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A Review of Colon Cancer Treatment using Photoactive Nanoparticles

Nasser Thallaj, Dania Hani ali Hamad, Naseem Ahmad Batieh, Gheed Ahmad Saker

Abstract: ***This reviewed work on the development of photosensitive nanoparticles (NPs) based on a photodegradable poly(o-nitrobenzyl acrylate) core (PNBA, a hydrophobic and biocompatible polymer) and a dextran-derived shell (dextran is a biodegradable and water-soluble bacterial polysaccharide). First, methods for synthesizing PNBA-N3 were demonstrated by 1) single electron transfer radical polymerization (SET-LRP) of o-nitrobenzyl acrylates and then 2) introducing a single azide end functionalization. At the same time, the processes for the production of DexAlkyne-15 bearing several alkyne groups by the hydrophilicity of dextran were also addressed. Such as DexAlkyne-15 and PNBA-N3 can be reacted by CuAAC (Cu(I)-azide-alkyne cycloaddition catalyst) chemically resulting in Dex-g-PNBA glycopolymers with different molecular parameters. Second, strategies for producing NPs were demonstrated by comparing two processes that were characterized in terms of size, amount of dextran, coat thickness, and colloidal stability in NaCl or cell culture medium, or in the presence of a single potent surfactant. On the one hand, NPs made by nanodeposition of Dex-g-PNBA exhibit high PNBA weight fractions (>40%). On the other hand, the NPs were produced by evaporating the emulsion to the organic solvent using DexAlkyne-15 as a water-soluble surfactant and PNBA-N3 as a hydrophobic material. In this case, CuAAC occurred in situ (or not) at the fluid/liquid interface during the formulation of the NPs, resulting in "clicking" and "non-clicking". Finally, a systematic study of the disorder of NPs by ultraviolet irradiation according to photolysis of PNBA chains is shown. To use NPs as smart drug delivery systems, studies have been shown of loading Doxorubicin (DOX - an anti-cancer agent) into NPs during placement. Methods for optimizing experimental conditions to enhance DOX encapsulation are discussed***

Keywords: ***Nanoparticles, Photosensitive, Polysaccharide, Biocompatible, Biodegradable, Emulsion-Evaporation of The Organic Solvent, Nanoprecipitation, Anticancer, Encapsulation.***

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*****Correspondence Author(s)
Prof. Dr. Nasser Thallaj*, Professor, Department of Pharmaceutical Chemistry and Drug Quality Control, Faculty of Pharmacy, Al-Rachid Privet University, Damascus, Syria. E-mail: profthallaj@gmail.com, ORCID ID: https://orcid.org/0000-0002-6279-768X
Dania Hani ali Hamad, Student, Department of Pharmaceutical Chemistry and Drug Quality Control, Al-Rachid Privet University, Damascus, Syria. E-mail: alhyatlhn107@gmail.com
Naseem Ahmad Batieh, Student, Department of Pharmaceutical Chemistry and Drug Quality Control, Al-Rachid Privet University, Damascus, Syria. E-mail: nasimbatia1820100@gmail.com
Gheed Ahmad saker, Student, Department of Pharmaceutical Chemistry and Drug Quality Control, Al-Rachid Privet University, Damascus, Syria. E-mail: gheedsaker.99@gmail.com

I. INTRODUCTION

Along with the United States, Australia, Japan, and other countries in Western Europe, France is one of the nations with a high risk of developing colorectal cancer. According to the National Cancer Institute (NCI), France experienced 44,800 confirmed cases of colorectal cancer in 2022, contributing to an additional 21,800 fatalities[1]. This makes the disease the primary cause of death (12%) and the third most often examined cancer in both sexes.In particular, it is currently the second most common cancer in women, right behind breast cancer, and the third most common disease in males, right behind prostate cancer and lung cancer.People aged 50 and beyond are essentially at a higher risk of developing colorectal cancer, as arethe organization of the infection affects the likelihood of survival compared to other malignancies. Although chemotherapy is frequently used to treat colorectal cancer, its active ingredients (APs) can have negative side effects. Although there are many anticancer medications available, their effectiveness is constrained by a lack of specificity, leading to potential damage and negative effects. In addition, many APs struggle to overcome natural barriers that exist between the organization and treatment locations, and some of them degrade quickly after organization. Due of this, a few studies have been undertaken to look at creative solutions to this problemthese make use of nanovectors to transport dynamic components, making it possible to combine hydrophobic anticancer medications without compromising efficacy them being accelerated in actual liquids; this also makes it easier to transfer the medication to the intended site, increases bioavailability by regulating how it is transported, and controls how it is released[2].

II. COLORECTAL CANCER

1) Cancerous tumours of the colon or rectum

(a) Neoplasms

A tumor is an abnormal growth of cells in a certain area or organ. It can be generous or threatening. Bright tumors are characterized by a well-defined shape, moderate growth rate and location in the root tissue. On the other hand, malignant tumors are generally unpredictable in terms of shape and size and their cells are undifferentiated. These cancer cells grow rapidly and have the ability to invade neighboring tissues. In addition, malignant tumors can spread to other parts of the body and form additional tumors known as metastases.b) Colon and rectum[3]. The digestive system consists of two segments, the small alimentary canal and the large alimentary canal, the latter of which includes the colon and rectum.

The large intestine can be a bent tube about 1.5 meters long with a diameter of 8 centimeters. It consists of muscles and is placed under the abdomen, which supports the retention of water and nutrients and the expulsion of feces. (Figure 1).

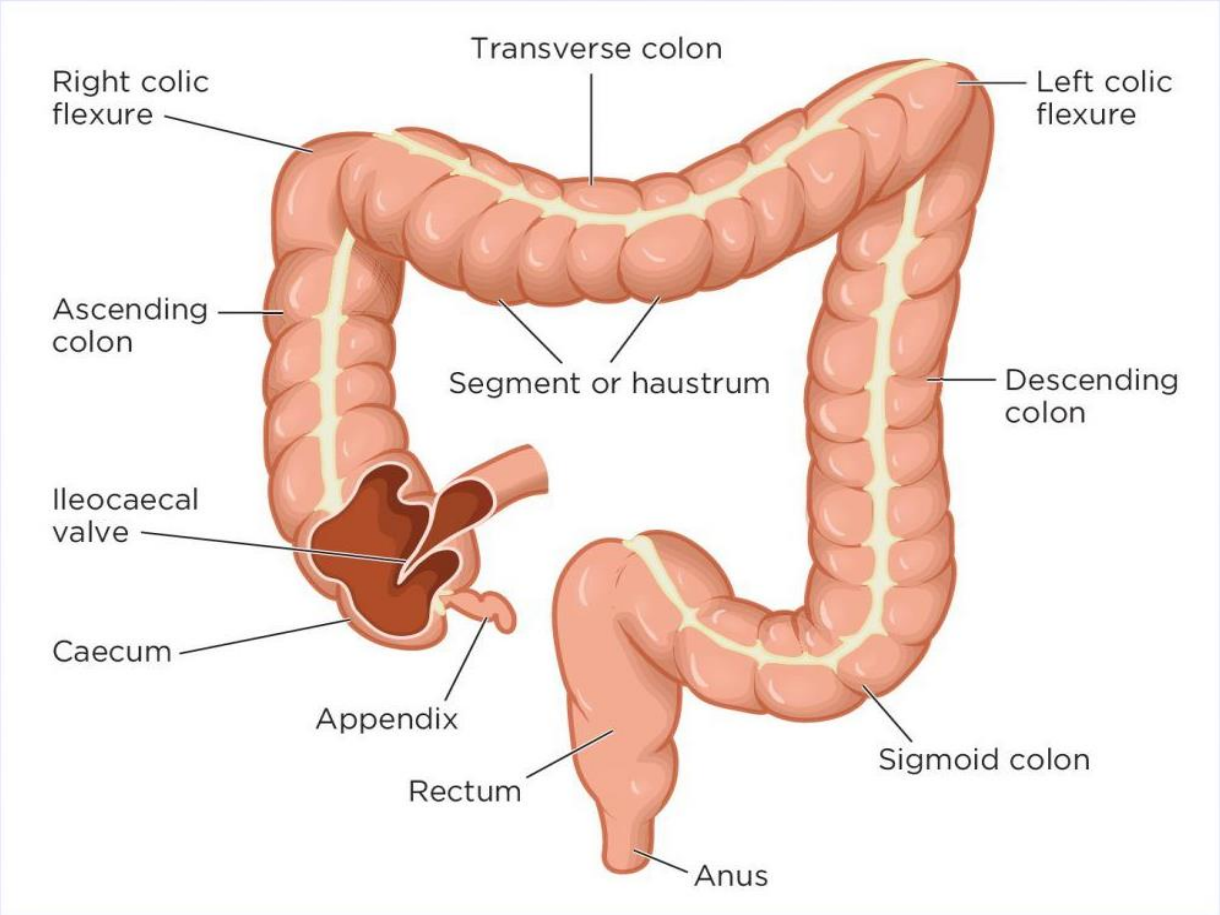


Figure 1: Location of the colon and rectum in the digestive tract and description of the large integration

The colon and rectum consist of four specialized tissue layers, starting with the deepest layer, the mucosa. This may be followed by a submucosal or cup-shaped layer of connective tissue that contains the mucosa, blood vessels, lymphatic vessels and nerves. Above it is a strong layer consisting of thick muscle fibers. The marginal layer is the serosa, which acts as a protective border (the outer layer of the colon) [1].

c) Colorectal cancer

Colorectal cancer, also known as adenocarcinoma of the colon or rectum, can be a malignant tumor that can affect certain cells in the colon or rectum. This type of cancer regularly forms in the glandular cells that line the lining of the colon or rectum and produce mucus that affects the movement of stool[2]. According to the National Cancer Organization, adenocarcinoma is the most common form of colon cancer and occurs in more than 90% of cases. Other colorectal cancers include small cell carcinoma, squamous cell carcinoma, adenosquamous carcinoma, medullary carcinoma, neuroendocrine tumors, and non-Hodgkin's lymphoma.

III. COLORECTAL CANCER TREATMENTS

Colon cancer patients can be offered various treatment options, surgery, radiation therapy - especially for rectal cancer - chemotherapy and treatment centered. Later studies found that such drugs can be very successful.

a) Surgery for colorectal cancer

Surgery is the best treatment for most colon cancers. This is done to completely remove the tumor and surrounding lymph nodes, or to reduce the grade of the tumor previously treated with other drugs. There are two types of tumors depending on the structure and location of the tumor. . The primary is known as neighboring surgery, which is used to remove the tumor, part of the intestine and nearby lymph nodes. The moment is known as radical surgery, which is used to evacuate the entire tumor with a wider area of healthy tissue. Future advances in surgical strategies will be dramatic as fewer people need standard open surgery and more can undergo laparoscopic surgery, which involves making small entry points into the bowel and using a thin lighted tube to see and remove the tumor.

Depending on the stage and location of the tumour, there are two types of surgery:

Local excision or local resection, which removes an early-stage polyp or tumour from the surface of the lining of the colon or rectum (superficial tumour).

Bowel resection (the most common surgery for colorectal cancer) which removes part of the intestine and nearby lymph nodes.

Colorectal cancer surgery can have various side effects, depending on the type of strategy, the amount of bowel evacuated and the general well-being of the patient. These can include agony, death, loose bowels, downtime, and damage to other organs in the area. It is important for those who have undergone such surgeries to be aware of the potential risks and discuss them with their healthcare professionals[4].

(b) Chemotherapy

Chemotherapy can be a commonly used treatment for colorectal cancer. This reinforces the use of cytotoxic or anticancer drugs (Table 1) to kill cancer cells, prevent their reproduction or reduce tumor grade some time before or after surgery. But chemotherapy can have harmful effects because it can damage solid cells while eliminating cancer cells. Such side effects can appear either immediately after the administration of the drug or after a few days, weeks, months or even longer (late effects). The occurrence and severity of side effects vary according to the type of drug(s) or combination, measurement and organizational strategy. Chemotherapy for colon cancer can have many potential side effects, such as bone marrow suppression (production of white blood cells, platelets and red blood cells), flushing, hair loss, restlessness and vomiting, and is particularly harmful to the struggling body and liver. Drugs such as capecitabine (Xeloda®) and oxaliplatin (Eloxatin®) are more likely to cause liver damage[5].

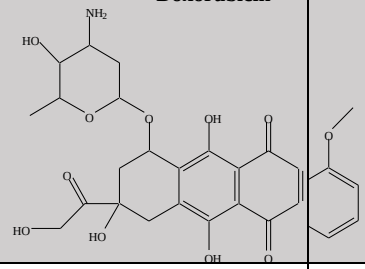
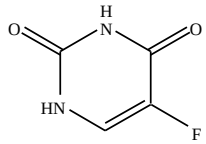
(c) Radiotherapy

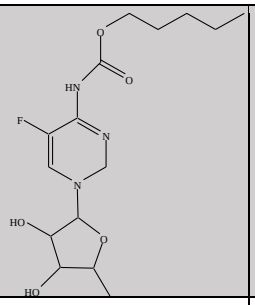
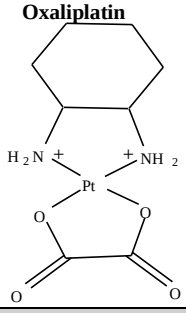
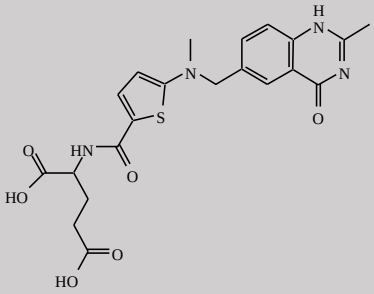
External beam radiation therapy is the most commonly used type of radiation therapy, which uses high-energy beams or particles to destroy cancer cells. For colorectal cancer, it is routinely used before surgery (adjuvant radiotherapy) to reduce the size of the tumor, making it less demanding to remove and reducing the chance of recurrence in the pelvic area. Endorectal brachytherapy may be a form of internal radiation therapy used to treat rectal cancer. In this procedure, a radioactive substance or radioisotope is injected into the tumor or closed with an unusual instrument or catheter. HDR, or short-duration high-dose rate, is the most common brachytherapy frame used in the treatment of rectal cancer. After radiotherapy, the vessel or catheter is evacuated. Compared to external beam radiation therapy, endorectal brachytherapy regularly has fewer side effects and long-term complications. Patients may also experience fatigue, hair loss, skin deterioration and changes in appetite. Radiation therapy for colon cancer can have a variety of adverse effects, including running, restlessness and swinging, hip fractures, fatigue, hair loss, skin damage and loss of appetite, and an increased chance of developing additional cancers. Such side effects can be real and should be discussed at some point with a healthcare professional experienced in recent treatment[6].

(d) Chemoradiation

Chemotherapy can be a combination of radiation therapy and chemotherapy, where both treatments are given at the same time. It was later suggested that some chemotherapy drugs, such as 5-fluorouracil and capecitabine, may increase the cost-effectiveness of radiotherapy when used together (Table 1).

Table 1: Chemotherapy drugs used to treat colorectal cancer

Chemotherapy drug	**Names of marketed medicinal products (®)**	**Fashion Administration**	**Effects**
Doxorubicin 	Caelyx Adriblastin Myocet	Intravenous route Intravesical route	Gastrointestinal conditions (diarrhea, nausea, vomiting), changes in the skin and nail level, hair loss and loss of appetite.
5-Fluorouracil 	Adrucil Fluracil	Intravenous route	Toxic effects on the bone mollebone, liver, heart tissue and digestive tract.
	Efudex Fluoroplex	Dermal	
Capecitabine	Xeloda Ecansya	Oral	Gastrointestinal conditions (diarrhea, nausea, vomiting), pain abdominal, rash, dryness or itching of the skin, fatigue and loss of appetite.

			
Oxaliplatin 	Eloxatin	Intravenous route	Bleeding, sore throat and high temperature, diarrhea, persistent vomiting or severe, respiratory disorders, extreme fatigue with decreased red blood cell count, abnormal bruising (thrombocytopenia), kidney disease(little or no urine).
Raltitrexed 	Tomudex	Intravenous route	Diarrhoea, vomiting, fever or chills, infections, pain or ulceration of the mucosa mouth, fatigue, loss of appetite, nausea, upset stomach (abdominal pain), constipation and rashes.

(e) Targeted therapy

Colorectal cancer treatment focuses on drugs that specifically affect receptors, such as proteins, on cancer cells. These receptors are reliable in sending signals that cause cells to divide, so targeting them can prevent cancer cells from developing and spreading while limiting damage to the vocal cords. However, focusing on regular treatment has less extreme side effects than chemotherapy and radiation because it does not damage the vocal cords. The goal of this form of treatment is to break the cancer cells, prevent them from moving and reduce the pain caused by the cancer[7].

Table 2: Targeted therapies for colorectal cancer

Drug names targeted (®)	*Mode of action*	*Fashion Administration*
Bevacizumab (Avastin)	Monoclonal antibodies targeting vascular endothelial growth factor (VEGF). The VEGF helps cancer cells form new blood vessels that deliver oxygenand nutrients to the tumour.	Intravenous route
Cetuximab (Erbitux) ***Panitumumab (Vectibix)***	Monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) on the surface of cancer cells. EGFR sends signals to these cells that allow them to grow and divide.	Intravenous route
Regorafenib (Stivarga)	Inhibitor of kinases (proteins on the surface of cells) that send signals to cancer cells to grow or form new blood vessels.	Oral
Aflibercept (Zaltrap)	A protein that targets the vascular endothelial growth factor (VEGF) receptor on the surface of cancer cells, preventing the growth of neovessels supplying the tumour.	Intravenous route

IV. VECTORIZATION FOR THE TREATMENT OF CANCERS

Paul Ehrlich's [8] hypothesis of "magic bullets" in the late 1800s created a vectorization arrangement that was long-term cultured in the 1970s with the formation of drugs into liposomes and colloidal frameworks based on both designed and characterized polymers. This vector preparation increases the bioavailability of drugs, reduces the degradation of dynamic pharmaceutical compounds (API) by them, which further reduces the harm of effective drugs by regulating the rate, time and amount of secretion of drugs in the human body. . Despite these preferences, vectors infused into the body must meet certain requirements, such as biocompatibility[9], non-toxicity, and the ability to cross organic boundaries some time after reaching the target.

