water molecules are surrounded by surfactant monomers, which are hydrogen bonded together to form a cage around these surfactant molecules. Close to clathrate hydrates, this blue cage is. Such

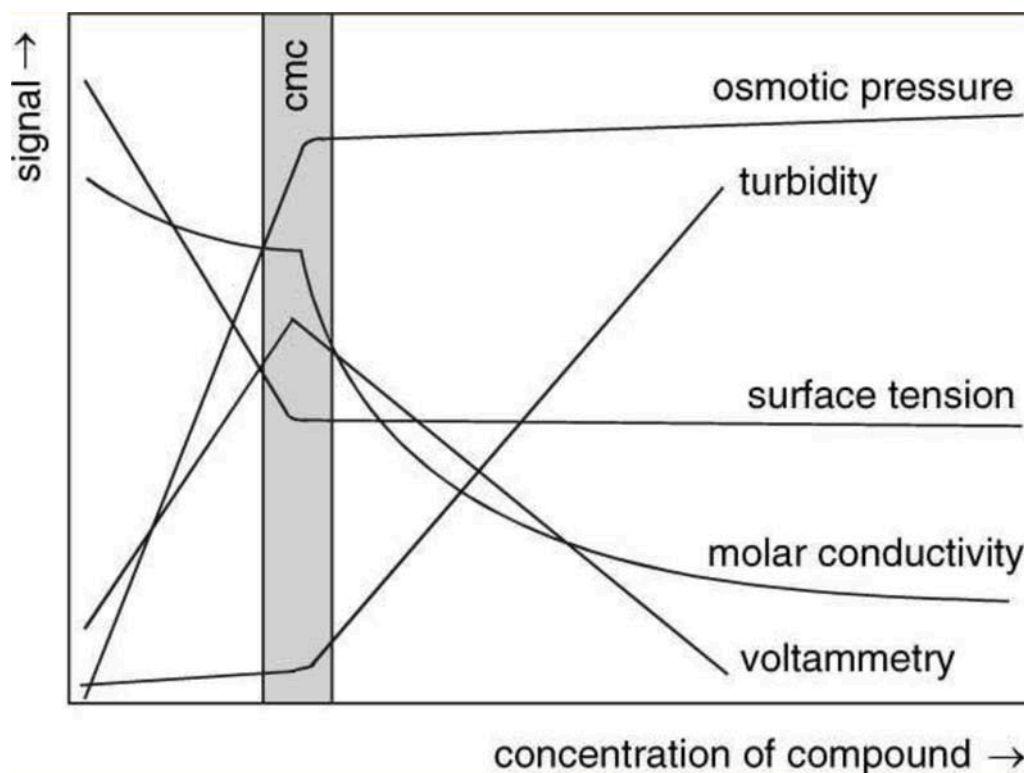


Fig. 41. Critical Michelle Concentration (Gabizon et al., 1994).

hydrated clotting hydrates are stable crystals dependent on water and are mechanically identical to ice crystals. Where the host molecule is water and the guest molecules are usually gas or liquid (Thassu et al., 2007), clotting hydrates or clotting compounds are used. A schematic view of these clotting hydrates can be seen in Fig. 42. The guest molecule is surrounded by these water molecules and they enclose and capture these guest molecules like the railings of a cage with the hydrogen bonds they keep together (Kreuter, 1994). Tiny non-polar molecules (typically gas), or polar molecules with large hydrophobic fractions, may be these

guest molecules. Lipid solubility is calculated by the unfavorable contribution of entropy (Hanna et al., 2002; Patra et al., 2018; E. Kianfar, 2021).

4.5. Polymeric micelles

A large number of polymers approved by the Food and Drug Administration (FDA) are used to make polymer nanoparticles. These structures are more stable than liposomes and have a smaller size range

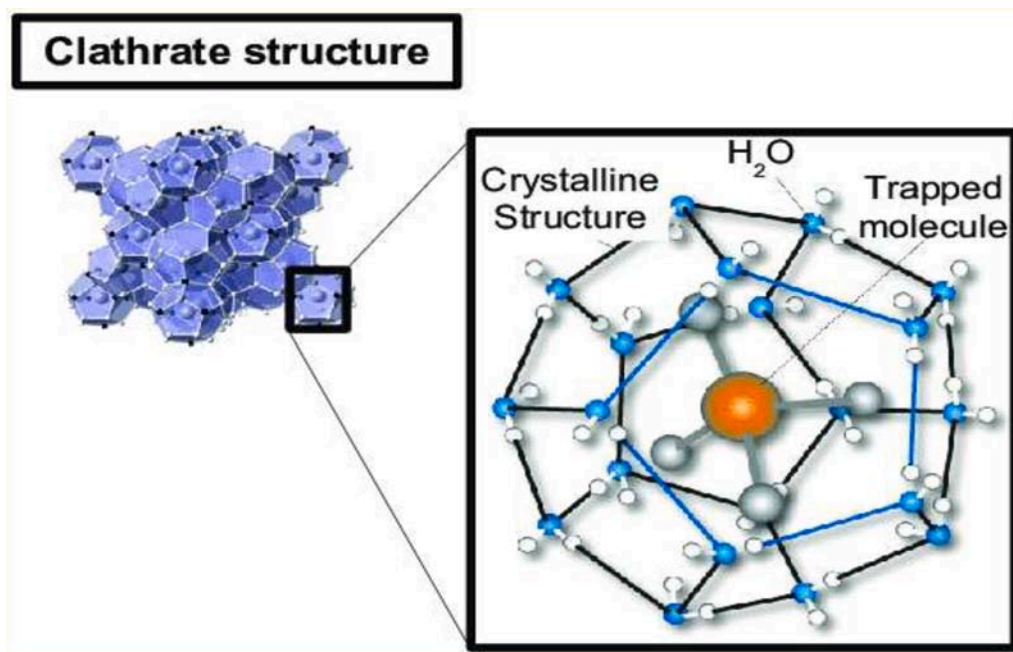


Fig. 42. Shows a schematic view of the clotting hydrates. In this form, water molecules surround the gas molecules like a cage (Gogotsi, 2006).