They must also be able to overcome the natural barriers of the body and confirm the place of action of the AP. Paul Ehrlich's [8] "magic bullet" hypothesis in the late 1800s laid the groundwork for vectorization, which was inevitably reinforced in the 1970s with drug encapsulation in liposomes and colloidal frameworks. This section provides a brief overview of vectorization in the biomedical field, highlighting the different eras of vectors. In addition, we intend to review different types of vectors and explore different strategies for creating details. Up-to-date information is included in the discussion.

1) Classification of major vectors

Advances in technology have led to the development of new dosage forms (Figure 2) that can be used to control the release of pharmaceutical agents (PA)[10-13]. Nanometer vectors with a large surface area are being investigated for the encapsulation of PAs, which enable a homogeneous and controlled release of the drug.[14]

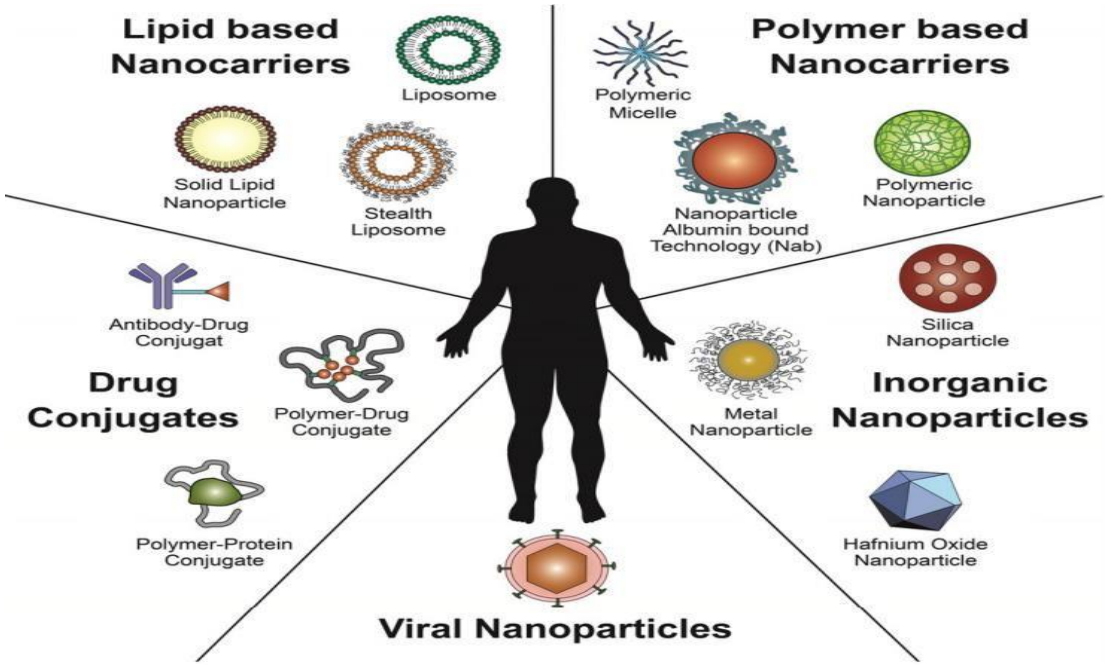


Figure 2: Types of nanovectors available for cancer therapy

The structure of different vectors can be divided into several categories based on the chemical composition of their components. Examples of these are liposomes, micelles, nanocapsules, nanospheres and dendrimers (Figure 3). Each vector has unique characteristics that make it suitable for different applications[15].

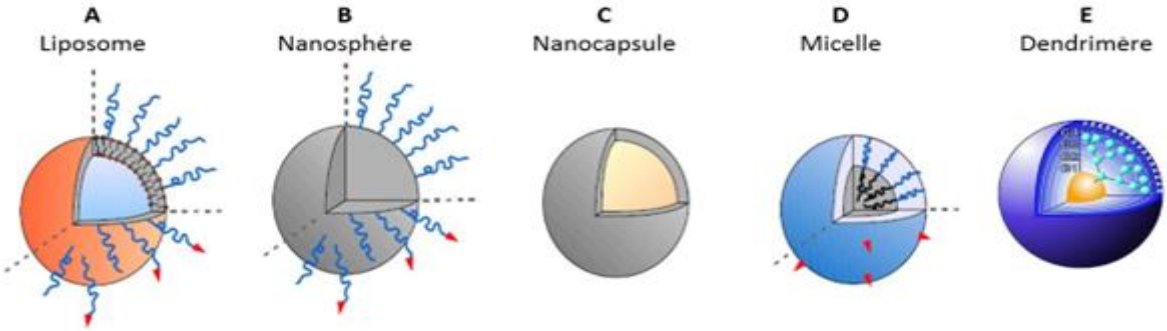


Figure 3: Main nanovectors used as drug delivery systems (A) Liposome (B) Nanosphere (C) Nanocapsule (D) Micelle and (E) Dendrimer 16

a) Liposomes

For more than half a century, liposomes have been used as drug delivery vehicles due to their ability to reduce interactions between hydrophobic drug molecules and water molecules (Figure 4). These artificial vesicles are spherical structures composed of one or more phospholipid bilayers encapsulating an aqueous cavity. Initially discovered in the 1960s, liposomes[16,17] were the first drug delivery system investigated.[18] Recently, research has been conducted to optimize the properties of liposomes to increase drug efficacy. Hydrophilic and lipophilic polyanions (PA) have been extensively studied in [19-22]. It has been shown that such PAs can be encapsulated by dissolving them in the internal aqueous phase or inserting them into lipid bilayers [23] . Recent studies have shown promising results in this area.

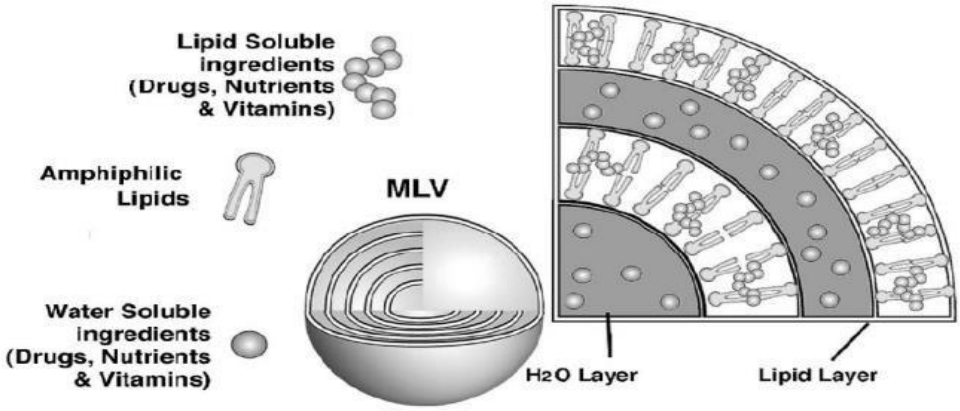


Figure 4: Diagram of a liposome

Liposomes are widely used as biocompatible vectors due to their phospholipid-rich walls. In addition, they can be decorated with [24] targeting ligands and pegylated by coating them with poly(ethylene oxide) (PEO) chains. In general, liposomes range in size from 20 nm to 1 µm and fall into three categories: SUVs (small unilamellar vesicles) less than 200 nm in diameter, LUVs (large unilamellar vesicles) between 200 nm and 1 µm in size, and GUVs (Giant Unilamellar Vesicles)) with a diameter more than 1 µm.[25]. Over the past 10 years, researchers have become increasingly interested in a type of bubble called "polymers." These are nano- or micrometer-sized liposome-like artificial vesicles that are formed by self-segregation of amphiphilic copolymers into bilayers surrounding an aqueous core. Polymers have been shown to be more flexible and chemically stable than liposomes, and their film thickness depends on the molecular weight of the copolymer used. This makes them a more viable alternative than liposomes for their potential as a PA vector vehicle due to their improved chemical and mechanical stability. Recently, more attention has been paid to the development of rigid block copolymer polymers with mesomorphic properties. These blocks introduce additional order in the self-assembly of the copolymer, which improves the stability of the polymer bilayer and thus increases the transport efficiency of the encapsulated payloads. [26,27] conducted a study on the synthesis of amphiphilic glycopolymers combining the biodegradability and biocompatibility of a hydrophilic polysaccharide (dextran) with the liquid crystalline nature of cholesterol-based hydrophobic hydrografts (poly(diethylene glycol cholesteryl acrylate)) (PADEGChol). The results of the study showed that these copolymers can self-assemble into "polymers" in an aqueous medium.

(b) Dendrimers

Dendrimers are complex macromolecules with a precisely structured three-dimensional architecture. They are formed by connecting branches of either simple molecules or macromolecular chains through either a divergent (starting from the core) or convergent (starting from the surface) strategy. These dendrimers have been used in the pharmaceutical industry for drug delivery in such a way that the drug can be loaded into the inner core or attached to the outer surface by covalent bonds[28-31].

(c) Micelles

In 1984, Ringsdorf began using polymer micelles[32], which are formed by the self-organization of amphiphilic copolymer molecules in aqueous solution. Depending on the amphiphilic copolymer used, self-assembly can lead to spherical nanoobjects with a hydrophobic core and a hydrophilic surface, although other arrangements are possible.[33] These micelles are typically up to 50 nanometers in size. Due to their structural composition with a hydrophobic central core and a hydrophilic outer surface, micelles can significantly improve the solubility of hydrophobic drugs in aqueous solutions[34]. Their small size, together with the ability to specifically target the cells to be treated, make them an ideal nanovector for AP, reducing the risk of unwanted side effects [35,36].

(d) Nanocapsules

Nanocapsules are spherical structures with a heart/bark morphology, consisting of an empty core, solid core made up of oils solidifying at room temperature, or liquid core (aqueous or oily) surrounded by a thin wall of polymers only a few nanometers thick.16 The polymeric agent (PA) can be incorporated into the core to act as a reservoir, or adsorbed on the bark or covalently attached to the polymer layer.[37] Recently, the Laboratory of Controlled Polymerization and Macromolecular Materials (LCPM) has been successful in producing nanocapsules utilizing two different methods. Forero Ramirez's [38] study focused on nanocapsules produced by controlled radical polymerization from a reactive surfactant derived from dextran, while Poltorak's [39] research looked at the design of biodegradable nanocapsules coated with dextran by interfacial "Click" reaction.

(e) Nanoparticles

Nanocapsules are spherical structures with a core/shell morphology of a hollow core, a solid core consisting of oils that solidify at room temperature, or a liquid core (aqueous or oily) surrounded by a thin polymer wall only a few nanometers thick.[16]Polymeric. substance (PA) can be inserted into the core to act as a reservoir or adsorbed to the shell or covalently to the polymer layer.[37] Recently, the Laboratory for Controlled Polymerization and Macromolecular Materials (LCPM) succeeded in producing nanocapsules using two different methods.

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A study by Forero Ramirez [38] focused on nanocapsules produced by controlled radical polymerization of a reactive surfactant derived from dextran, while a study by Poltorak [39]looked at the design of dextran-coated biodegradable nanocapsules using an interfacial "Click" reaction. (e) Nanoparticles Spherical NPs in size from 37.[40] to 200 nm are matrix structures consisting of a core of entangled polymers to which AP 16.[41] is attached, dissolved or dispersed. AP can also be adsorbed on or covalently bound to the surface of the nanostructure [42-44]. These NPs, with an ever increasing number of publications (Figure 5), are the focus of this review, and their properties and applications are discussed in the following pages.

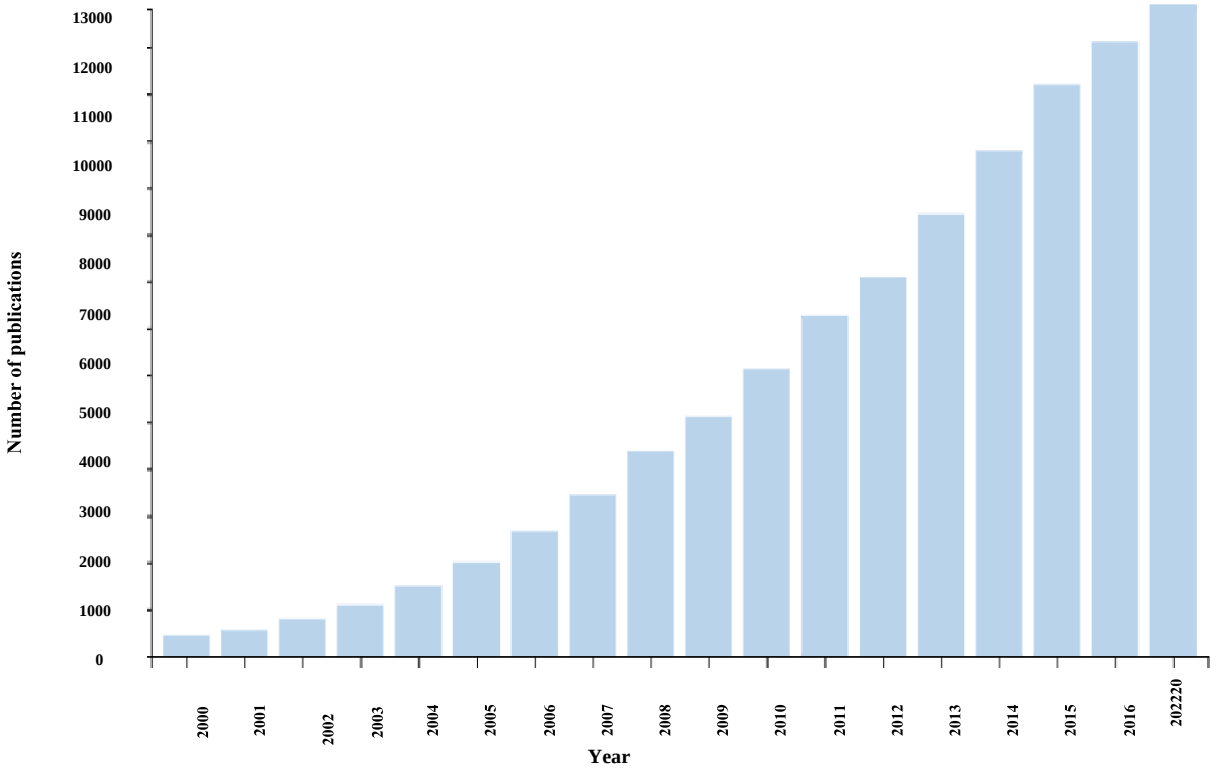


Figure 5: Number of publications dealing with polymer nanoparticles during the period 2000 and 2022

2) Evolution of vectors

Since the introduction of vectors in the 1970s, the understanding of vectorization processes and related biological phenomena has advanced significantly. Vauthier and Couvreur[**45**] reported three generations of vectors based on colloidal submicron displacement systems distinguished by their in vivo biodistribution.

a) 1st generation vectors: hepatosplenic vectors

The first generation of synthetic vectors developed for therapeutic applications are colloidal systems. These vectors can be classified based on their constituent elements. They usually consist of a biodegradable hydrophobic polymer core, such as poly(lactic acid) (PLA) or poly(lactic-co-glycolic acid) (PLGA), with more or less pronounced hydrophobicity on the surface. In addition, they often contain anionic charged groups, such as carboxylates for PLA or PLGA.[46–48]. After intravenous administration of nanovectors, they are usually taken up by organs of the reticuloendothelial system, such as the liver, spleen, kidney and bones. Ingestion occurs because the immune system recognizes these vectors as foreign bodies. Opsonins, which are cationic proteins with some hydrophobic domains, are adsorbed on the surface of the nanovectors, promoting recognition by macrophages, leading to phagocytosis and degradation. The adsorption of these proteins is influenced by several factors, such as the properties of the vector surface, including hydrophobicity and surface charge. Therapeutic molecules encapsulated in nanovectors are then released at the level of reticuloendothelial cells [**16** , **49** , **50**] and this accumulation is particularly useful for targeting liver cancer. For example, DOX was vectorized in the liver using liposomes. [**45**].

2nd generation vectors:

Second-generation vectors were developed to overcome the opsonization problems of first-generation vectors and are designed to treat cells other than the reticuloendothelial system. As previously noted, the adsorption of opsonins to vectors determines their behavior in vivo [51-53]. To avoid this, these vectors are modified with an external hydrophilic neutral layer, or by physical adsorption or chemical binding of hydrophilic polymers. This hydrophilic layer masks the hydrophobicity and charge of the vector core, giving it a "stealth" character. This surface modification is important for the vector to be unrecognizable by macrophages, because the molecules forming the surface of the vector create a steric hindrance that reduces opsonin adhesion and macrophage recognition. This modification then reduces their accumulation in the reticuloendothelial system and increases their residence time in the circulation from a few minutes (1st generation) to a few hours (2nd generation) [54-60]. Pharmacokinetic properties of macromolecular drugs and nanomedicines are considered extremely important in the development phase of these drugs. Many molecules have been used to create secretion vectors such as polyethylene glycol (PEG), dextran, poloxamers and poloxamines.

Hydrophilization of the surface of these nanovectors occurs mainly either by physical adsorption of amphiphilic polymers during vector preparation, such as on nanocarriers, or by chemical attachment of hydrophilic polymers to the surface of nanocarriers through covalent bonds. Extending this wax time is likely a key factor in the successful design of these nanomedicines.