(Kianfar, 2020a, 2020e, 2020d; Kianfar et al., 2019). The release of the drug by these particles is also more controllable. Dual-friendly polymers are often used to make nanoparticles. The following methods can also be used to load the drug in these particles (Mahmud et al., 2007; Kabanov et al., 1989):

- A drug can enter them while making nanoparticles. For example, with the help of nanoprecipitation technique, a water-miscible solvent such as acetonitrile is used to dissolve hydrophobic drugs and dual- copolymer. This solution is then mixed with water and nanoparticles are formed by mixing the solvent with water and evaporating it.
- In another method, a chemical bond can be established between the drug and the polymer and then this conjugated polymer can be used in the fabrication of nanoparticles (Nobs et al., 2004).

They can also be used for therapeutic purposes by surface optimization of polymers. Micelles are also considered as one of the suitable options for multiple loading of drugs due to their dual nature of friendliness (Hanna et al., 2002; Kianfar, 2020c, 2020b, 2015b; Kianfar et al., 2016). Fig. 43 shows some of the polymers used in the fabrication of nanoparticles and the type of host in which the experiments were performed.

4.6. Worm-like micelles

Cylindrical polymer micelles that are used as a new type of carriers are these structures. Though micelles are about a meter long, like worms, they can move through tiny holes. They have been used for drug distribution to tumors by loading the drug within these structures and modifying the surface (Torchilin, 2008). The capacity to join cream-like micelles is also present with lipophilic medications (Fig. 44).

4.7. Polymersomes

Polymersomes are structures similar to liposomes, except that they consist of dual-friendly polymers/peptides and occur in the form of

globular structures (Fig. 45). They are more compact and resilient than liposomes in these systems. The polymersomes form spontaneously when the copolymer is moisturized. The heavier the copolymer, the longer the body persists with the substance (Nobs et al., 2004; Gu et al., 2007; Kabanov et al., 1989; Bae et al., 2005; Torchilin, 2008; Lindman and Wennerström, 1980; Mukerjee and Yang, 1976; McBain, 1913; Patra et al., 2018; E. Kianfar, 2021; van der Meel et al., 2019; Dalby et al., 2019; Hauschild et al., 2020; L. Wu et al., 2020; Yin et al., 2017, 2014; Abderrahmane et al., 2023; Wang et al., 2022; Xiao and Smaism, 2022; Mourad et al., 2022; G.F. Smaism et al., 2022; Abderrahmane et al., 2022; Tan et al., 2023; Mir et al., 2022; Ruhani et al., 2022; Cai et al., 2022; Moarrefzadeh et al., 2022; Hai et al., 2022; Fadhil Smaism et al., 2022; G.F. Smaism et al., 2022; Jiang et al., 2022; M.W. Tian et al., 2022a, 2022b; Alharbi et al., 2022; Wu et al., 2022; Brontowiyono et al., 2022; Y. Tian et al., 2022c; G.F. Smaism et al., 2022e, 2022d, 2022f, 2022c, 2022i, 2017b, 2017a; Mozafarifard et al., 2022; Sharba et al., 2022; AbdulHusein et al., 2022; Ahamad et al., 2022; Doss et al., 2022; Lefteh et al., 2022; Perforated; Al-Madhhachi and Smaism, 2021; Smaism, 2018; G. Smaism et al., 2016b, 2016a; Farahani et al., 2023; Mir et al., 2023; F. Wang et al., 2023a; Chen et al., 2023; M.P. Narayanasamy et al., 2023; Y. Wang et al., 2023; Farahani et al., 2023; Mir et al., 2023; Abderrahmane et al., 2023; Chen et al., 2023; M.P. Narayanasamy et al., 2023; Elmasry et al., 2023; Mahdi et al., 2023; Pal-lathadka et al., 2023; Z.H. Mahmoud et al., 2023c, 2023b, 2023e, 2023d, 2023a, 2022d, 2022c, 2022b; Siswanto et al., 2023; S.A. Jasim et al., 2023; Al-Obaidi et al., 2023; S.A. Jasim et al., 2023b, 2022b, 2022a, 2022a; Bokov et al., 2022; Mansoor Al Sarraf et al., 2022; Hameed Mahmood et al., 2022; I. Raya et al., 2022; Mahmood et al., 2022; Bahadoran et al., 2022; I. Raya et al., 2022; Rheima and Al-Salman, 2022; Chupradit et al., 2021; Mahmoud et al., 2021; G.F. Smaism et al., 2022; Kianfar, 2023; Kianfar and Sayadi, 2022; Fattah et al., 2023; Bokov et al., 2021; Chupradit et al., 2022; Aldeen et al., 2022; Suryatna et al., 2022; Abdelbasset et al., 2022; S.A. Jasim et al., 2022; E. Kianfar et al., 2022a, 2022b; Ansari et al., 2022).