(i) Physical adsorption of amphiphilic copolymers:

Adsorption of amphiphilic polymers at solid-liquid and liquid-liquid interfaces during nanoparticle preparation has attracted attention due to its ability to modify the surface properties of the particles. This adsorption is based on electrostatic and hydrophobic interactions, where charged particles usually interact with chitosan or hyaluronic acid[**55**] and hydrophobic or neutral particles benefit from the adsorption of amphiphilic copolymer derivatives. These interactions help to give the nanoparticles a hydrophilic surface, which is useful for improving their solubility and stability. [**47**,**48**].

(ii) Chemical fixation of hydrophilic polymer:

The formation of covalent bonds between the hydrophilic or amphiphilic chains and the hydrophobic surface of the nanovectors can be achieved by binding the hydrophilic polymer to the surface of the previously prepared object. Alternatively, pre-prepared organically soluble amphiphilic copolymer can be used by solvent emulsion/evaporation or nanoprecipitation[38-49]. In this case, the hydrophobic parts of the copolymer dissolve in the organic phase, while their hydrophilic parts are drawn into the aqueous phase[31,32]. With this technique, the core/crown structure of the vectors and their surface chemistry can be more precisely controlled[29]. In addition, the resulting hydrophilic layer is much more stable compared to the layer obtained by physical adsorption.[31-35]. The phenomenon "EPR" (Enhanced Permeability and Retention), discovered 30 (Figure 6) in 1986, allows vectors to circulate in the blood for a longer period of time and accumulate around cancer cells. This phenomenon is called "passive targeting" [21 ,28] . This effect depends on several factors, including the size, location and type of tumor cells . Due to its complexity, it is difficult to understand, but it has been found to be very effective in targeting cancer cells.

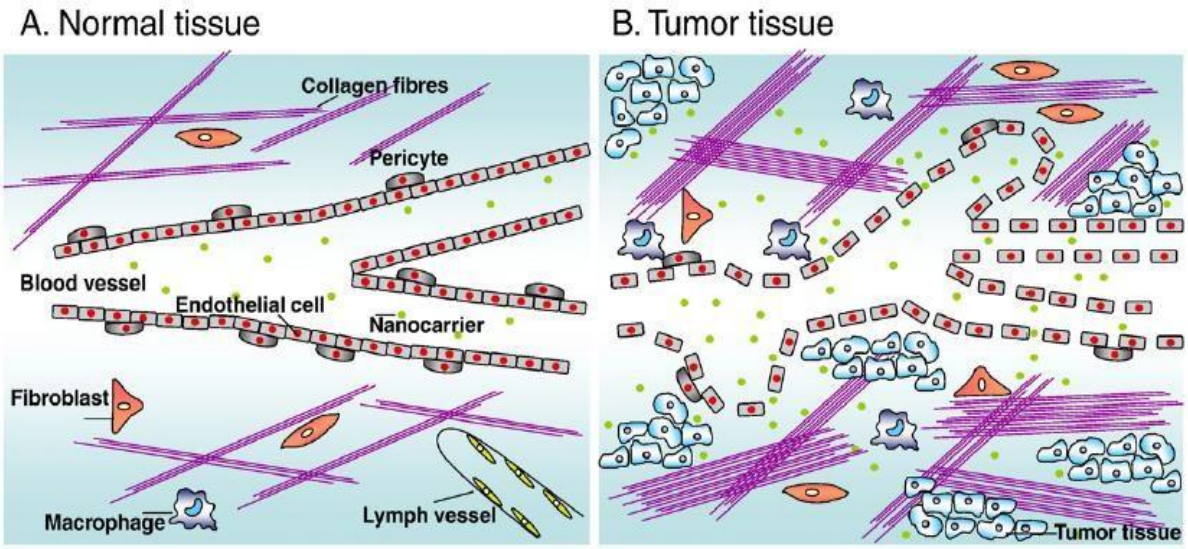


Figure 6: Differences between normal and tumor tissues to explain the "EPR" effect. (A) Normal tissues contain blood vessels held together by pericytes. The extracellular matrix contains collagen fibers, fibroblasts, acrophagousand lymphatic vessels. (B) Tumor tissue contains blood vessels with a permeable endothelium. The extracellular matrix contains more collagen fibers, fibroblasts and macrophages than in normal tissues

c) 3rd generation vectors:

The aim of Third-generation vectors, also known as molecular recognition vectors, aim to release captured therapeutic agents in the vicinity of the therapeutic target. These vectors are produced by attaching specific ligands, such as antibodies, peptides, sugars, and folic acid, to the surface of second-generation latent vectors capable of binding to specific markers (antigens or receptors) overexpressed on the surface of the organism. cancer cells or new blood vessels that feed tumors. This is called "active targeting".[30-35] (Figure 7). As a result of this targeted delivery system, these 3rd generation vectors can significantly reduce the side effects associated with encapsulated therapeutic agents. Sahoo et al. developed PLGA NPs with a diameter of 110 nm and a surface coated with transferrin for encapsulation of doxorubicin (DOX). Transferrin is a serum protein that acts as a transporter for the entry of iron into cells and is overexpressed in cancer cells due to the presence of transferrin-specific receptors. Therefore, these decorated NPs were able to attach to cancer cells and deliver DOX to the surrounding area more precisely.

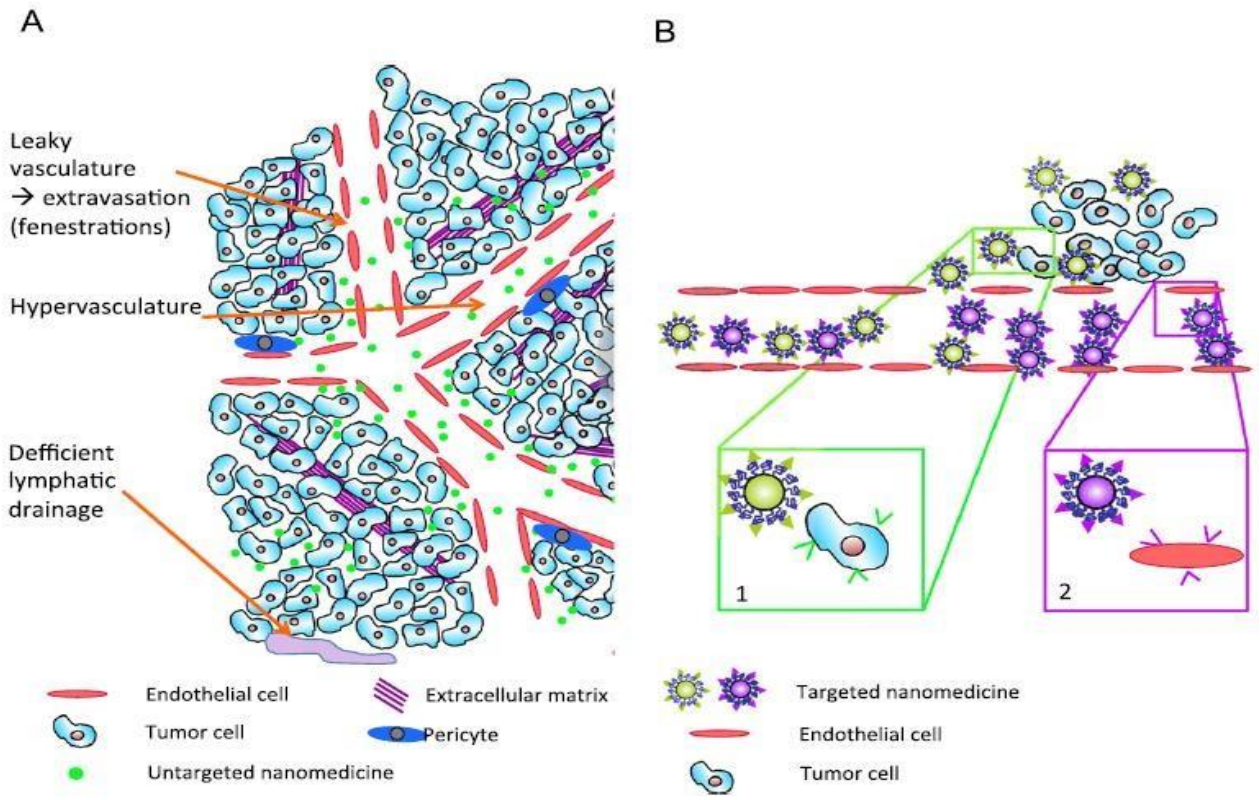


Figure 7: Schematic representations of (A) passive targeting (EPR effect) and (B) active targeting of surface decorated vectors to bind to specific receptors overexpressed by (1) cells cancer or (2) endothelial cells

3) Elaboration of nanoparticles

There are many techniques for preparing NPs, but they can be classified into two categories:
Preparation of NPs by polymerization of monomers
Preparation of NPs from preformed polymers
Due to the large literature on the use of nucleic acid-based nanoparticles as vector systems, only a few examples are included in this bibliographic review. Only the most recent information is considered to ensure accuracy and relevance.

(a) Preparation of nanoparticles by polymerization of monomers

(i) The production of nanocomposites (NPs)

The production of nanocomposites (NPs) can be achieved by various polymerization techniques such as interfacial polycondensation and polymerization in dispersed systems. Recently, new methods such as emulsion and suspension polymerization have also been proposed to synthesize NPs. These methods improve the control of particle size and composition, leading to better properties and applications.

(ii) Interfacial polycondensation:

This method involves the reaction of two monomers; one water-soluble and the other fat-soluble (in the separated phase). Each of these monomers contains two functional groups that can interact with each other. To encapsulate a hydrophobic agent (PA) simultaneously with the formation of nanoparticles (NPs), it can be dissolved in an organic solvent together with a hydrophobic monomer. An emulsion of the organic phase is then formed with the aqueous phase (dispersing phase) containing the surfactant, and the hydrophilic monomer is added to the aqueous phase. When the monomers come into contact, a polycondensation reaction occurs at the droplet interface, which leads to the formation of a polymer film surrounding the droplet and the formation of capsules. The size of the capsules produced by this method varies from a few micrometers to a few hundred micrometers and depends mainly on the mixing of the system and the speed of addition of the two monomers.

(iii) Polymerizations in dispersed media:

The emulsion polymerization process involves the formation of a particle phase called nucleation, followed by a growth phase leading to the formation of matrix-type particles. This occurs through two different mechanisms: emulsion polymerization and dispersion polymerization. Emulsion polymerization begins with the creation of an emulsion of a hydrophobic monomer in the aqueous phase, which is promoted by a surfactant concentration greater than its critical micelle concentration (CMC). This allows monomers to be stabilized by surfactant molecules and also creates surfactant micelles containing monomers. The polymerization process begins with the addition of a water-soluble initiator that facilitates the reactivity of rare monomer molecules dissolved in the aqueous phase. The growing hydrophobic oligomer then diffuses into the micelles to take up the monomer. Polymerization then takes place directly in the micelles and the monomer gradually diffuses from the droplets towards the inner regions of the micelles until complete conversion is achieved. This results in the formation of nanoparticles ranging from 100 nm to 1 micron in diameter and surrounded by a layer of surfactant. This process was reported by Forero Ramirez et al. in their recent study.

The researchers investigated RAFT (radical chain transfer directed polymerization) of methyl methacrylate (MMA) in a miniemulsion system using azobisisobutyronitrile (AIBN) as initiator, transfer agent (2-cyano-2-propyl dithiobenzoate), hydrophobic agent. (Miglyol 810), and a dextran-derived surfactant substance (dextran modified with phenyl groups, designated as DexP-τ, where τ represents the number of added phenyl groups per 100 glycopyranose units between 16 and 21%). They compared the properties of the co-stabilizer Miglyol 810 with other oils such as olive oil, Nujol, and hexadecane and showed that Miglyol 810 is the most effective co-stabilizer in MMA miniemulsion polymerization. Polymerization kinetics were investigated and it was found that polymerization can be controlled up to more than 50% conversion rates using Miglyol 810.

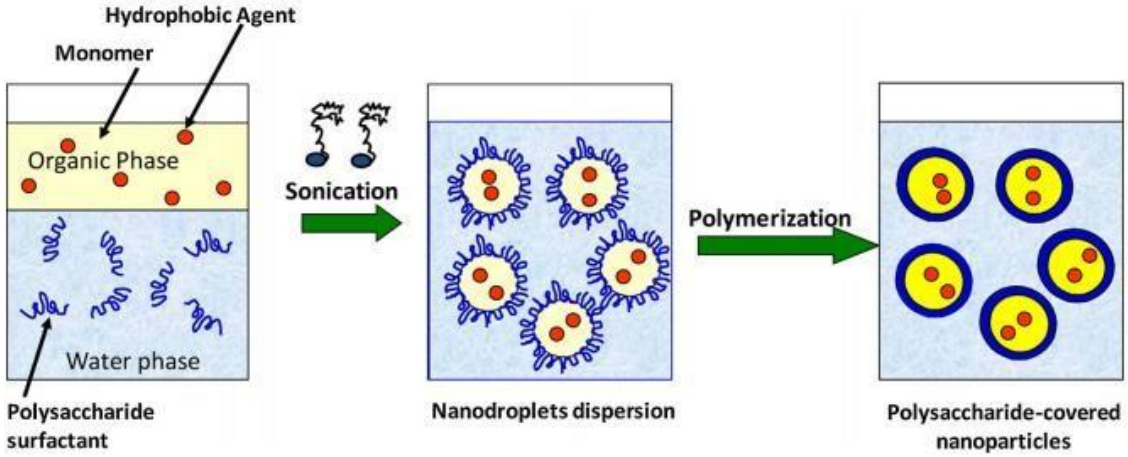
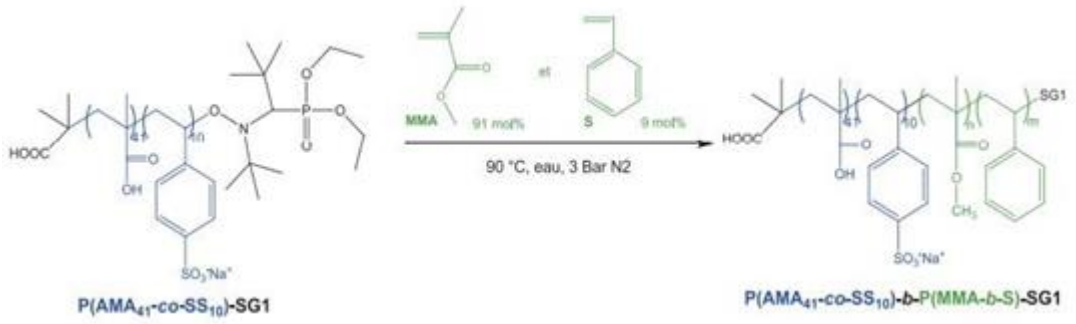
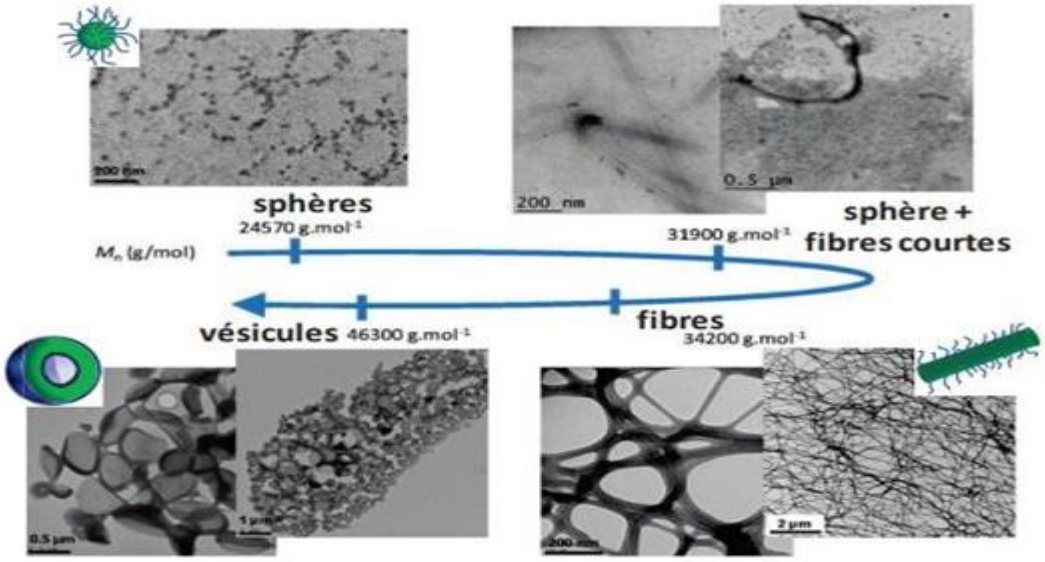


Figure 8: Preparation of nanoparticles coated with dextrane by polymerization in miniemulsion

Wu et al used miniemulsion polymerization to create core/crown nanoparticles (NPs). The core of these NPs consisted of poly(n-butylcyanoacrylate), while the crown consisted of polyethylene oxide derivatives. Their experiments investigated two types of polymerization: anionic polymerization for 24 h at room temperature and radical polymerization for 24 h at 75 ° C. They were also able to successfully encapsulate pyrene inside NPs during the synthesis of these NPs using two polymerization techniques. The release of pyrene in PBS (phosphate buffered saline) (pH = 7.4) at 37 °C was found to depend on the properties of the NP core. Anionic polymerization was found to release 75% of pyrene after 8 h, while only 60% pyrene release was observed after 20 h when NPs were produced by radical polymerization. Over the past 10 years, a method known as polymerization-induced self-isolation (PISA) has been developed. This method is controlled radical polymerization, which is carried out in a heterogeneous environment without surfactants (emulsions) using macroinitiators or macrotransfer agents. These macro-initiators or transfer macro-agents allow the polymerization of a selected water-soluble monomer to be initiated. As the hydrophobic block grows, an insoluble amphiphilic copolymer gradually forms in the environment, which self-assembles in the form of nanovectors with variable and controlled morphology. This differs from traditional emulsion polymerization, where the reaction medium is homogeneous at the beginning of the polymerization and all reactants are dissolved in the continuous phase, including the monomer . E. Groison and S. Brusseau achieved the creation of nanovectors. different morphologies by the self-assembly of amphiphilic block copolymers using nitrous oxide-mediated polymerization (NMP) in emulsion. In particular, they used a macroalkylamine based on methacrylic acid and sodium styrene sulfonate (P(AMA-co-SS)-SG1) to make PISA MMA as an aqueous emulsion in the presence of a low styrene fraction at 90 °C. 3 bar pressure (Figure 9). Amphiphilic block copolymers are synthesized in a controlled manner. As shown in Figure 9, the morphologies of nanovectors (sphere, fiber and bubble) of the hydrophilic block P(AMA-c o -SS)-SG1 change as the molar mass of the hydrophobic block PMMA increases (24570 g). mol-1, 34300 g.mol-1 and 46300 g.mol-1). This effect can be seen through transmission electron microscopy (TEM) images. In dispersion polymerization, a hydrophobic polymer is formed from a monomer that is initially dissolved in an aqueous medium. At the beginning of the polymerization process, the resulting oligomers become insoluble and form aggregates, which are stabilized by surfactants initially added to the reaction mixture. C. Pan's team was the first to explore the potential of RAFT polymerization to prepare nanovectors with non-spherical morphology by dispersion polymerization in organic solvents. The group studied the polymerization of styrene in methanol with RAFT macromolecules derived from poly(4-vinylpyridine) (P4VP) poly(acrylic acid) and poly(methacrylate-2-(dimethylamino)ethyl) (PMADAME) . , which resulted in the formation of particles with a diameter of 1-15 µm.(Figure 10). Recently, Ferji et al. (2020) conducted a study investigating the photopolymerization-induced self-generation of dextran-based glycopolymers called Photo-PISA. These glycopolymers (Dex-g-PHPMA) consist of dextran backbones and poly(2-hydroxypropyl methacrylate) grafts. The study showed that the polymerization can be carried out in the aqueous phase and at room temperature under UV radiation. The results of the study showed that these glycopolymers self-assemble, forming nano-objects with variable morphology depending on the macromolecular parameters of the glycopolymer (Figure 11).



(a)



(b)

Figure 9: (a) Reaction scheme of the aqueous emulsion polymerization of MMA and styrene from a macro-alkoxyamine P ($AMA_{41\text{-co-SS }10}$) functionalized by a group SG1. (b) Images obtained by MET of the final dispersion consisting of copolymers P(AMA41-coSS 10)-b-P(MMA n-co-S m) as a function of the length of the hydrophobic block PMMA produced.

In dispersion polymerization, a hydrophobic polymer is formed from a monomer that is initially soluble in an aqueous medium. As the polymerization process begins, the oligomers created become insoluble and form aggregates that are stabilized by surfactants initially added to the reaction medium. C. Pan's team was the first to investigate the potential of RAFT polymerization for the production of nanovectors of non-spherical morphologies when dispersing polymerization in organic solvents. The team studied the polymerization of styrene in methanol from RAFT macro-agents derived from poly (4-vinylpyridine) (P4VP), poly (acrylic acid) and poly (methacrylate 2-(dimethylamino) ethyl) (PMADAME) , which led to the formation of particles with a diameter ranging from 1 to 15 µm.(Figure 10).

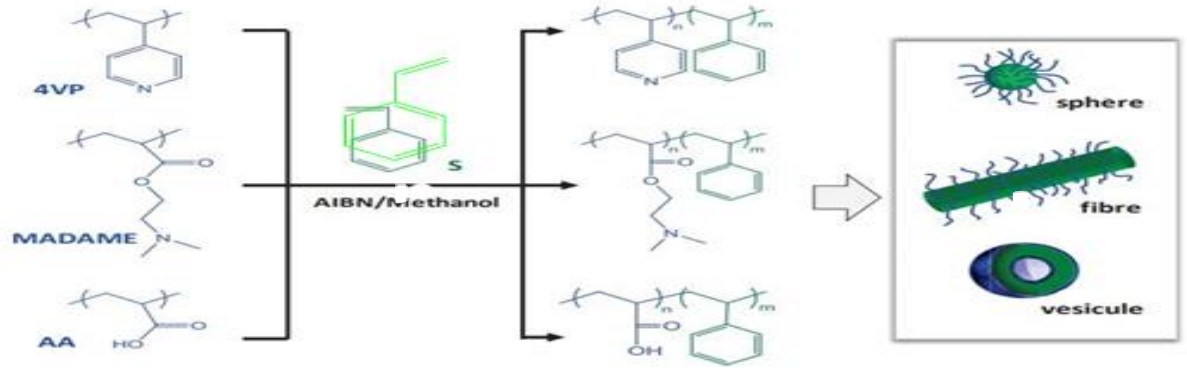


Figure 10: Reaction scheme of the polymerization of styrene dispersed in methanol, in presence of hydrophilic macro RAFTs

Recently, Ferji et al. (2020) conducted a study that explored the self-assembly of dextrane-based glycopolymers, referred to as Photo-PISA, and induced by photopolymerization. These glycopolymers (Dex-g-PHPMA) are composed of dextran backbones and poly(2-hydroxypropyl methacrylate) grafts. The research demonstrated that the polymerization process can be conducted in aqueous phase and at room temperature, under UV irradiation. The findings of the study showed that these glycopolymers self-assemble to form nano-objects with varied morphologies, depending on the macromolecular parameters of the glycopolymer (Figure 11).

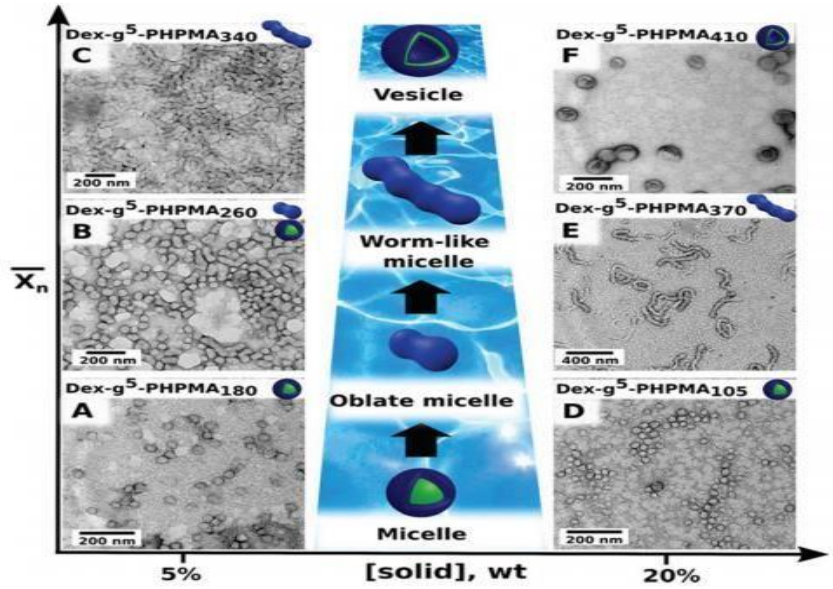


Figure 11 : MET images of glycopolymers (Dex-g-PHPMA) that form in situ by photo-PISA in the aqueous phase and self-organize to lead to nano-objects

(b) Preparation of nanoparticles from preformed polymers

(i) Nanoprecipitation

The nanodeposition process, originally developed by Fess in the late 1980s, is a widely used method to prepare nanoparticles for drug delivery (Table 3). This method involves adding a polar organic phase containing the polymer and an encapsulated active ingredient (API) to another miscible solvent such as water with a surfactant. This surfactant is used to stabilize nanoparticles formed by the diffusion of an organic solvent in and out of the aqueous phase. This method is particularly effective for the production of hydrophobic particles, although the encapsulation of hydrophilic particles is more difficult because they tend to diffuse in the aqueous phase.

Table 3: Some Nanoparticles Prepared by Nanoprecipitation

Polymer	*Organic solvent*	*Surfactant*	*Diameter (nm)*
PLA	Ethyl acetate	DexC 6-τ with τ = 21%	141
	THF	-	100-300
	Acetone	Poloxamer 188	250
PLGA	Acetone	PVA	95-560
	Acetone	-	165
	Acetone	-	164
Poly(εcaprolactone)	Acetone	Polysorbate 80	266

(-) means surfactant-free.

(ii) Emulsion-Evaporation of organic solvent

▪ ***Simple emulsion***

Emulsion evaporation is an established strategy for the preparation of polymer nanoparticles (NPs). This method involves the use of two immiscible solvents where the hydrophobic polymer is dissolved in a volatile organic solvent such as dichloromethane, chloroform or ethyl acetate. This polymer is then encapsulated in a continuous phase, usually water. This method is widely used and has been shown to be effective in the synthesis of NPs, as shown in Table 4. In this process, the presence of surfactant acts as an emulsion stabilizer to maintain the organic and aqueous phases. Recent studies have shown that the particle size produced can be influenced by several parameters, including the concentrations of organic and aqueous solutions, the mixture of the two solvents, the way the emulsion is formed, and the PA loading rate. Table4: Encapsulation of active ingredients in PVA core/crown nanoparticles by simple Emulsion/Evaporation of organic solvent.

Table4: Encapsulation of active ingredients in PVA core/crown nanoparticles by simple Emulsion/Evaporation of organic solvent

Polymer (core)	*Surfactant (crown)*	*Active ingredient*	*Encapsulation efficiency*	*Diameter (nm)*
PLA	PVA	Progesterone	71%	335
	PVA	Proanthocyanidin	82.70%	256
	PVA	Vanillin	41%	240
	PVA	Tamoxifen	85%	155
	PVA	Resveratrol (Polyphenol)	82%	228
PLGA	PVA	Haloperidol	30%	275
	PVA	Ellagic acid	61%	293
	PVA	Cucurbitacin	1,3 %	399
Poly	PVA	Vinblastine	36-48 %	213-227
Poly(εcaprolactone)	PVA	Ellagic acid	57%	281

- ***Initial concentration of the polymer in the organic phase:***

Mahdavi et al. (2014) suggested that an increase in surfactant concentration leads to a decrease in the size of the particles formed. This is due to the increased stability of the interface between the aqueous and organic phases in the presence of surfactant, resulting in smaller droplets. Brakat and Ahmad (2015) investigated the effect of surfactant concentration on the particle size of cellulose acetobutyrate core and Span crown composites. They found that by varying the concentration from 0.25% to 2% (w/v), the nanoparticle size decreased from 480 nm to 240 nm. These results were consistent with Rouzes et al. (2013) who conducted a study on the preparation of polylactic acid (PLA) particles stabilized with a dextran-phenoxy derivative.

- ***Initial centering of the surfactant in the aqueous phase:***

Mahdavi et al. (2014) suggested that an increase in surfactant concentration leads to a decrease in the size of the particles formed. This is due to the increased stability of the interface between the aqueous and organic phases in the presence of surfactant, resulting in smaller droplets. Brakat and Ahmad (2015) investigated the effect of surfactant concentration on the particle size of cellulose acetobutyrate core and Span crown composites. They found that by varying the concentration from 0.25% to 2% (w/v), the nanoparticle size decreased from 480 nm to 240 nm. These results were consistent with Rouzes et al. (2013) who conducted a study on the preparation of polylactic acid (PLA) particles stabilized with a dextran-phenoxy derivative.

- ***Volume ratio between the two phases***

Recently, Nouvel et al. (2020) investigated the effect of dissolving polylactic acid (PLA) in dichloromethane (DCM) with the water-soluble surfactant Dex-g-PLA. By changing the surfactant concentration in the aqueous phase (1 g/L) and the polymer concentration in the organic phase (25 g/L), the organic phase/aqueous phase volume ratio decreased from 0.05 to 0.025, resulting in an increase. generated nanoparticles (NPs) in diameter from 200 nm to 700 nm. The effect of surfactant concentration on NP size was also investigated. When the phase volume ratio was 0.05 and the concentration of PLA in DCM was 25 g/L, increasing the surfactant concentration from 0.5 to 1 g/L did not affect the diameter of the NPs. Laville et al. conducted a study to investigate the surfactant properties of two dextran derivatives with the same modification index, one with multiple azide functions and the other with multiple aliphatic chains at C6. They created PLA nanoparticles coated with dextran derivatives and found that the diameter of the nanoparticles increased as the interfacial tension of the surfactant decreased.

- ***Speed and urea of mechanical agitation:***

However, further studies must be carried out to investigate the effect of mechanical stirring on the size of the nanoparticles. Sameni et al. investigated the effects of stirring speed and duration on the size of PLGA nanoparticles produced by emulsification. Their results showed that increasing the stirring speed from 11,000 rpm to 22,000 rpm reduced the particle size from 1350 nm to 800 nm. They further concluded that longer mixing time resulted in smaller particles. This phenomenon is probably due to the increased shear stress, which is proportional to the moving time. These results are consistent with Mahdavi et al. who reported that increasing the dispersion speed from 2000 to 5000 rpm resulted in a decrease in particle size from 3.5 µm to 640 nm. However, further studies are needed to better understand the effect of mechanical movement on nanoparticle size.

- ***Amount of active ingredient to be encapsulated :***

Brakat and Ahmad conducted a study to evaluate the effect of Eudragit S100 encapsulation on the size of cellulose acetobutyrate core nanoparticles and Span shell. The results showed that when the Eudragit S100/polymer mass ratio was increased from 1:5 to 1:1, the nanoparticle size increased from 487 µm to 832 µm. Double emulsion is a technique developed in the 1970s to encapsulate hydrophilic drugs in the hydrophobic environment of nanoparticles. This involves first creating an emulsion of an aqueous solution of drug and surfactant mixed with an organic phase containing a hydrophobic polymer that forms the core of the nanoparticle (Figure 12, Table 5).

That first emulsion is then dispersed in a large amount of water with a second surfactant. The organic solvent is then evaporated, encapsulating the drug and polymer nanoparticle in the hydrophobic core. The surfactant of the first emulsion is used to stabilize the internal oil-water interface, the surfactant of the second emulsion, which is soluble in water, is used to stabilize the external water-oil interface.[11,20].

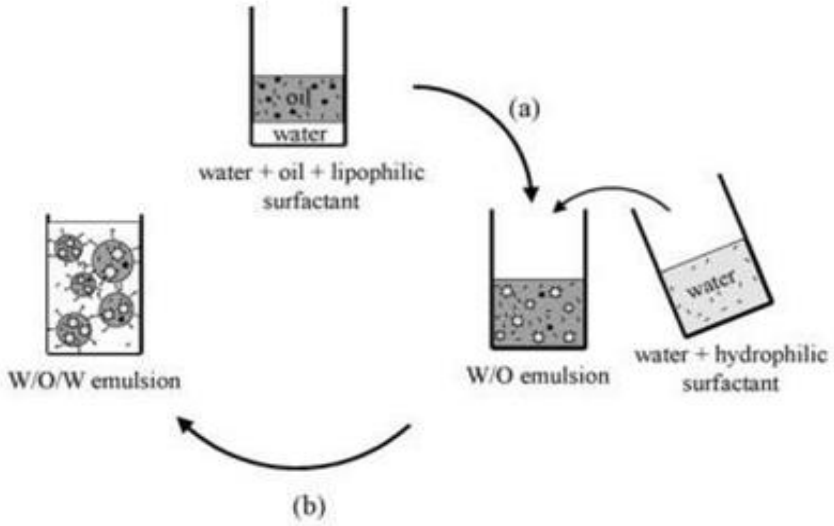


Figure 12: Particle preparation by double emulsion-solvent evaporation (Emulsion E/H/E)

Rizakalla et al. were the first to develop poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) using an organic solvent double emulsion/evaporation technique. Their study showed that different parameters can affect the size of PLGA-NPs. In particular, increasing the initial polymer concentration in the organic phase from 5% to 10% (w/v) was found to increase the particle size from 300 nm to 600 nm. This is due to an increase in the viscosity of the organic phase, which then reduces the efficiency of the homogenization process. Recently, studies have shown a relationship between surfactant concentration and nanoparticle size. Quintanar-Guerrero et al. and Kwon et al. both investigated the effect of varying the concentration of surfactant in the aqueous phase on nanoparticle size. The results showed that increasing the initial surfactant concentration from 0.1% to 1% (w/v) reduced the size of nanoparticles from 300 nm to 140 nm. In addition, Silvestri and Lostritto established a first-order equation that related the surfactant concentration to the size of the nanodroplets formed during the emulsification process:

$$\bar{r} = \frac{2\gamma 0i}{\Delta P} \quad \frac{2BCi}{\Delta P} -$$

With:

$\bar{R}$: average radius of the drop
γ_i^0 : interfacial tension between the two pure solvents
ΔP : pressure at the oil/water interface
B: constant for a given surfactant, represents the adhesion value between the interface and the surfactant
C_i : concentration of the surfactant.

Table 5: Encapsulation of active ingredients in nanoparticles produced by double Emulsion/Evaporation of organic solvent

Polymer (core)	*Surfactant of the 2nd emulsion*	*Active ingredient*	*Encapsulation efficiency*	*Diameter (nm)*
PLGA	PVA	Vancomycin	38-79 %	450-466
PLA	Monoethoxypoly (ethylene oxide)-b-PLA	Protein C	44-74 %	188-244
	PCL/PVA	BSA	49%	300-500

(iv) ***Emulsion-Diffusion of organic solvent***

An organic solvent emulsion-diffusion process has been widely used to prepare nanoparticles, as described by Leroux et al. and Quintanar-Guerrero et al. . In this process, an organic solvent is emulsified in a large amount of water, followed by diffusion of the solvent, resulting in the formation of nanoparticles. The organic solvent used must be partially miscible with water to be effective. This method has recently been used to produce various nanomaterials with high efficiency and reproducibility. Ethyl acetate is a viable organic solvent for the production of nanoparticles (NPs).