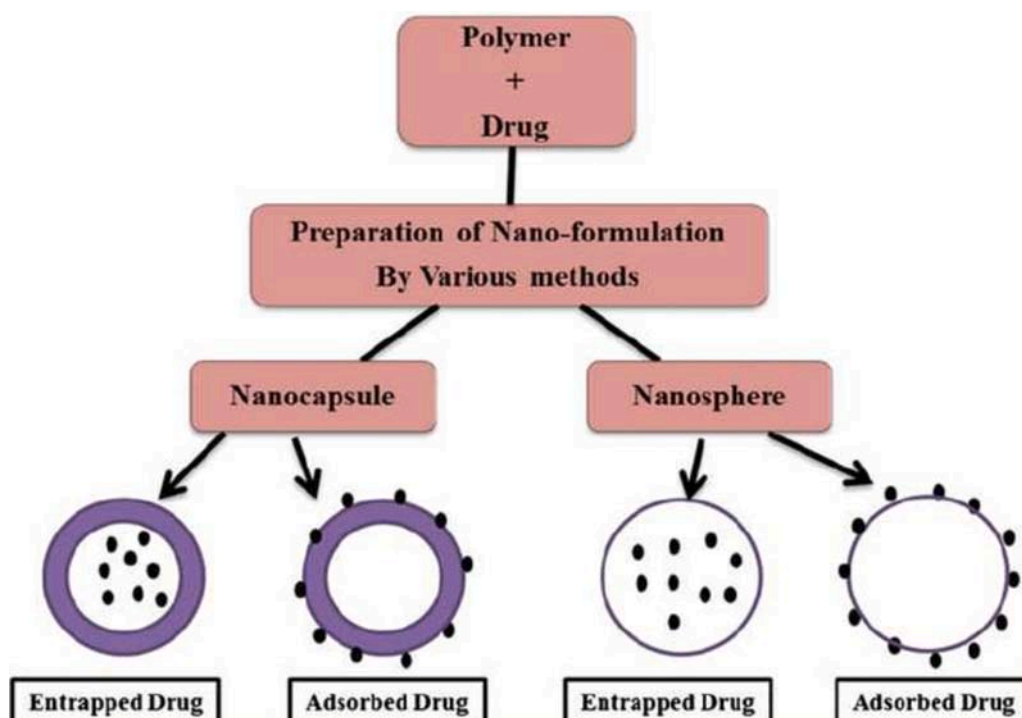


Fig. 43. Various forms of nanoparticles based on polymers (Bae et al., 2005).

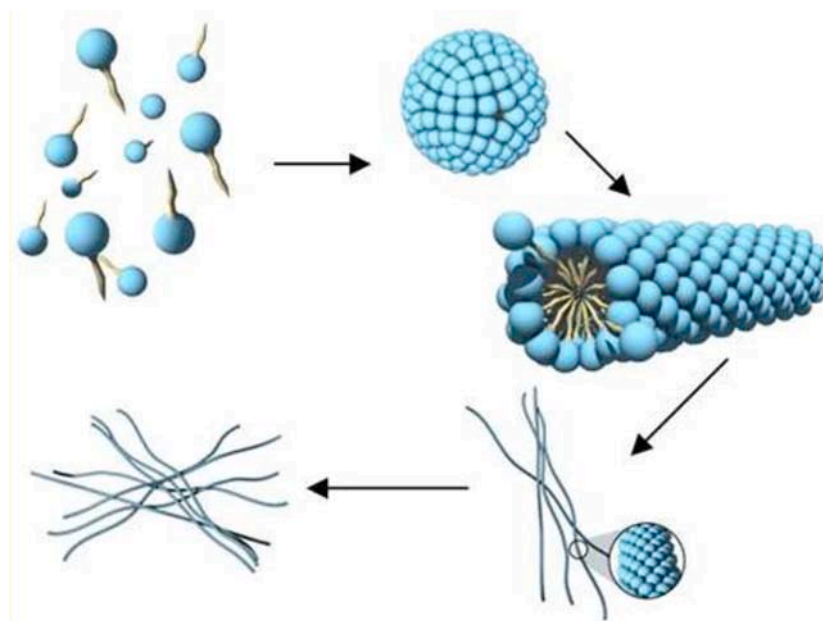


Fig. 44. Step actions within the microstructure of the worm-like micelle (Torchilin, 2008).

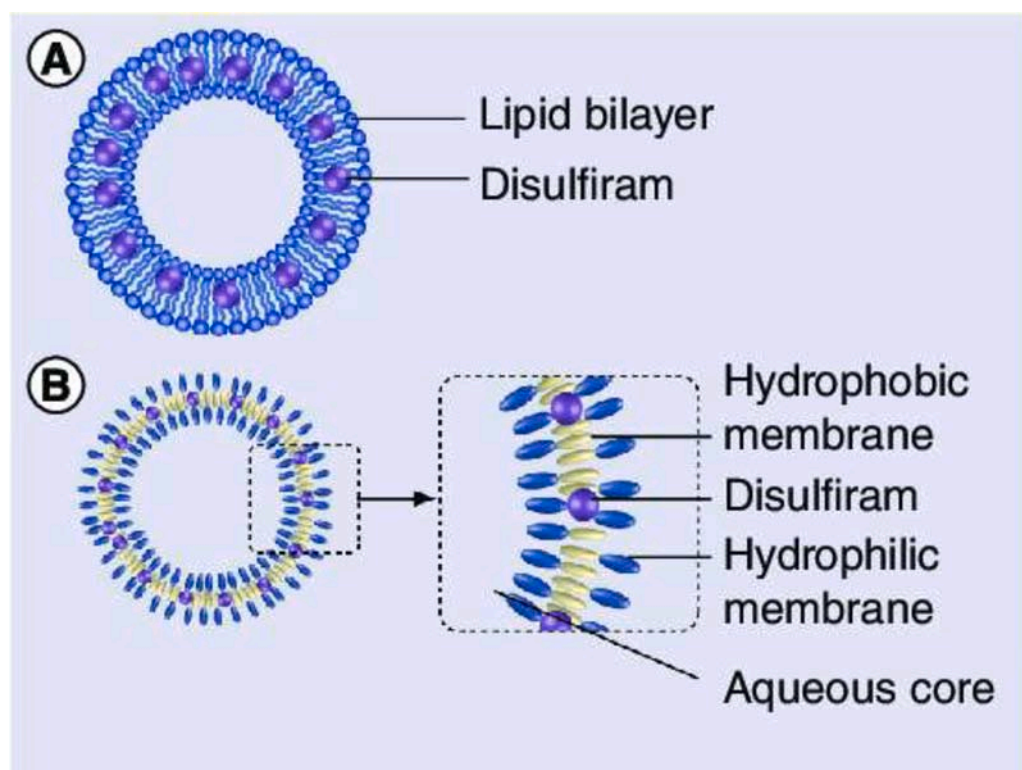


Fig. 45. Structure of liposomes and polymersomes. (a) The liposomes and (b) the polymersomes have a hydrophobic membrane through which the aqueous center is encapsulated. Membranes are formed from hydrophilic and hydrophobic domain molecules (lipids in liposomes and block copolymers consisting of two separate polymer chain units united in polymersomes) that self-assemble into vesicle-like structures in water. It is necessary to encapsulate hydrophobic compounds like disulfiram in the hydrophobic membrane (Lindman and Wennerström, 1980).