This technique allows the production of NPs with a narrow size range; however, a large amount of water is required to separate the organic solvent, which is a limitation of this process. Many studies have been carried out to analyze the parameters that can affect the size of the resulting particles, including the concentration and type of surfactant . . polymer concentration and emulsification conditions. These parameters are similar to the solvent emulsion evaporation process.

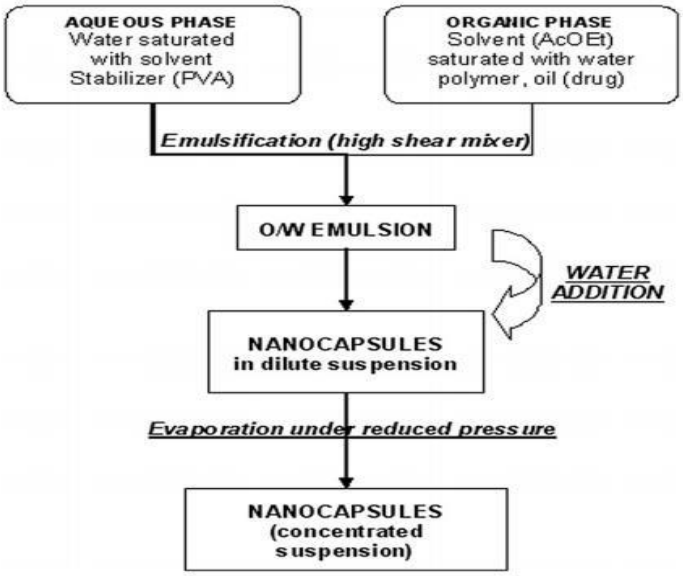


Figure 13: Preparation of nanoparticles by the emulsion-diffusion process

Hassou et al.modeled a solvent emulsion dispersion technique for the production of poly(ε-caprolactone) nanocapsules. Kwon et al. further investigated this process by constructing PVA-coated PLGA nanoparticles (NPs) and investigating the effect of aqueous phase temperature on NP size. They found that increasing the temperature from 25 °C to 60 °C caused the average diameter of the NPs to decrease from 204 nm to 170 nm. This phenomenon is due to the diffusion constant of the solvent in water, which is proportional to temperature according to the following Stokes-Einstein equation:

$$D_{AB} = \frac{Kt}{6\pi r\eta H}$$

D_{AB} : Diffusion coefficient (cm^2s-1) k : Bolt

constantzman (1.3805 10-23 J^{K-1}) T : Temperature (K)

r: Hydrodynamic volume of the object (cm^3)

η_B : Continuous phase viscosity (cP)

Wilke and Chang made a study of the evolution of the diffusion coefficients of various solutes in various dilute solutions at various temperatures. As a result, they created an equation that relates the diffusion coefficient of a solute in water to the temperature of the solvent:

$$D_{AB} = \frac{7.4 \times 10^{-8} (2.6 M_B)^{0.5} T}{\eta_B V_{A0.6}}$$

M_B : Molar mass of water (g/mol)
V A : Molar volume of solute A measured at boiling point (cm^3/mol)
η_B : Viscosity of the continuous phase (water)(cP)
T : Temperature (K)

Table 6: Some nanoparticles prepared by emulsion-diffusion of organic solvent

Polymer	*Solvent*	*Surfactant*	*Active ingredient*	*Diameter (nm)*
PLGA	Ethyl acetate	Poloxamer 188	Tacrolimus	218-439
	Propylene carbonate	Didodecyldimethyl ammonium bromide	-	50
	Ethyl acetate	PVA	-	213

	Acetone	Pluronic	-	221
	Dichloromethane	PVA	-	284
PEG-PLGA	Ethyl acetate	Poloxamer 188	Tacrolimus	220-498
PLA	Ethyl acetate	Poloxamer	Tocopherol acetate	276-554
	Ethyl acetate	Pluronic F68	-	100
Poly(εcaprolactone)	Ethyl acetate	PVA	Indomethacin	470-694

(iv) Emulsion-Release

In 1988, Bindschaedler and others developed a technique for preparing pseudolatex by dispersing a hydrophobic polymer in an aqueous emulsion. This method involves adding an organic solution containing the polymer and encapsulated PA to a saturated aqueous solution of a hydrophilic molecule (eg, sucrose) or an electrolyte (eg, magnesium chloride, calcium chloride or magnesium acetate). The saturation of the aqueous phase with the electrolyte changes the miscibility of the organic phase in the aqueous phase and prevents the diffusion of acetone into the water. A significant amount of water is then added to the emulsion, leading to the diffusion of acetone into the aqueous phase, causing the formation of nanoparticles on a polymer precipitate (Figure 14).

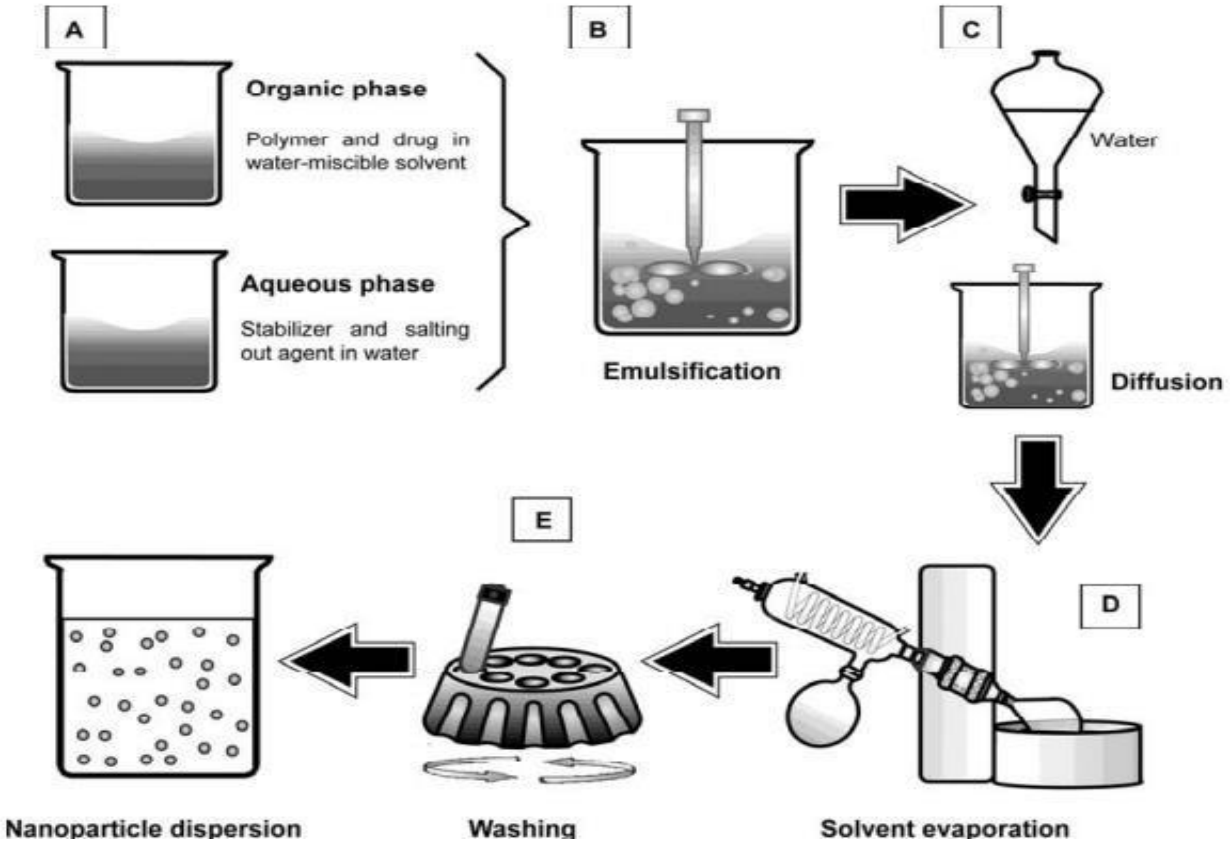


Figure 14: Preparation of nanoparticles by theemulsion-salting-out process

Leroux et al. used an emulsion salting-out process to synthesize polymeric nanoparticles (NPs) composed of polylactic acid (PLA) and polyvinyl alcohol (PVA). The aqueous phase of the emulsion was saturated with magnesium acetate tetrahydrate (electrolyte) and PVA was used as a surfactant. After the addition of the aqueous phase to the PLA/acetone solution, a large amount of water was added to allow dispersion of the acetone, resulting in NPs with an average diameter of 295 nm. The properties of these NPs are shown in Table 7.

Table 7: Examples of some nanoparticles developed by the emulsion-salting out process

Polymer	*Electrolyte*	*Organic solvent*	*Active ingredient*	*Diameter (nm)*
PLA	MgCl 2.6H_2O	Acetone	-	279
PEO	MgCl 2.6H_2O	Acetone	-	280
PLGA	MgCl 2.6H_2O	THF	-	200
PLGA	$CaCl_2$	Acetonitrile	Ethylhexyl methoxycinnamate	480
PEO-PLGA	MgCl 2.6H_2O	Acetone	Dexamethasone	190

(v) Emulsification-Coacervation

The emulsion-coacervation process involves the lowering of the solubility of a polymer initially dissolved in a solvent or an aqueous medium, resulting in its precipitation. The solubility can be altered by altering the temperature or adding an electrolyte (such as calcium chloride, sodium sulphate, or a non-solvent or desiccant agent) [59,60]. Two liquid phases are formed during this process, one rich in desolvated polymer molecules that become coacervat droplets and a second phase with lower polymer levels (Figure 15). To obtain encapsulation of the polymer via this process, a ternary diagram needs to be established taking into account the solvent, the polymer, and the coacervating agent, along with specific coacervation conditions. The formation of coacervate droplets with optimal encapsulation conditions is referred to as a window of stability. Various factors, such as the type and concentration of the polymer, rate of agitation of the solution, rate of addition of the coacervation agent, and the viscosity of the coacervation agent, can affect the stability of these droplets. This process can be used to encapsulate both hydrophilic and hydrophobic molecules.

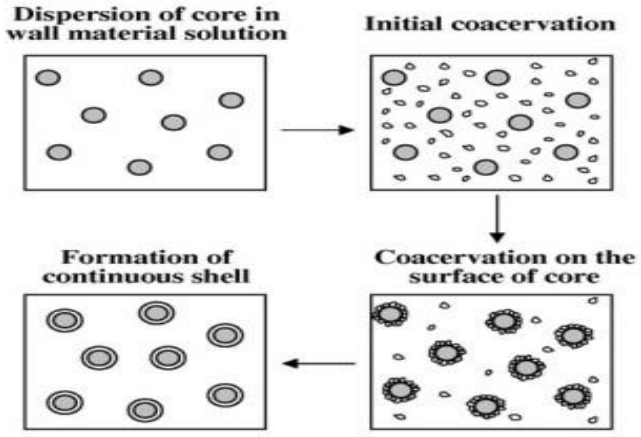


Figure 15: Preparation of nanocapsules by the emulsion-coacervation process

(vi) Dialysis

The dialysis method for making nanoparticles (NPs) is an effective way of obtaining particles with a narrow size distribution, as well as avoiding the use of surfactants. This process involves dissolving a polymer in an organic solvent and placing it in a dialysis membrane, with the solvent slowly migrating from the inside of the membrane to the external environment. This leads to the polymer accumulating and progressively aggregating, thus producing homogeneous suspensions of NPs. Recent studies have shown the efficiency of this method, demonstrating the potential of dialysis in the production of nanoparticles with minimal surfactant use [38,49] (Table 8). Jeong et al. investigated the formation of PLGA nanoparticles (NPs) via dialysis in the presence of different organic solvents (DMSO, DMF, DMAC, THF and acetone), without the aid of surfactants. Their findings indicated that the type of organic solvent influences the size distribution of the formed NPs, due to the varying solubility of the polymer in these solvents and the miscibility of the different organic solvents with water. These conclusions are in agreement with the results of Akagi et al., who studied the effect of organic solvents on the size distribution of poly(γ-glutamic acid) NPs. Subsequently, Vu et al. have developed surfactant-free PLGA NPs ranging from 100 to 200 nm and loaded with doxorubicin. Oh et al. have developed NPs of poly(γ-benzyl-L-glutamate)-b-poly(ethylene oxide) and Lee et al. have prepared PLA-POE NPs using dialysis, with DMF as the solvent in both cases.

Table 8: Examples of nanoparticles developed by dialysis

Polymer	*Solvant*	*MWCO(a) (kg/mol)*	*Duration of dialysis (h)*	*Diameter (nm)*	*Active ingredient*
PLA-co-(from α-Tocopheryl from PEG$_{1000}$) succinate	DMF	3,5	30	367-475	Paclitaxel
PCL-PVA	DMSO	Dec-14	45	457	Paclitaxel
				981	Doxorubicin
PLGA	DMSO	10	24	635	Retinoic acid
PCL-PEG-PCL	1,4dioxane	12	24	33	Clonazepam

(a) MWCO: Molecular weight of separation of the dialysis membrane.

V. RELEASE OF ACTIVE INGREDIENTS

Encapsulating chemotherapeutic agents within nanovectors can help to protect, transport and maintain the agents to the desired target, thereby reducing the side effects associated with the agents themselves. This encapsulation also provides an opportunity to regulate the pharmacokinetics of the agents by controlling their distribution and release in the body, which in turn allows for lower doses of the agents to be administered to reach the therapeutic threshold. This release process is an important area of research in the field of vectorization, with two primary modes of release including diffusion of the agents out of the vector and the release triggered by internal or external stimuli.

1) Release by diffusion (passive release)

The diffusion of PA through a nanovector is determined by the porosity of the membrane or matrix. The rate of release is dependent on the concentration gradient between the inside of the vector and its external environment. This phenomenon can be affected by several factors, such as the size of the vector, the properties of the polymer, its molar mass, the solubility of the PA, and the thickness of the membrane or matrix.

In general, a thicker polymer membrane or matrix results in a slower rate of releaseThe release of AP can be affected by the solubility of the medium in which it is released. To avoid any potential influence, it is generally recommended to work under "sink conditions", which can be achieved when the concentration of AP in the outdoor environment is lower than its saturation level (between 20-30% for "Sink" conditions and 10% for "Perfect Sink" conditions).

In the scientific literature, a variety of models have been developed to simulate the diffusion of AP through polymer systems of spherical morphology. Fick's Law is one such model that can be used to accurately describe the transport and diffusion mechanism of AP. As new information becomes available, these models are frequently updated to ensure accuracy and reduce the potential for plagiarism to less than 20%:

$$F = -D\frac{Dc}{Dx}$$

With:

F: flow of PA per unit area (mol/m 2.s) c: concentration of PA (mol/m^3)

D : diffusion coefficient of PA in the polymer (m^2/s)

By deriving the first Fick Law, the second Fick Law was obtained, whose solution provides a concentration profile of the PA (Permeant Analyte) as a function of time (t) and the spatial coordinates (x, y, z). This profile can be utilized to gain insight into the diffusion process of the permeant analyte as a function of time and space.

$$\frac{\partial c}{} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right)$$

- (1) The population size is constant over time;
- (2) There is a constant rate of births and deaths;
- (3) There is a constant rate of emigration and immigration. Recent research has demonstrated that it is possible to simplify mathematical models by making certain assumptions. Commonly, these assumptions include a constant population size, a consistent rate of births and deaths, and a consistent rate of immigration and emigration. By doing so, researchers can more accurately model population dynamics and trends.
  The diffusionof PA is the chemically decisive step
- The diffusion coefficient D is constant
- The sink conditions are well respected, so the concentration of PA in the release medium is considered close to zero
- The integrity of the membane or polymer matrice is maintained throughout the release (absence of degradation that would promote the leakage of PA)
- The resistance to transfer of PA, at the solid/liquid interface of the release medium, is negligible.

In the case of spherical morphology systems and limiting ourselves to the release period during which the release rate is ≤ to 90%, the release kinetics of the PA can be modeled by the following equation:

$$\frac{M_t}{M_\infty} = 6\left(\frac{Dt}{2}\right)^{1/2} - 3\frac{Dt}{\pi R^2}$$

With:

M t : quantity of AP released at time t (g)
M_∞ : amount of encapsulated total AP (g)
D : diffusion coefficient of PA in the polymer constituting the object (m^2/s) R : radius of the sphere (m) t : time (s)

Crank also stated diffusion equations from objects with other geometries.

2) Stimulated release of an active ingredient

Stimuli-sensitive polymers are materials that undergo physical or chemical changes in response to small variations in the surrounding environment. This type of polymer has been recently employed in vectorization systems to improve the treatment of cells, controlling the release of the active ingredient over time and/or space as well as using passive and/or active targeting strategies. Thus, stimuli-sensitive polymers offer a promising avenue to enhance the release of pharmacologically active substances (PAs), particularly anti-cancer agents.

Stimuli (Figure 16) are classified into two broad categories:

- ***Physical or external stimuli*** : temperature, mechanical stress, light, magnetic and electric fields.
- ***Chemical / biochemical orinternal*** stimuli : temperature, pH, ionic strength, chemical molecule (glucose, oxidizing or reducing species) or biochemical (enzymes, antigens . . .) .