4.8. Surface modification

These changes can be split into changes that (1) maximize residence and circulation time, (2) target a targeted tissue, and (3) deliver a medication payload to a target tissue selectively. Any discussion of the surface of the nanoparticle is woefully insufficient without taking into consideration the protein corona, which effectively masks the substance of the bulk nanoparticle, stabilizes the particle, and The biological reaction to the nanoparticle is eventually driven (Fig. 44) (Weitman et al., 1994). The true in vivo particle response (Fisher et al., 2008) is

determined by surface charge/hydrophobicity and the route of administration (Fig. 46) (Kabanov et al., 1989; Bae et al., 2005; Torchilin, 2008; Lindman and Wennerström, 1980; Mukerjee and Yang, 1976; McBain, 1913).

4.9. Application of micelles in imaging

One of the uses of micelles is to use them as carriers to bring differentiating agents for imaging and imaging purposes to identify target cells. Ligand-modified micelles can identify and bind reliably to

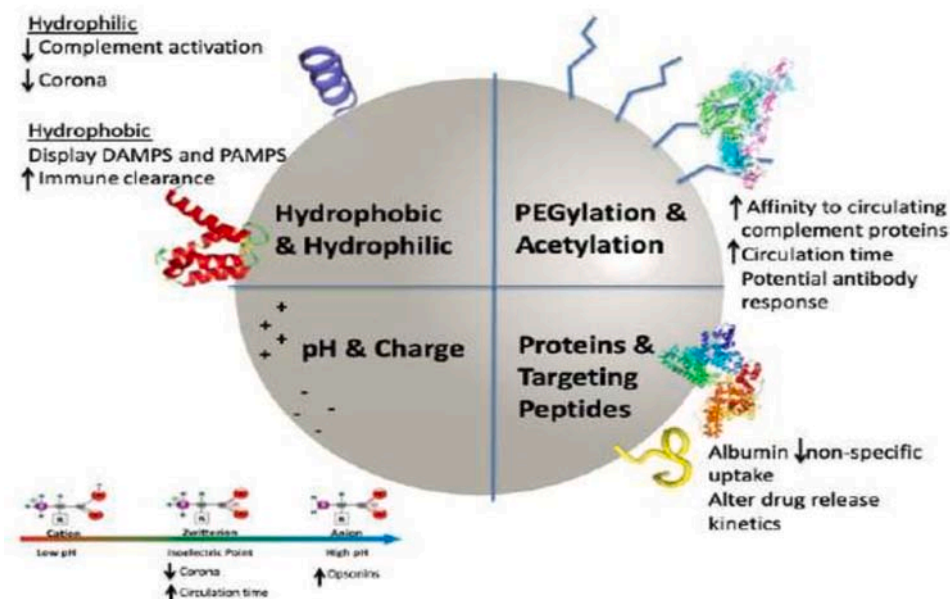


Fig. 46. Surface changes to the nanoparticle have a direct effect on a number of protein corona components (Wang et al., 1992).

tumor cell overexpressed receptors and can be controlled in vivo by chelating or combining an imaging component (Brannon-Peppas and JO, 2004) for bio-distribution studies. In cancer diagnosis and determination of the therapeutic response, nuclear imaging, magnetic resonance imaging (MRI) and computed tomography (CT) play an important part. Therefore, for the transmission of differentiating variables, the evolution of transmission systems is important. For MRI and CT, which are less sensitive than nuclear imaging, the evolution of carriers is particularly required. Therefore, to improve the efficiency of the methods described, various types of micelles were created and developed:

- For nuclear imaging, micelles equipped with gamma irradiators (Duncan et al., 2005; Hanna et al., 2002) were used.
- Micelles mixed with iron oxide particles or using chelators to mix paramagnetic metals with hydrophilic blocks For MRI imaging, microplate block copolymers have been used (Gu et al., 2007; Abou-Jawde et al., 2003; Nobs et al., 2004; Wilson and Szostak, 1999).
- This approach is not appropriate for high molecular imaging due to the comparatively high concentration of differentiating agents needed for CT imaging.

Consequently, the differentiating variables are removed by combining with micelles by increasing circulation time, and this CT defect is therefore eliminated (Brisette et al., 2006).

4.10. Drug delivery of anticancer drugs by micelle carriers

Due to diminished absorption of these products, the bioavailability of anticancer drugs following oral administration is typically decreased (Sudimack and Lee, 2000). In addition, intravenous injections of these medications are difficult and require organic solvent and classical surfactant formulations. These problems (Brannon-Peppas and JO, 2004) can be solved by the degradation of hydrophobic drugs in the nucleus of micelles. In preclinical trials to increase medication effectiveness, several drug-loaded polymer micelles for anticancer therapy are currently being tested (Ehsan Kianfar, 2015; Kianfar et al., 2015; Kianfar, 2019). A schematic view of NK012 polymer micelle micelles is shown in Fig. 47. In the hydrophobic nucleus of micelles, this diagram