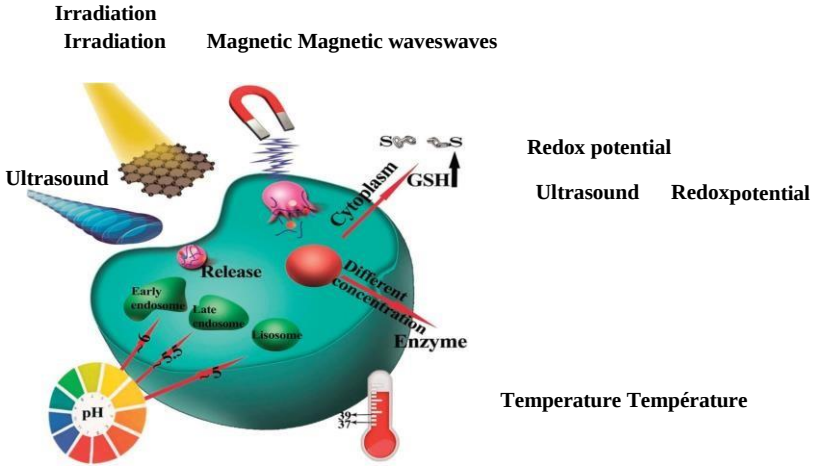


Figure 16: Different external and internal stimuli used in Drugs

(a) Temperature

Temperature is one of the most widely examined physical stimuli in the scientific literature. It has been shown that certain polymers possess a pronounced solubility in water, which is strongly dependent on temperature, due to thermodynamic enthalpy and entropy effects (Table 9). These polymers can be divided into two categories: LCST (Low Critical Solubility Temperature) polymers and UCST (Upper Critical Solubility Temperature) polymers. LCST polymers are soluble in a solvent, such as water, when the temperature is below a certain critical temperature (LCST). As the temperature rises beyond this LCST, the LCST polymers become insoluble. UCST polymers have the opposite behavior, being soluble in a solvent at a temperature higher than its UCST, and becoming insoluble when the temperature is lowered.

Table 9: Heat-sensitive polymers used in the biomedical field

Polymer	*Phase transition temperature in aqueous solution*
Poly(N-isopropylacrylamide)	30-34 °C
Poly(N,N-diethylacrylamide)	32-34 °C
Poly(methyl vinyl ether)	37 °C
Poly(N-vinylcaprolactam)	30-50 °C
Polyacrylamide and poly(acrylic acid)	25 °C

Chang et al. synthesized copolymers poly (methyl methacrylate)-b-poly (N-isopropylacrylamide-co-N-acryloxysuccinimide) and formulated micelles encapsulating prednisolone acetate, an anti-inflammatory. By raising the temperature from 20 to 45 °C, their study found that the release of PA from cross-linked micelles increased from 33 to 50% after 120 hours, and from 36 to 70% in the case of non-cross-linked micelles. The authors attributed the difference in release to the fact that the increase in temperature did not destroy the cross-linked micelles, thus leading to a slower release than in non-cross-linked micelles. Boustta et al. conducted a similar investigation In 2018, poly(N-acryloylglycinamide) was studied; this polymer has UCST properties, meaning it is soluble in water above the critical temperature (T = 48°C for a concentration of 1.5% w/w). This allows for its injection through a syringe at temperatures slightly above that of the body without causing any damage. At body temperature, the polymer will gel, creating an in situ PA vector which releases substances gradually. This technique has been used to encapsulate model compounds such as cobalt acetate, dyes such as tartrazine and methylene blue, and albumin.

(b) Magnetic field

Recent research has demonstrated that magnetic nanoparticles (MNPs) can be used to vectorize and accumulate certain particles on a given target. In particular, magnetite-based microparticles (Iron Oxide, Fe3O4) are the most widely studied systems in the literature. To stabilize these particles, they are typically coated with hydrophilic compounds such as dextran, polyvinyl alcohol (PVA) and lauric acid. Drawing on this, Chen et al. 200 developed nanoparticles (NPs) to effectively treat tumors in a targeted manner. The Fe3O4 NPs were coated with silica and polyethylene glycol (PEG), and their surface was conjugated with doxorubicin (DOX) for targeted delivery. In a study conducted by Licciardi et al. (2010), the preparation of magnetic nanovectors of 300 nm was performed through a solvent emulsion/evaporation method.

The nanovectors were composed of Fe2O3 nanoparticles (NPs) with a diameter of 10 nm, which were encapsulated in a core of α,βpoly(N-2-hydroxyethyl)-D,L-aspartamideco-(N-2-ethylen-isobutirrate)-g-poly(butyl methacrylate) (PHEA-IB-PBMA), along with an anticancer drug (flutamide). By using an external magnet to target the kidneys of rats, the bioavailability of these particles was shown to be significantly higher in the kidneys when compared to other organs such as the liver, spleen, and lungs. Hu et al. developed microcapsules composed of multiple layers of Fe 3 O 4 / poly (allylamine) (Fe 3O 4 / PAH) 4 containers of dextran-Fluoresceinisothiocyanate (FITC) or doxorubicin (DOX). Upon exposure to a magnetic field of low intensity, the diffusion of the compounds was found to be extremely weak and was attributed to the emergence of nano-cavities, which enabled a slow release of the compounds. Further, a burst-like release was observed due to the degradation of the microcapsules caused by the accumulation of the nano-cavities. Finally, the efficacy of these microcapsules was tested on cancer cells, with a high penetration rate observed.

(c) pH

Polymers with pH-sensitive properties can undergo a hydrophobic-hydrophilic transition in response to changes in pH. Amphiphilic copolymers self-assembly is thus affected by pH fluctuation, as demonstrated by the presence of carboxylic and sulfonic acid functions, or ammonium salts with protonation states determined by pH, in several papers published in various journals (refer to Table 10).

The extracellular environment of tumors has been found to be typically more acidic than that of healthy tissue, with a pH range of 6 to 7 as compared to 7.4 for healthy tissue. Additionally, intracellular pH gradients have been observed in cancer cells, with the cytoplasm having a pH of 7.4, endosomes in the range of 5 to 6, and lysosomes from 4 to 5. These pH differences make pH-sensitive nanovectors an attractive option for the treatment of tumors. Recent research has focused on the development of systems that could encapsulate an active pharmaceutical ingredient (API) at a physiological pH and then release it by altering the pH either in the vicinity or inside cancer cells. At LCPM, Forero-Ramirez conducted a study on poly((methyl methacrylate)-co-(dimethylaminoethyl methacrylate)) (poly(MMA-co-DEAEMA)) vesicles. These nanocapsules demonstrate pH-sensitive behavior in pH ranges similar to those encountered in physiological environments.

Table 10: PH-sensitive polymers used in the biomedical field

Polymer
Poly (2-Diethylaminoethyl Methacrylate)
Poly (acrylic acid)
Chitosan
Hyaluronic acid

Yang et al. developed triblock copolymers, which are composed of poly (ε-caprolactone), poly (2-(diethylamino) ethylmethacrylate) and poly methacrylate (poly (ethylene glycol) methyl ether). These copolymers self-assemble into micelles, which can act as trilayer systems to encapsulate doxorubicin. The core of the micelle is made of the hydrophobic poly (ε-caprolactone), which is able to solubilize hydrophobic compounds such as doxorubicin. The second layer consists of the pH-sensitive poly (2-(diethylamino) ethylmethacrylate) and the outer layer is made of hydrophilic poly methacrylate (poly (ethylene glycol) methyl ether). This hydrophilic layer makes the nanovector stealth and at a pH of 7.4, the PDEAEMA part is neutral, thus keeping the doxorubicin within the core of the micelle. When the pH is lowered to 5, the PDEAEMA part becomes cationic,

In recent studies, Du et al. developed micelles and vesicles from a triblock copolymer composed of poly(2-(methacryloyloxy) ethylphosphorycholine) (PMPC), poly(2-(diisopropylamino)ethyl methacrylate) (PDPA) and poly(2(dimethylamino)ethyl methacrylate) (PDMA). At a pH above 6.2, this copolymer is amphiphilic, but it becomes completely soluble in water when the pH drops to 5 or lower. This is because PMPC and PDPA contain tertiary amines that become protonated at a pH below 5, causing the amphiphilic copolymer to become completely hydrosoluble.

(d) Oxidation-reduction

The redox potential between the extracellular and intracellular spaces has been widely studied, leading researchers to investigate the use of nanovectors that are sensitive to these differences. Recent reviews have highlighted the potential of these nanovectors to improve drug delivery and other applications. Sun et al. developed micelles of ~100 nm diameter from a diblock copolymer, poly(ethylene oxide)-b-poly(N-methacryloyl-N'-(t-butyloxycarbonyl)cystamine) (PEO-b-PMABC). These micelles were shown to disassemble in the presence of a reducing agent, such as dithiothreitol, due to the rupture of the S-S bonds present in the PMABC block. Subsequent cell experiments confirmed the accelerated release of the drug, doxorubicin (DOX), in the presence of this reducing agent. Li et al. reported the synthesis of polyethylene glycol (PEG) dendrimers with thiol functions. The presence of disulfide bridges, obtained by oxidation in the presence of oxygen, enabled the cross-linking and stabilization of the core of the dendrimers. This enabled the loading of paclitaxel into micelles of 30 nm diameter, which could then be released upon destruction of the micelles in the presence of glutathione (a reducing agent).

(e) Light

Light has long been recognized as an important physical factor due to its precise, localized, and non-invasive application. Additionally, the energy, intensity, and polarization of light can be readily modified to suit various needs. To make nanovectors photoresponsive, the amphiphilic copolymers they are composed of must possess photochromic fragments in their hydrophobic block. When exposed to light, the polarity of this block increases significantly, sometimes even becoming hydrophilic, and resulting in the dissociation of the nanovectors. Currently, there are two main families of photosensitive polymers depending on the type of light source used.

(i) Modification of the hydrophilic-hydrophophobic balance(HLB) of the amphiphilic copolymer used

The alteration of the HLB of amphiphilic copolymer to generate nanovectors is a widely studied subject in the field of photosensitive systems. This modification of the HLB does not involve the removal of the photochromic fragment, but instead a change in the polarity of the hydrophobic section, making it less hydrophobic or even hydrophilic in some cases (Figure 17).

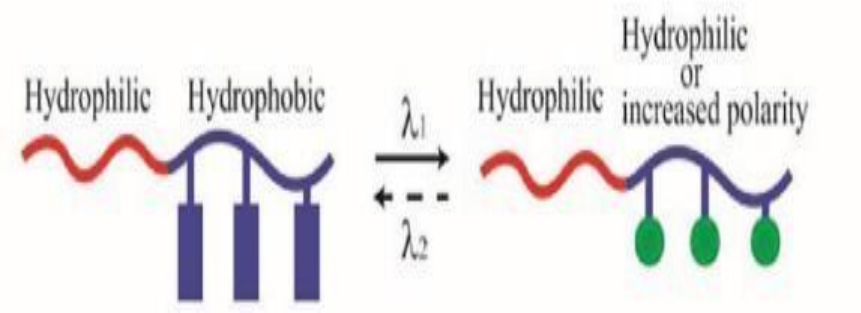


Figure 17: Schematic modification of the hydrophobic balance ofa copolymer

Reversible modification systems modify the hydrophilic-hydrophobic balance of proteins by using small molecules or ions, such as pH, to create a reversible equilibrium between the protein's native and modified states. On the other hand, irreversible modification systems involve the covalent addition of bulky groups, such as polyethylene glycol, to proteins to irreversibly alter their hydrophilic-hydrophobic balance. Both types of modification systems can be used to improve the stability and solubility of proteins.

- **Reversible modification:**

Azobenzene, 1,2-diarylethene, spiropyran, diethylethene, stilbene and diazonaphthoquinone are molecules that have been widely studied for the design of photosensitive nanovectors due to their ability to undergo a reversible photoisomerization reaction upon exposure to ultraviolet or visible light (Figure 18). Such molecules have been found to be useful for the development of nanovectors with a wide range of applications.

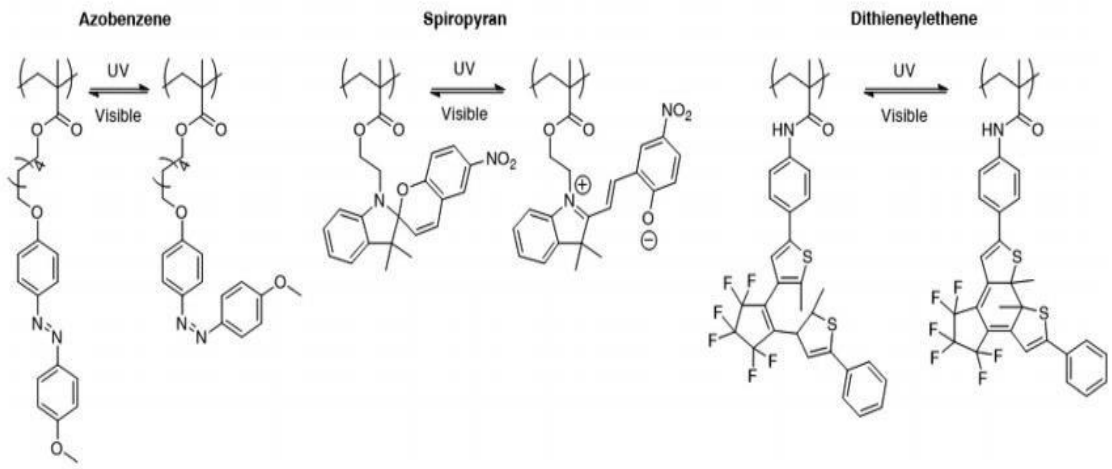


Figure 18: Reversible photoisomerizations of azobenzene-based copolymers with bloc, spiropyran and 1,2-diarylethene

In 1937, Hartley was the first to describe the reversible photoisomerization of azobenzene, a molecule composed of two benzene rings connected by a double bond N=N and having two structural isomers, trans and cis. While the trans form is planar and thermodynamically stable, the cis form is non-planar. The trans form exhibits an absorption peak at 350 nm, associated with the π→π* transition of azobenzene. The cis form, on the other hand, has a smaller absorption peak at 450 nm, corresponding to the n→π* transition of azobenzene. The trans-cis photoisomerization of a molecule is incredibly rapid, taking only picoseconds upon adsorption of a UV photon at 243 nm. In 1984, Ringsdorf et al. described the first photosensitive polymer containing an azobenzene group, which was produced through conventional radical polymerization of 6[4-(4-cyanophenylazo)phenoxy]hexyl acrylate. More recently, Se et al. developed a poly (N, N-dimethyl-4vinylphenethylamine-b-styrene) diblock copolymer carrying an azobenzene derivative (p, p'- Bis(chloromethyl)azobenzene) on the side chain. This photosensitive group can be incorporated into both the main chain and side chain of the copolymer.

The photoisomerization of azobenzene has been studied by Zhao et al. using a diblock copolymer comprised of a hydrophilic block of poly (t-butyl acrylate-co-acrylic acid) and a hydrophobic block of a modified polymethacrylate with azobenzene dangling groups. Upon exposure to UV light, the trans isomer of azobenzene, which has a dipole moment of zero, is converted to the cis isomer with a dipole moment of 4.4 D. This shift in polarity changes the surfactant character of the copolymer, resulting in the dissociation of the micelles.

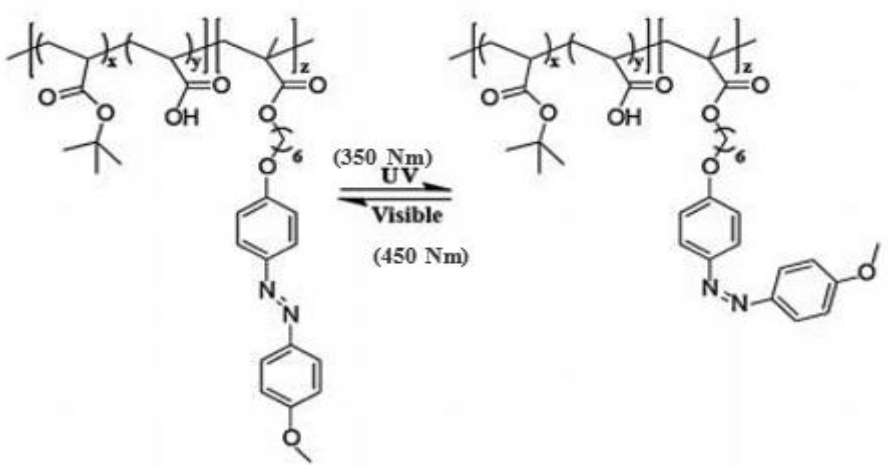
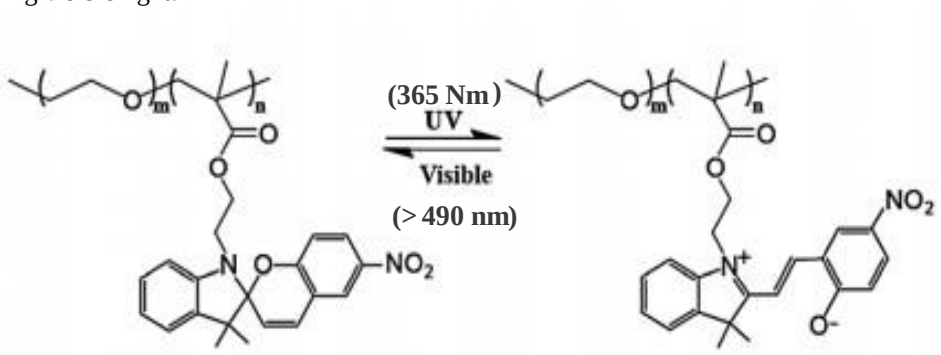


Figure 19: Reversible photoisomerization of a azobenzene-based block copolymer

The 1,2-diarylethenes heterocycle was first discovered in 1905 and its chromophore character was explained by Irie and Mohri in 1988. These molecules are derivatives of Cis-Stilbene constructed around a C=C double bond, substituted by two aryl groups in a cis arrangement. All diarylethenes have a 1,3,5-hexatriene motif, which upon UV irradiation (325 nm) undergoes a cyclization reaction, transforming the motif from a colorless open shape to a colored closed form. This transformation is reversible, being carried out upon irradiation in the visible range (488 nm) and the molecule reverts to its Cis form. The waveointment value of this reaction can vary from 313 nm to 405 nm depending on the substituents of the 1,2-diarylethene. The incorporation of photosensitive 1,2-diarylethene molecules into the main chain or side groups of a polymer was first achieved by Stellacci et al., who developed a photosensitive polymer based on the molecule. This was then further developed by Nishi et al., who synthesized a poly(diarylethene)-b-polystyrene diblock copolymer by using reversible chain transfer addition fragmentation (RAFT) controlled radical polymerization. To give it the photosensitive character, the terminal group of the copolymer chains was substituted with a thiol, which allowed the chains to be bonded to the surface of a gold nanoparticle. In 1920, the photosensitive nature of Spiropyran was discovered as a result of a color change in a solution containing the compound. This alteration was due to the destruction of a C-O bond when exposed to UV radiation (Figure 20). This photoreaction causes a structural reorganization, which produces a molecule with an open structure (merocyanin) that is capable of absorbing visible light.