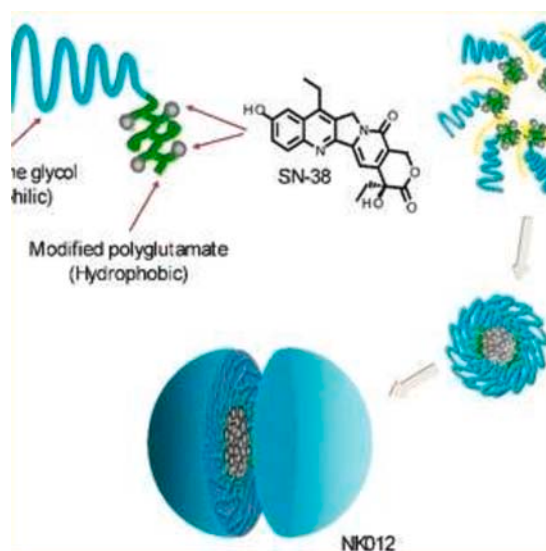


Fig. 47. Schematic view of NK012 polymer micelle (Maeda et al., 1992).

indicates the sequence of SN-38 (Maeda et al., 1992; Gabizon et al., 1994; Gangadharam et al., 1995; Kreuter, 1994; Mahmud et al., 2007; Kabanov et al., 1989; Bae et al., 2005; Torchilin, 2008; Lindman and Wennerström, 1980; Mukerjee and Yang, 1976; McBain, 1913).

4.11. Gene therapy by micelle carriers

The creation of modern nucleic acid-based therapies such as plasmid DNA and siRNA as new drugs has led to recent advances in understanding the biological mechanisms that cause molecular-level life processes (Chatelut et al., 2003; Hajimirzaee et al., 2020; E. Kianfar, 2021; Huang et al., 2021). Their therapeutic use has issues, such as volatility due to their high molecular weight and the existence of their negative charge under physiological conditions such as poor cellular uptake. They are easily eliminated after DNA or RNA is inserted directly into the bloodstream, often leading to DNase and RNase attacks. For

their functional usage, therefore, the placing of DNA and RNA in a Nano-carrier is necessary. In addition to aggregation in target tissues, intracellular conduction is necessary in order to deliver genes to the nucleus. Because of this daunting criterion, in clinical trials (for gene therapy), viral vectors such as retroviruses, adenoviruses, and adeno-associated vectors are widely used for gene delivery. However, issues with immune responses, such as the risk of recombination of oncogene-causing intracellular genes (Carroll et al., 2011), have limited their use in clinical therapy. Preparing large-scale viral vectors is not suitable from a planning point of view, so vectors are limited to clinical trials. In other words, relative to viral vectors, non-viral vectors containing polymers and lipids are substitutes for supremacy in terms of protection, large volume and price. For this reason, due to their advanced and customizable requirements, the method of polymeric micelles promises the right formulation for nucleic acid distribution. A nucleic acid-containing polymeric micelle is formed by polyioncomplexation between the negatively charged DNA and RNA and the positively charged copolymer block and the hydrophilic part (Chatelut et al., 2003; Walters et al., 2013; Armstrong et al., 2013; Kelemen et al., 2010). Plasmid DNA (pDNA) is spontaneously combined with PEG-polycation such as PEG-polylysine, resulting in a scale of around 100 nm complex ionic micelle (PIC or polyplex micelle) (Kelemen et al., 2010; Choi and Mason, 2000; Stokstad, 1990). Zeta-potential polyplex micelles say that, even in the case of additional concentrations of PEG-polycation, it is attributed to the PEG shell. It is also predicted that nonspecific contact with proteins and cells in the bloodstream would cease. Finally, because of the influence of EPRR, prolonged blood circulation as well as tumor aggregation are expected (enhanced permeability and retention). In specific, pDNA micelles of the micro-ion complex display the active insertion of the gene into cultured cells and also show gene expression in the liver following intravenous injection into the rat tail vein. A long circulation in which pDNA persists in the blood for 3 h is accomplished by wrapping DNA within polymer micelles, while this pDNA is quickly degraded in the blood in fewer than a few minutes without the use of polymer micelles. These findings demonstrate that in current drug delivery, polymeric micelles are excellent carriers of gene delivery (Fig. 48) (Maeda et al., 1992; Gabizon et al., 1994; Gangadharam et al., 1995; Kreuter, 1994; Mahmud et al., 2007; Kabanov et al., 1989; Bae et al., 2005; Torchilin, 2008; Lindman and Wennerström, 1980; Mukerjee and Yang, 1976; McBain, 1913).

5. Targeted drug delivery nanoparticles

A high propensity for cancer treatment has been shown by selective NP therapeutics as they have improved effectiveness and decreased side effects (Chatelut et al., 2003). The distribution of NP drugs may be either an active or a passive operation. Passive delivery refers to NP transfer through the interstitial tumor and cells through passive diffusion or convection via leaky tumor capillary fenestrations (Carroll et al., 2011). The already described characteristics of the tumor microenvironment then yield selective accumulation of NP and medicine (Fig. 49). Active targeting requires drug distribution dependent on molecular identification to a particular site. One such strategy is to pair a ligand to an NP, such as monoclonal antibodies, lectins, aptamers, folate, and peptides, so that the ligand can bind at the target cell site with its receptor (Fig. 49). The rate of cellular internalization can vary based on the form of ligand-receptor interaction. As rates of internalization may influence the aggregation of NP in tumor sites, this is a significant consideration. Cellular uptake of the drug through receptor-mediated endocytosis is often enabled by the use of a targeting moiety, which is an aggressive mechanism involving a slightly lower concentration gradient across the plasma membrane than basic endocytosis. There is also plenty of space for these mechanisms to be improvised to solve the above problems, and numerous groups are trying to enhance the targeting properties of NPs and to establish targeted therapeutics (Walters et al., 2013; Lindman and Wennerström, 1980; Duncan et al., 2005).

6. Nanoparticles in precision medicine

Precision medicine pushes for the development of patient-specific treatments in a clinical setting, to overcome the many limitations of traditional one-size-fits all approaches and improve therapeutic outcomes. In oncology, patient stratification through biomarkers and companion diagnostics has become the norm for drug development, as most cancer nanomedicines fail to produce positive results in unstratified studies. Even though patient stratification has been essential in the clinical development of several precision medicines for cancer, nanoparticles-based clinical trials are currently conducted in unstratified patient populations. However, this will likely change in the near future, as the importance of stratification becomes more apparent and nanoparticles begin to be developed with specific patient populations in mind. The progression of nanoparticles through clinical trials may

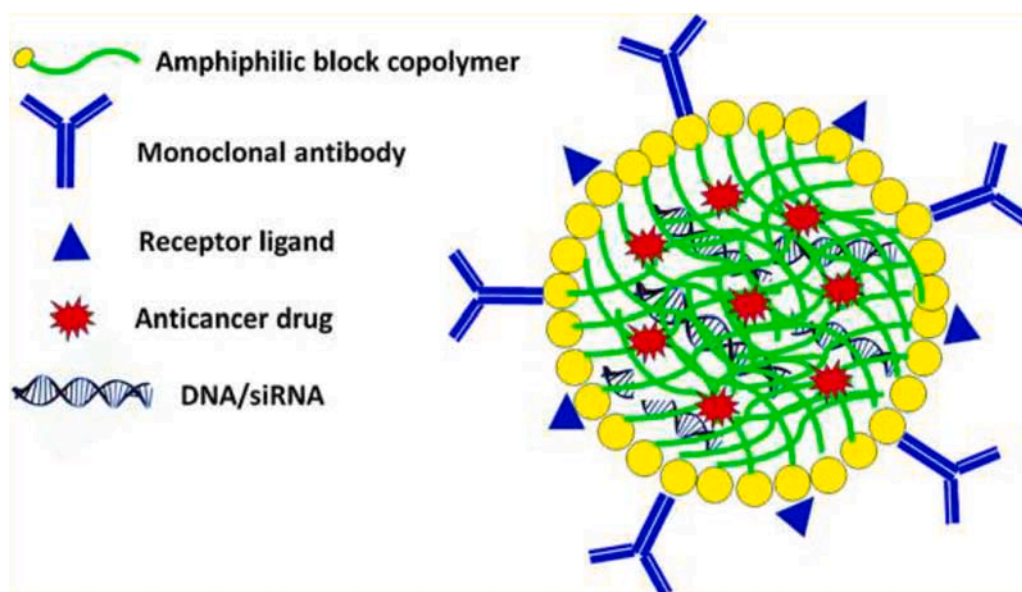


Fig. 48. Multifunctional micelle configuration for the aggressive targeting of cancer cells in the tumor (antibody-based or receptor-mediated) for use in combination therapy (drug and gene therapy) (Maeda et al., 1992).

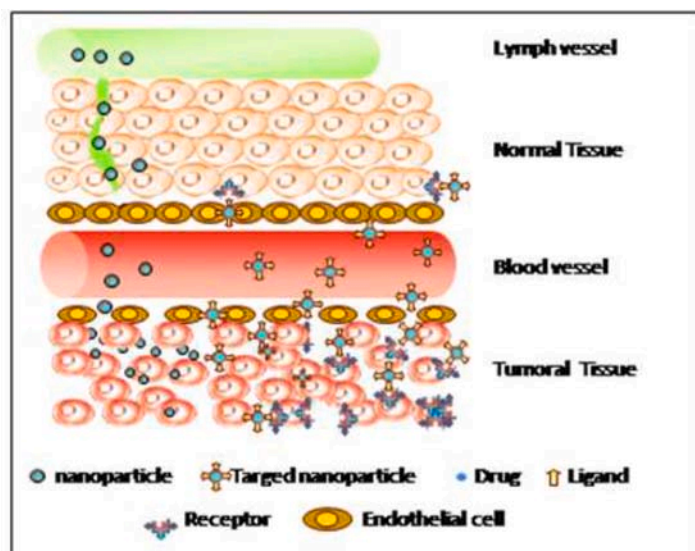


Fig. 49. Due to the properties of tumor tissue, NPs are more capable of accessing tumor cells by passive targeting (vascular disorganization, fenestrations, discontinuous basement membrane, etc.). The lower volume of nanoparticles capable of accessing it are extracted by lymph vessels in normal tissues, whereas the lymphatic network is too weakened in tumor tissues to fulfill its function promoting the lymph vessels. The aggregation in the tissue of nanoparticles. Not only by passive targeting but also through active targeting, the functionalized nanoparticles are internalized. This active targeting is more efficient in tumor tissue due to the over expressive receptors of tumor cells that allow them to better absorb functionalized nanoparticles (Walters et al., 2013).

similarly be hastened by the incorporation of stratified patient populations, as these populations will likely respond more uniformly to treatment. Furthermore, nanoparticles are particularly well placed to broaden the potential patient populations that qualify for precision medicine therapies by neutralizing factors, such as comorbidities or heterogeneous biological barriers, that may have made patients previously unqualified. As nanoparticles overcome many of the current limitations to delivery potentially improving the potency and therapeutic efficacy of precision medicines, they may allow more patients to qualify for clinical trials and benefit from individualized therapies (van der Meel et al., 2019).

7. Nanoparticles for cancer therapy

Cancer remains the second leading cause of death worldwide. Cancer is heterogeneous, and the development of effective cancer therapies is very challenging partially because of this complexity. However, precision medicine has emerged as a promising approach, and targeted chemotherapeutics have been developed that can treat patients who express specific biomarkers. The first drug of this type, imatinib (Gleevec; Novartis), is given to patients with chronic myeloid leukaemia who express the BCR–ABL fusion protein from the Philadelphia chromosome. FDA approval of imatinib opened the field for many other successful targeted chemotherapeutics. However, these therapies and others could be more effective if delivery is improved. For example, imatinib has also been delivered using a nanoparticles system, which enhanced tumor accumulation and regression in vivo, improving the survival ratio to 40% after 60 days in a melanoma mouse model (Dalby et al., 2019). Improvements in delivery could overcome some limitations of therapeutics that have failed to make it to the clinic, including small-molecule drugs with limited water solubility or antibodies with low stability. Similarly, many chemotherapeutics have off-target toxicity and induce adaptive resistance, which limit efficacy. Furthermore, there are many biological barriers associated with cancer, specifically at the tumor site. Improved delivery techniques could offset many of these concerns. In order to best leverage our knowledge and treatment of individual cancer patients, both therapeutics and their delivery systems can be personalized for a given patient (Hauschild et al., 2020).