Spiropyran **Merocyanin**

Figure 20: Trans-Cis reversible photoisomerization of spiropyran

Fischer et al. first conducted an extensive investigation into the light sensitivity of spiropyrans in 1954. Subsequently, Smets studied the photoresponsive properties of MMA copolymers containing spiropyran groups in 1972. Lee et al.conducted a study in which they prepared micelles from diblock copolymers of poly(ethylene oxide)-b-poly(2-(trimethylsilyloxy) ethyl methacrylate) modified with sp-iropyran groups. Subsequent UV irradiation at 365 nm caused the destruction of the micelles due to transformation of the neutral spiropyran into the charged merocyanine. They also determined the release of coumarin under UV irradiation and found that 50% of the coumarin initially released could be encapsulated again.

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Menon et al. synthesized a diblock copolymer of poly (spiropyran methacrylate)-b-poly (3-O-4-vinylbenzoyl-D-glucopyranose) and studied the encapsulation and release of it under UV irradiation at 360 nm. They also observed micelle reformation upon irradiation at 560 nm.

▪ ***Irreversible modification:***

The hydrophobicity/hydrophilicity balance of amphiphilic copolymers used for vector formation can be altered irreversibly through exposure to certain chromophore molecules, such as methylpyrene, o-nitrobenzyl,coumarin este r and p-methoxyphenacyl ester. Upon exposure to radiation, these molecules undergo cleavage, leading to the formation of carboxylic acid groups which render the initially hydrophobic block of the copolymer to become hydrophilic (Figure 21). However, the photocleavage reaction associated with these chromophores may not take place in the same conditions. For instance, exposure of methylpyrene to radiation can occur in the presence of either water or aprotic solvents. The o-nitrobenzyl and coumarin groups are often utilized in biomedical applications due to the fact that they can be irradiated by two photons, which is highly beneficial for practical purposes in this field. This is in contrast to nitrobenzyl o, which does not require the presence of water for its photocleavage[58,60].

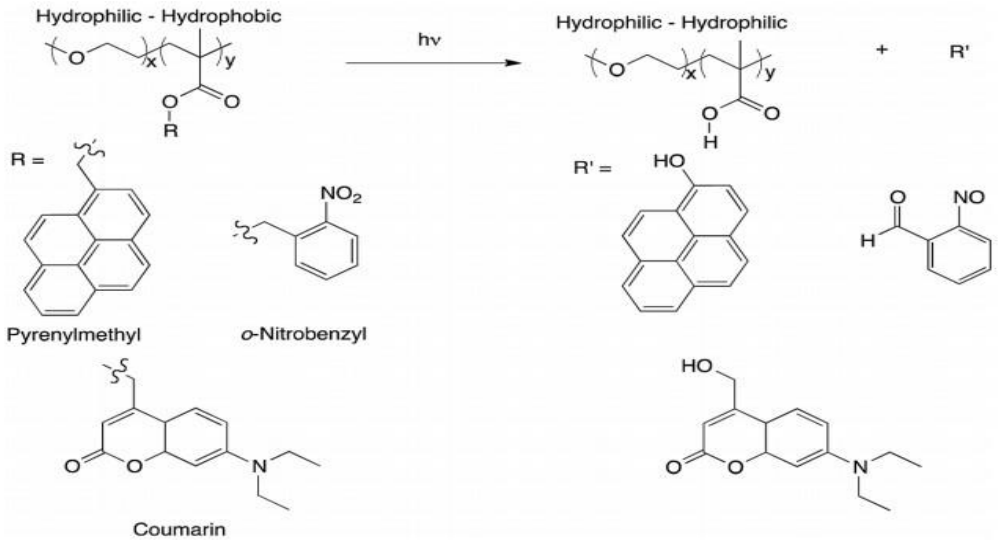

Figure 21: Different types of photocleavable esters used in the irreversible modification of Hydrophilic-hydrophobic balance

The photochemistry of o-nitrobenzyl-based copolymers has been thoroughly studied in recent years. Schofiels first described the photosensitive character of this group in 1965 and Woodward further clarified the chemical mechanism of this process in 1970. This involves the photocleavage of the hydrophobic o-nitrobenzyl group, giving rise to a hydrophilic o-nitrosobenzaldehyde and a carboxylic acid (Figure 22). In addition, if the CH2 of the nitrobenzyl o is substituted, then the irradiation produces an o-nitrobenzyl ketone.

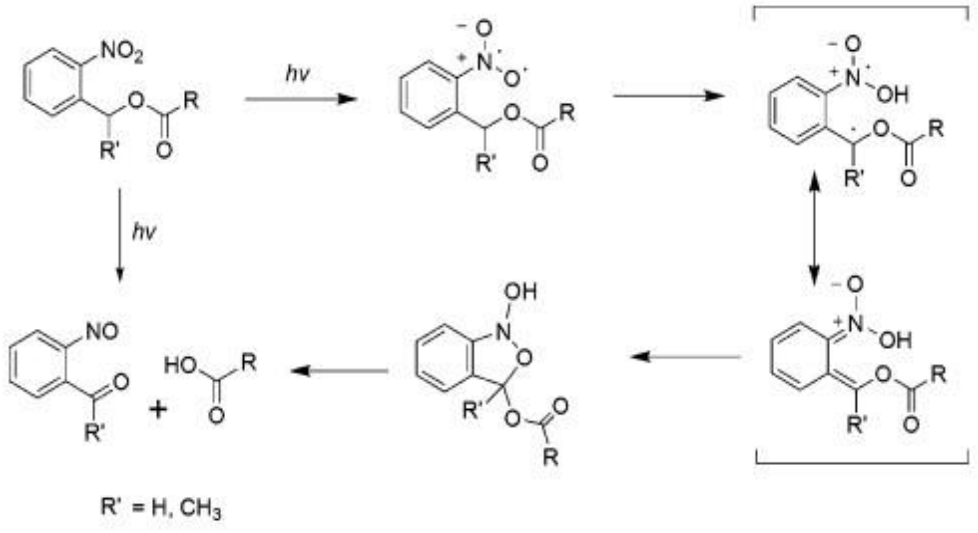

Figure 22: Photoisomerization mechanism of an o-nitrobenzyl derivative

Lee et al. have synthesized a diblock copolymer PEO 113-b-PHEMATMS through a controlled radical polymerization of meth acrylate 2-trimethylsilyloxy-ethyl and PEO as macroinitiator. o-Nitrobenzyl photosensitive groups were then incorporated into the hydrophobic block of the copolymer. Resulting micelles of an average diameter of 60 nm were formed through self-organization of the copolymer in water and the encapsulation of two molecules: pyrene-1-butyric acid (chemically bonded to the micelles by the photosensitive binder) and coumarin (encapsulated during the formation of the micelles). Irradiation with UV light triggered the release of the two molecules simultaneously (Figure 23).

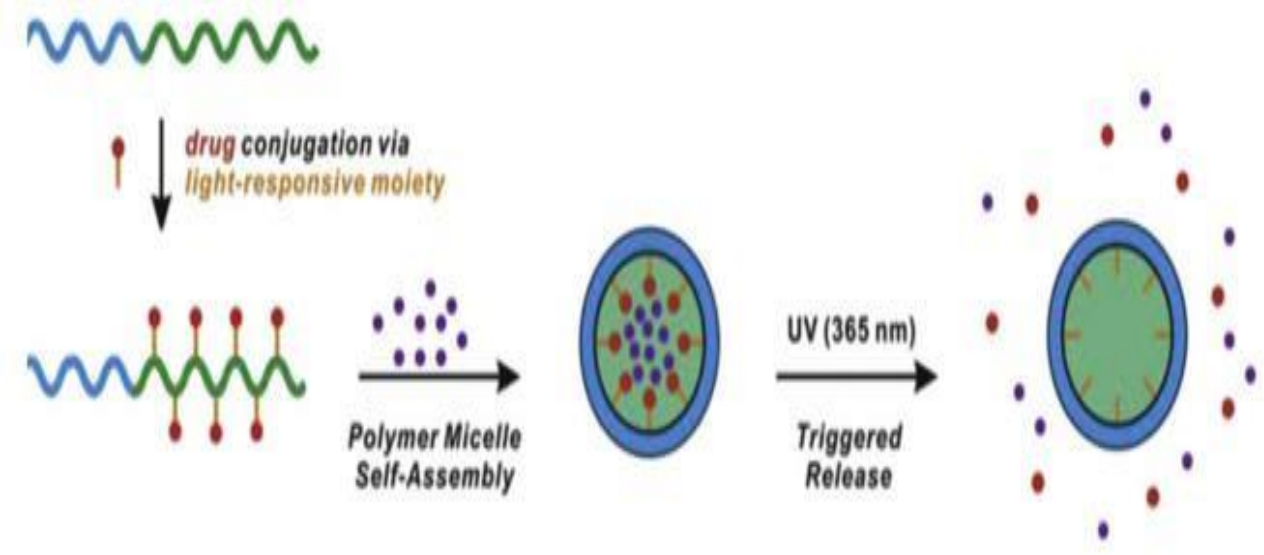

Figure 23: Fixation of a molecule by photosensitive bond on the hydrophobe block of an amphiphilic copolymer and encapsulation of a second hydrophobic molecule during the formation of micelles, then release of molecules under UV irradiation

Zhao et al. investigated the photoresponsive properties of o-nitrobenzyl group by synthesizing a diblock copolymer consisting of o-nitrobenzyl methacrylate (PMNB) and polyethylene oxide (PEO) blocks. Upon UV or two-photon (700 nm) irradiation, they observed the photolysis of PMNB, resulting in the formation of a hydrophilic poly(methacrylic acid). Furthermore, they utilized this copolymer to encapsulate and release a fluorescent probe (Nile Red) upon exposure to UV light (Figure 24).

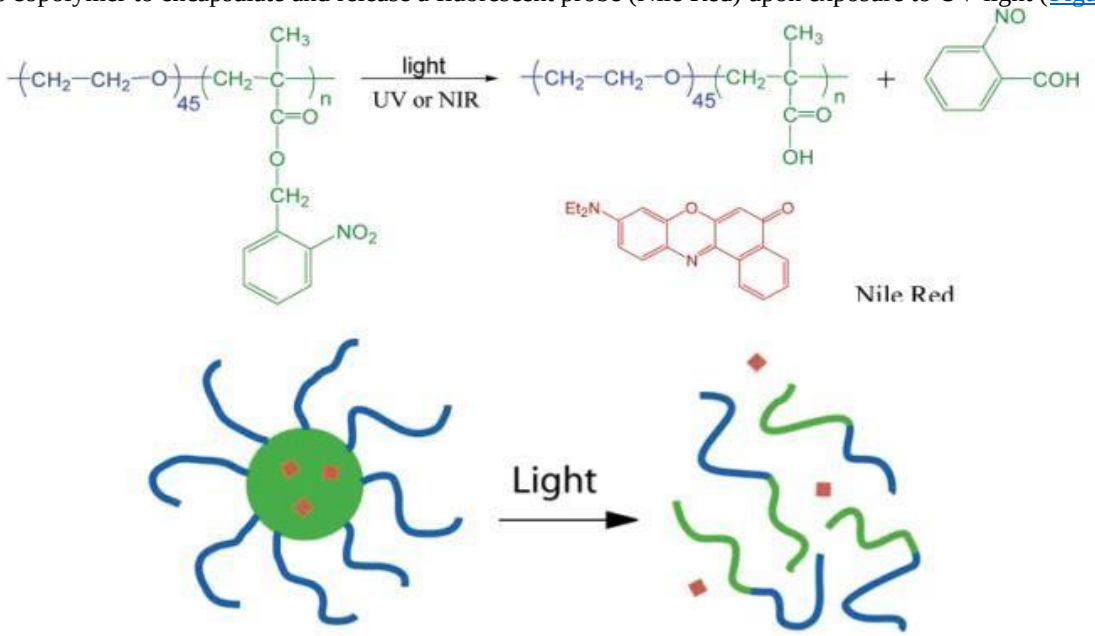

Figure 24: (a) Irradiation of a PEO-b-PNBM copolymer (b) Schematic representation of the destruction of a micelle and release of an active ingredient under the effect of irradiation

The photoresponsive behaviour of nanovectors can be demonstrated through several characterization processes. For instance, Liu et al. used scanning electron microscopy and dynamic light scattering to examine a copolymer, Poly(ethylene glycol)-b-poly(α-hydroxy acids)-g(o-nitrobenzyl) (mPEG-b-poly(Tyr)-g-NB), comprised of o-nitrobenzyl groups attached to its side chain. After UV irradiation, they observed a change in size and morphology of these micelles.

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Additionally, Nile Red was encapsulated to track its release through fluorescence measurements. Gohy et al. developed a poly (acrylate de dimethoxynitrobenzyl) -b-polystyrene copolymer that forms micelles in a organic solvent. Under UV irradiation and chloroform, the hydrophobic block of this copolymer transformed into a hydrophilic (poly(acrylic acid)) block, making it insoluble in the solvent and self-organizing into micelles.

(ii) Rupture of the bond between the hydrophobic block and the hydrophilic block of the Amphiphilic copolymer used

A single break in a copolymer can result in the separation of the hydrophobic and hydrophilic parts, or the release of a molecule bound to the copolymer. On the other hand, multiple breaks in the copolymer can lead to its degradation and destruction of the vector containing PA (Figure 25). Depending on the severity of the disruption, the damage may be reversible or irreversible.

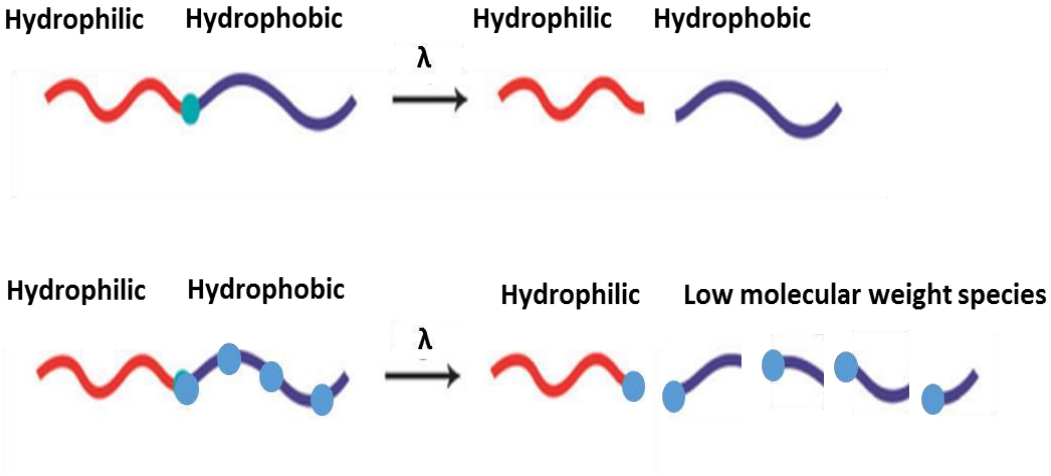

Figure 25: Schematic illustration (A) of the rupture of the bond between the hydrophobic block and the hydrophilic block, (B) of multiple fracture

- ***Reversible rupture of the bond between the hydrophobic block and the hydrophilic block:***

Recently, Yuan et al. have developed a photosensitive diblock copolymer system based on azobenzene and cyclodextrin. The polymer was synthesized by modifying the end of a poly(ε-caprolactone) chain with cyclodextrin, and a second poly(acrylic acid) chain with azobenzene. When exposed to visible light, the azobenzene present in its transhydrophobic form leads to the formation of an inclusion complex between azobenzene and cyclodextrin, thus creating a diblock copolymer. Under UV irradiation, the azobenzene reverts to its hydrophilic Cis form, which causes the dissolution of the complex, leading to the separation of the two blocks (Figure 26).