8. Nanoparticles for immunotherapy

Although immune checkpoint inhibitors have shown significant promise for cancer treatment, there are still challenges with efficacy,

patient variability and off-target effects when immunomodulators are used. Some immunotherapeutic, such as proteins, have limited delivery potential when administered freely, and thus nanoparticles have the potential to significantly improve delivery by protecting immunotherapeutics and enhancing their interaction with immune cells (L. Wu et al., 2020).

9. nanoparticles for genome editing

Recent advances in CRISPR, transcription activator-like effector nuclease (TALEN) and zinc-finger nuclease (ZFN) technologies are making it increasingly easy to engineer the genome for widespread use in biomedical research, drug development and discovery, and gene therapy. This is important in the context of precision medicine, as over 3000 human genes have been associated with Mendelian diseases but less than 5% of rare diseases have effective treatments. Advances in genome editing are now making it possible to correct many of these rare diseases. However, efficient and safe delivery is still needed for genome-editing systems to effectively target and enter tissues and cells of interest, while also minimizing toxicity (Huang et al., 2021, E. Kianfar, 2021c, 2021a). Delivery of genome-editing systems is challenging because these systems are multicomponent, hold sensitive cargo and need to overcome several extracellular and intracellular biological barriers to reach the genome of target cells. Lipid-based and polymer-based nanoparticles have delivered a range of nucleic acids in vivo, and are in various stages of clinical development. For example, a LNP siRNA drug termed Onpatro (patisiran) was recently approved by the FDA for the treatment of amyloidosis. In the context of genome editing, nanoparticles have the potential to be less toxic and immunogenic than viral vectors, which have a history of safety concerns (Yin et al., 2017, 2014; Syah et al., 2021; Alkhawaldeh et al., 2023; AL-Salman et al., 2023; Rheima et al., 2023).

10. Future challenges and perspectives nanoparticles in drug delivery

This Review has discussed numerous nanoparticles designs optimized for therapeutic delivery and engineered to overcome the heterogeneous biological barriers found across patient populations and diseases. These barriers to delivery are complicated by patient comorbidities, varying stages of disease progression and unique physiologies. This diverse array of needs can be met using nanoparticles designed for different patient populations or pathologies, or intersections of the two.

nanoparticles platforms offer an assortment of modifiable features such as size, shape, charge, surface properties and responsiveness that can be selected to optimize delivery for a specific application, therapeutic and patient population. This customization can be utilized synergistically with precision medicine therapies to improve patient stratification methods when screening nanoparticles platforms, widen the accessibility of precision therapeutics by allowing new patients to qualify for existing therapies with newly enhanced delivery mechanisms and, ultimately, increase the overall therapeutic efficacy of both precision medicines and nanoparticles delivery platforms.

Of these nanoparticles' characteristics, size and shape have been extensively studied across numerous biological states, and, in some cases, trends have been identified that can be used for intelligent nanoparticles design. For example, nanoparticles charge is of particular importance in muco-penetrating applications and intracellular applications that require endosomal escape, whereas targeting surface markers takes precedent in applications where specific cell types must uptake nanoparticles, as in many cancer and immunotherapy applications. However, as the design considerations become more complicated, so do efforts to generalize trends across large populations sacrificing the accuracy of the findings within a small population in the hope of generating an all-encompassing principle of delivery. Therefore, investigations of nanoparticles design and the resulting interactions within the human body need to be more thoroughly analysed to improve the specificity of these claims, especially as we move towards stratifying patient populations to determine the most suitable nanoparticles platforms for these subgroups. Through the continued exploration of nanoparticles technologies in laboratory settings, researchers have the opportunity to collect data and analyze outcomes to add to the ever-growing library of known design–function relationship trends in nanomedicine. However, it is imperative that the trends observed in research settings be contextualized before attempting to generalize findings broadly, as seemingly minor differences in nanoparticles composition, animal models and pathology may greatly alter the performance of nanoparticles and must be considered when moving nanoparticles technology towards clinical translation.

In precision medicine-relevant applications, the usage of nanoparticles allows for improved cellular targeting, fewer off-target effects and more tailored therapies such as multidrug treatments. All of this can be achieved by engineering nanoparticles for the application at hand, improving accumulation at the site of interest and introducing responsiveness for on-demand drug release, to minimize unwanted toxicities and enable a new range of dosages or combinatorial treatments. By optimizing this specificity and local activity of nanoparticles delivery systems, the effects of precision medicine therapeutics can be improved as well, widening the populations they benefit and improving patient outcome overall. As the work described in this Review shows, intelligent nanoparticles design can improve precision medicine as a whole and the insight provided by precision medicine — such as patient stratification and genetic profiling — can inform the rational selection of a nanoparticle's platform to, ultimately, generate the ideal nanoparticles -based precision therapy.

11. Conclusion

1 Drug distribution Nano systems have been considered in recent years. The purpose of designing these devices, which typically consist of medications, carriers, targeting ligands and surface modifiers, is to monitor the release of drugs and sustain drug concentrations for an acceptable amount of time within the therapeutic range. And precise drug distribution to the tissue of the target. These Nano medical structures contain, or have entered the industry, liposomes, micelles, nanoparticles, antibody conjugates, and polymer conjugates presently in the clinical process. The essence of tumor tissue and active and passive drug delivery methods to the tumor tissue is briefly described in this paper.

- 2 These architectures have been able to draw the interest of many researchers due to the many advantages of nanostructures, such as the ability to hold several drugs concurrently and decrease the toxicity of cancer cells for therapeutic purposes. In addition, to make nanoparticles, a number of carriers can be used, many of which have been approved by the FDA. To prepare these systems, there are a great range of techniques. Nanotechnology has the ability to treat cancer, and may shift from a clinical laboratory to the bedside of a patient, as a result of these characteristics.
- 3 In a liquid medium called liposomes, the amphipathic properties of phospholipids give rise to hollow spherical particles. The synthesis of these liposomes has a general mechanism that is basic but very diverse. There is space inside for various drugs to be stuck between the two phospholipid layers as well as on the surface of the liposomes (both hydrophilic and hydrophobic). In the current drug delivery system, liposomes, as drug carriers, play a significant role. Given the particular benefits of liposomes as drug carriers, such as: drug defense against weakening enzymes, drug physical response, and However, there are also drawbacks and weaknesses that do not concern the susceptible site of the medication, biodegradation and non-toxicity, including endothelial system phagocytosis, failure to pass the endothelial barrier, inadequate drug trapping, and sluggish drug release, which is difficult for anticancer drugs (because of drug resistance). On the other hand, liposomes are sluggish and appear to aggregate and form masses, which decreases their performance drastically. Therefore, various synthesis approaches and liposomes with different structural and changed properties are used according to different design purposes. Finally, it should be remembered that even the slightest improvements in the properties of synthetic liposomes will show distinct clinical variations in clinical applications, so they must be treated with great caution.
- 4 Nanoscience experts are actively hunting for drug delivery systems with sufficient properties for the drug to enter the body. Micelles, which consist of the concentration of surfactant molecules released in a colloidal liquid, are one of those significant and modern methods for drug distribution. After stating the background in this essay, how the micelle was formed, its elements, conditions of formation and stability. The specification of the essential concentration of micelles or CMC, the element and the conditions influencing those examined, is one of the significant factors in the creation of micelles by dual-friendly molecules. Chemical composition and resonance parameters influence CMC.
- 5 From the concentration of surfactant molecules dispersed in a colloidal liquid, micelles are formed, and an electrostatic attraction is produced between the ionic surfactants and the surrounding ions. Myelination is the method of the development of micelles. Based on their constituent molecules, step form, shape and size, micelles are classified into various forms, with polymer micelles being one of the most significant and commonly used. The value of this micelle form is due to its small size, surface properties and unique interaction with the target tissue relative to polymer liposomes and microspheres. In this paper, other properties of polymeric micelles are discussed in detail, and a good example of anticancer drug delivery with these micelles is cited. Furthermore, as drug carriers, micelles have been given particular consideration and how to pack the drug with them has been addressed separately.
- 6 Micelles are devices and, because of their significance as drug carriers in modern drug distribution, knowledge of the structure and properties as well as their applications is vital. Micelles are the densities released in a colloidal liquid of surfactant molecules. Myceliation is known as the phase of micelle forming. The hydrophilic head region of its constituent elements in interaction with the ambient solvent, and at the same time its single hydrophobic tail region in the middle of the micelles, forms a mass in the usual micelles in an aqueous solvent. Critical Micellization Concentrations (CMC) and micelles are referred to as the concentration at which

these micelles begin to develop only when the surfactant concentration is higher than the critical micelle formation concentration (CMC) and the device temperature is higher than the critical micelle temperature or the temperature of the kraft is formed. Hydrocarbon chain length, presence of side chains as well as double bonds, presence of benzene ring, polar group replacement, fluorocarbon chains, polar groups, counter ions, temperature, pressure (insignificant), added basic electrolytes, added non-electrolytes and dual friends are factors influencing CMC. With respect to the classification of micelles, it should be recalled that they are classified differently: according to the constituent molecules, the phase form or the shape and scale of the micelles. Among the types of micelles, owing to the regulatory properties and also the ease of synthesis of polymeric micelles relative to other micelle carriers in modern drug delivery systems, these types of micelles are increasingly used. The benefits of polymer micelle carriers over other carriers are generally: 1- Compact size relative to polymer liposomes and microspheres 2- Elimination of the association of polymer micelle with macrophages 3- Precise interaction with target tissue 4- Simple filtration planning, use and sterilization. Polymeric micelles are based on block copolymers with self-assembled hydrophilic and hydrophobic units in an aqueous medium against a hydrophobic core structure supported by a hydrophilic shell. Usually, the CMC of duplicate copolymer microspheres is in the range of 6–10 M to 10–7 M, whereas it is in the range of 3–10 M to 4–10 M for low molecular weight surfactants, which improves the circulation time. Compared to micelles from surfactants. We should, preferably, be able to monitor the release of drugs from polymer micelles. PH, temperature, light and ultrasonic-sensitive block copolymers provide power of micelle rupture and drug release initiation. Drug distribution based on Michelle has evolved in a series of ways, the two general forms of which are active and passive delivery of drugs. Their use as carriers for 1- delivery of differentiating agents for imaging and imaging purposes to classify target cells and 2- drug delivery are two uses of micelles. In pre-clinical trials, several drug-loaded polymer micelles for anti-cancer therapy are currently being tested to increase the efficacy of the drug. Compared to viral vectors, the use of vectors containing polymers and lipids is a replacement for supremacy in terms of protection, broad volume and price. The findings suggest that in current drug delivery, polymeric micelles are exceptional gene carriers.

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Consent for publication

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CRedit authorship contribution statement

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review & editing. **Zahra Muhammed Mahdi:** Writing – review & editing. **Zainab Sabri Abbas:** Writing – review & editing. **Safa K. Hachim:** Writing – review & editing. **Farah K. Ali:** Writing – review & editing. **Zaid H Mahmoud:** Writing – review & editing. **Ehsan Kianfar:** Investigation, Writing – original draft, Writing – review & editing.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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