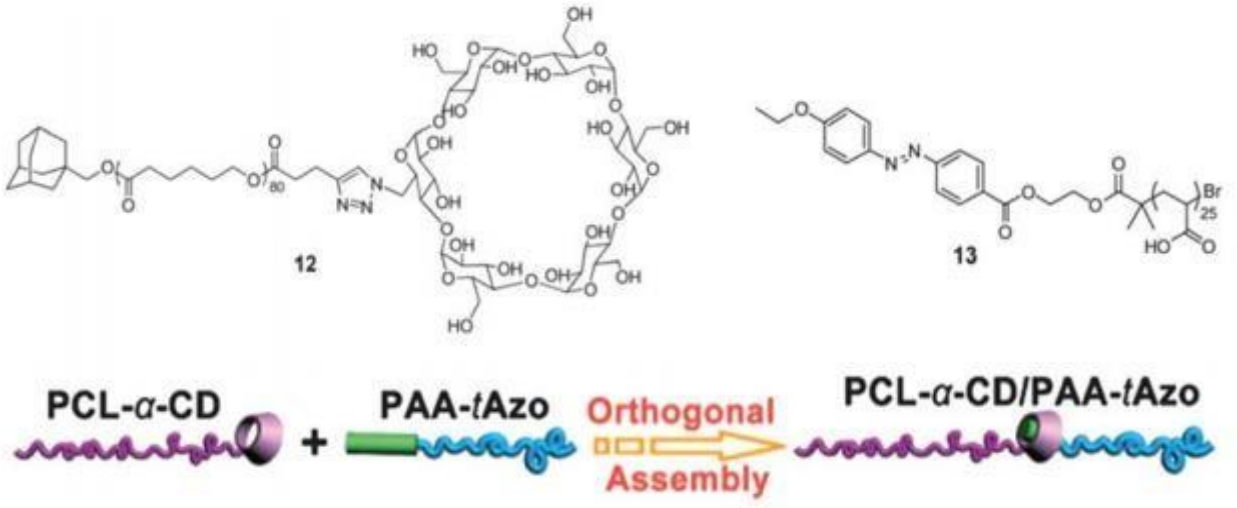

Figure 26: Supramolecular photosensitive assembly based on PCL-cyclodextrin and poly(acid acrylic)-azobenzene

- ***Irreversible rupture of the bond between the hydrophobic block and the hydrophilic block:***

In recent studies, the use of photosensitive bonds in amphiphilic copolymer systems has been explored in order to develop new photo-sensitive systems. These systems are characterized by an irreversible break between the hydrophobic and hydrophilic blocks of the copolymer, due to the insertion of a photosensitive group. Examples of such photosensitive groups include o-nitrobenzyl ester and derivatives of truxillic acid, as well as other compounds, as illustrated in Figure 27.

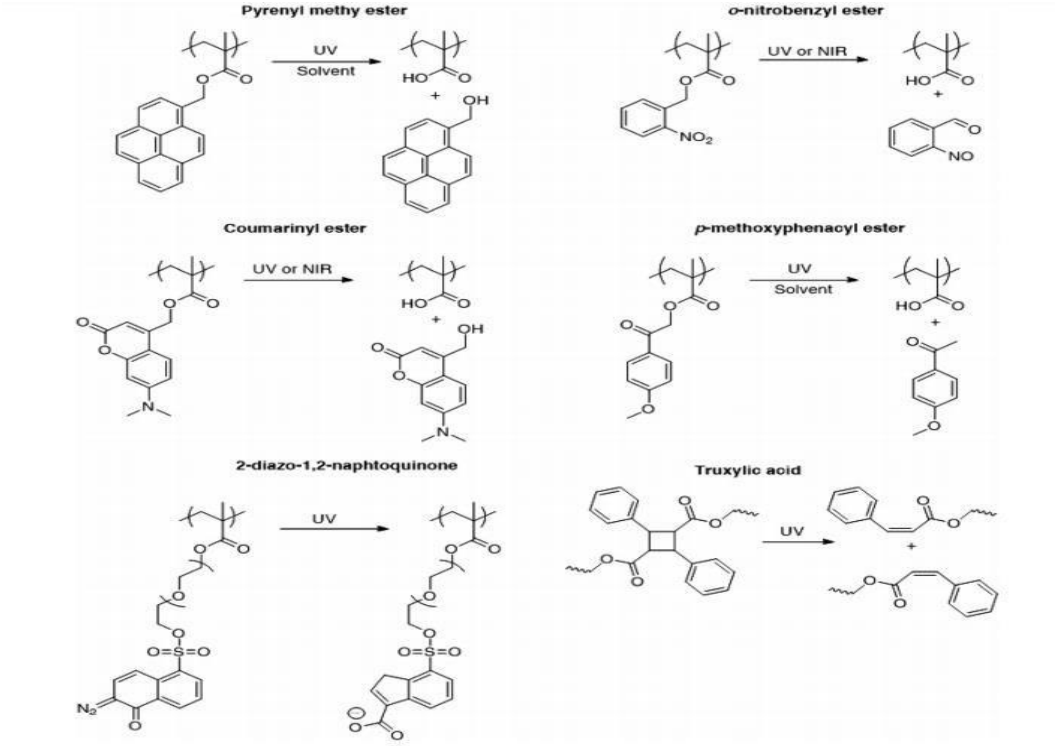

Figure 27: Different photosensitive groups used in the case of irreversible rupture of The junction between the hydrophobic and hydrophilic blocks

Moon et al. prepared a photosensitive film of a diblocPS-b-PEO copolymer in which the two blocks were connected by an o-nitrobenzyl photosensitive bond. Upon exposure to UV radiation, the o-nitrobenzyl bond was broken, forming an o-nitrosobenzaldehyde and a carboxylic acid, resulting in the separation of the copolymer (Figure 28) :

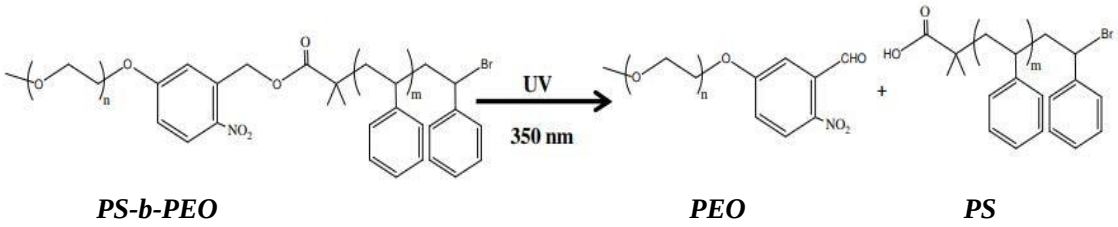

Figure 28: UV irradiation of the diblock copolymer Polystyrene-b-Poly(ethylene oxide)

Recent studies have shown that the destruction of micelles produced by self-organization of diblock copolymers can be achieved by incorporating chromophore groups between two hydrolyzable blocks. This was demonstrated by Cabane et al. who worked on a diblock copolymer, composed of a poly (methylε-caprolactone) hydrophobic block, substituted by a group of nitrobenzyl, and a poly (acrylic acid) hydrophilic block. After 60 minutes of irradiation with UV light at 365 nm, the micelles were completely destroyed, resulting in the formation of PCL aggregates and free PAA chains. Jiang et al. 40 also explored this approach by using a diblock copolymer containing a hydrophilic part (PEO) and a polymethacrylate hydrophobic part containing pyrene-based chromophore groups. Upon UV irradiation, the ester bond between each pyrene and acrylate group was broken, ultimately leading to the disintegration of the micelle. Additionally, Katz et al. have also investigated this phenomenon.Recently, researchers have explored the potential of biocompatible diblock copolymers based on poly(ε-caprolactone) and poly(ethylene oxide) to introduce a photo-labile junction (2-nitrophenylalanine) between the two blocks. Subsequently, biocytin-containing polymersomes have been prepared from these copolymers (Figure 29). Upon UV irradiation, the membrane of the initial bilayer of the polymerome is weakened, leading to a new organization of copolymer and the release of encapsulated biocytin. Similarly, Meier conducted investigations on the preparation of polymeric vesicles capable of encapsulating and releasing under irradiation active components such as proteins, enzymes or DNA.

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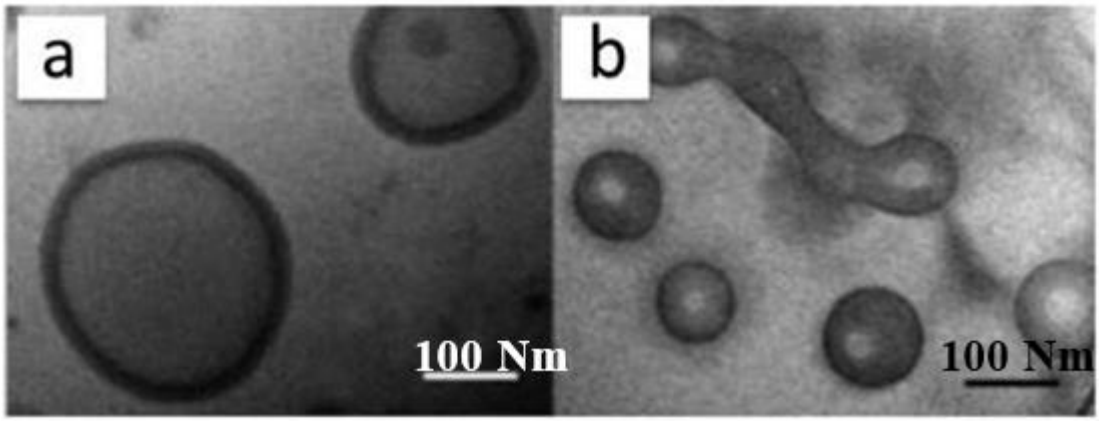

Figure 29: Cryo-MET images of PCL-b-PEO-based polymersomes whose blocks are bound by a 2-nitrophenylalanine bond (a) before and (b) after UV irradiation for 6 h

▪ ***Main chain degradation***

The design of this system is based on incorporating photosensitive groups within the hydrophobic block of amphiphilic copolymer. When exposed to UV light, this block of copolymer is broken down into small molecules, resulting in the destruction of vectors. Zhao et al. recently demonstrated that nanoparticles can be effectively destroyed if the photosensitive junction is distributed repeatedly within the hydrophobic block, but not when it only serves as a link between the hydrophilic and hydrophobic blocks of the copolymer (Figure 30).

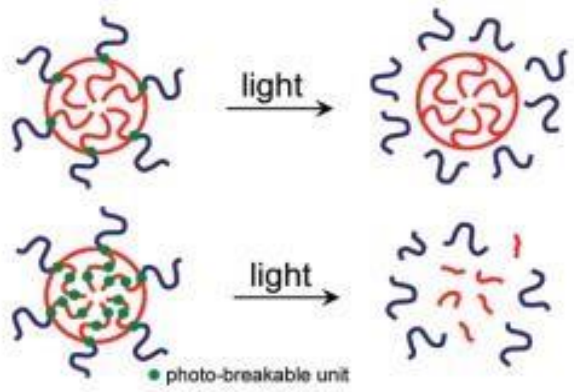

Figure 30 : Difference in irradiation sensitivity between particles with photosensitive junctions between the two blocks and particles with photosensitive groups placed in a repetitive manner in the hydrophobic block

Zhao et al. developed photodegradable micelles based on triblock copolymer PEO-b-PUNB-b-PEO, where PUNB is a hydrophobic block based on polyurethane containing photosensitive o-nitrobenzyl groups. Upon UV irradiation, the photosensitive groups are cleaved, resulting in the destruction of micelles. To demonstrate this, the authors encapsulated the molecule Nile Red within the micelles, and monitored its release. They also utilized steric exclusion chromatography (SEC) to assess the destruction of the amphiphilic copolymer, noting the disappearance of the high molar mass peak and the appearance of a low molar mass peak associated with the PEO block under UV irradiation.

(iii) Photo-crosslinking

Micelles are dynamic structures that can encapsulate an active ingredient (AI) but will disintegrate below a critical micellar concentration. To improve the stability of micellar structures and reduce the diffusion of APs once injected into the human body, scientists have developed cross-linked micelles. They can be cross-linked at the core or the crown by irradiation, although an excessive amount of cross-linking may decrease the release rate of the AI. To overcome this limitation, the concept of reversible photo-cross-linking of micelles was proposed. This technique has the advantage of not involving chemical reagents or creating any by-products, compared to the non-reversible counterpart.

▪ ***Reversible photo-crosslinking***

Reversible photo-crosslinking is a process in which micelles are formed with copolymers containing photosensitive groups that can undergo cycloaddition dimerization under visible light. Moreover, when exposed to UV radiation of wavelengths greater than 310 nm, the cycles formed can be broken down. The most extensively studied reaction of this kind is the cycloaddition photo-dimerization of coumarin groups. Additionally, when UV radiation of wavelengths below 260 nm is used, the pre-existing cyclobutane bridges can be destroyed.

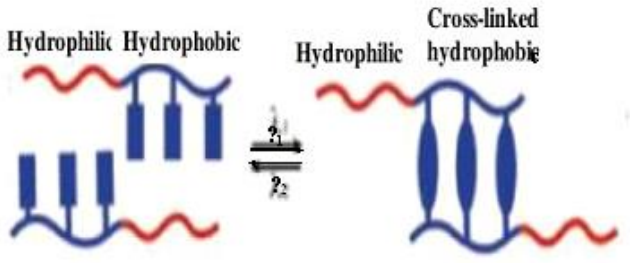

Figure 31: Schematic representation of a reversible photo-crosslinking of a copolymer dibloc

Zhao et al. employed a strategy to incorporate coumarin derivatives into block copolymers which stabilized the core or crown of micelles. This was accomplished using amphiphilic copolymers based on poly(ethylene oxide) and polymethacrylate, with hydrophobic blocks carrying coumarin side groups. When soluble in water, these copolymers self-assemble into micelles.

Upon photo-crosslinking through irradiation at wavelengths around 310 nm, the coumarin groups undergo a cycloaddition and create cross-links between multiple copolymer chains. These reticulations are capable of being broken down when irradiated at wavelengths beneath 260 nm. Nevertheless, and as stated before, the crosslinking of micelles limits the diffusion of molecules encapsulated within them, compared to non-crosslinked micelles(Figure 32).

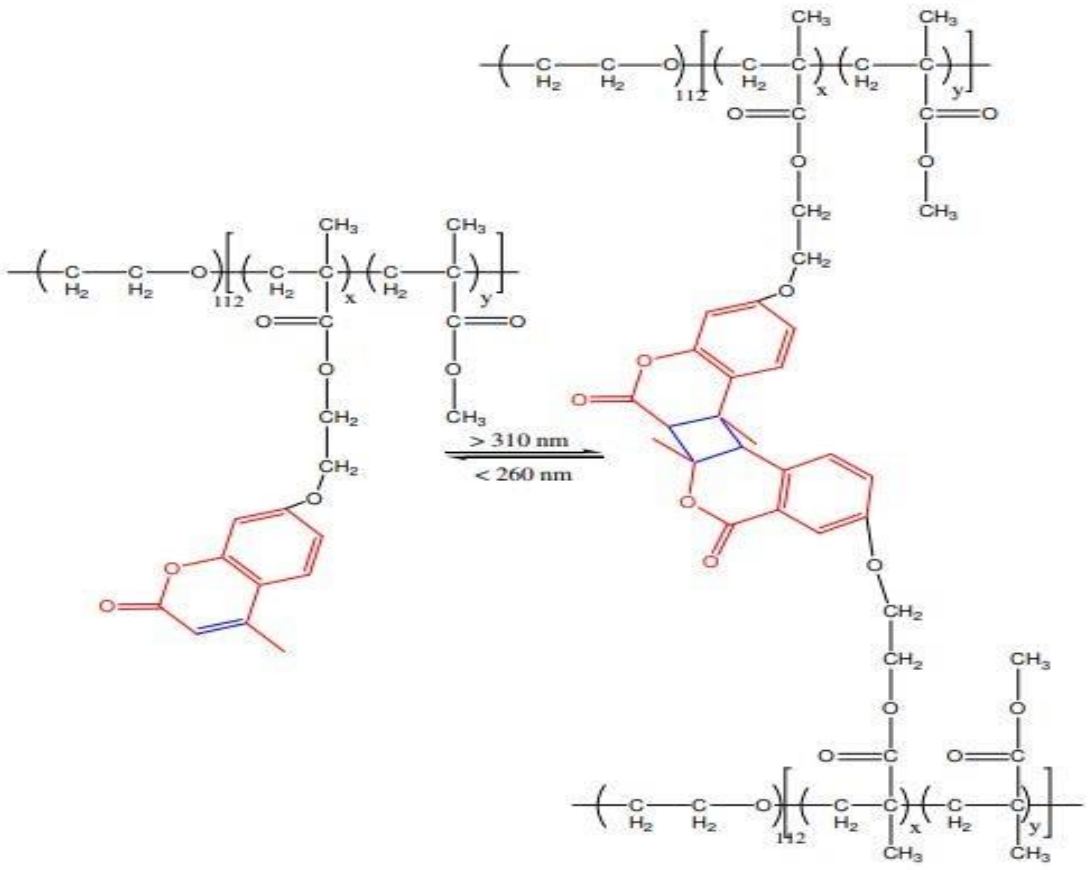

Figure 32: Reversible photo-crosslinking reaction of an amphiphilic copolymer via Coumarin groups

▪ ***Irreversible photo-cross-linking***

Liu et al. first reported the use of an irreversible photo-cross-linking technique to increase the stability of polymeric nanovesicles. The process involved the [2+2] photocycloaddition of cinnamic ester, which was used to self-organize diblocpolyisoprene-b-poly (2-cinnamyylethyl methacrylate) copolymers into vesicles in a hexane/THF mixture. Through the photo-cross-linking of the 2-cinnamylethylethyl methacrylate block, the researchers were able to generate more stable nano-objects (as depicted in Figure 33).

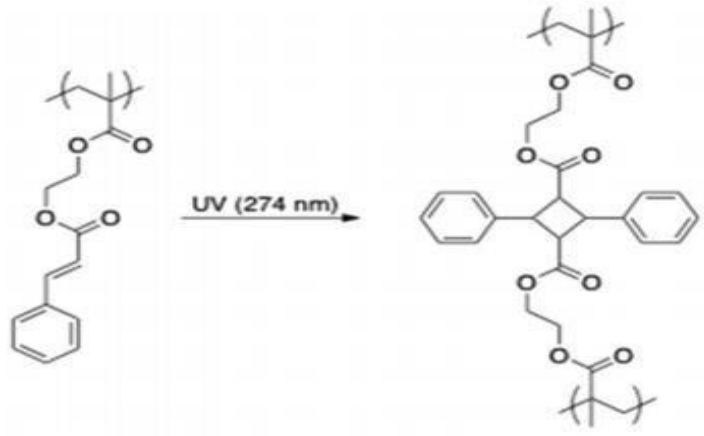

Figure 33: Photodimerization of the cinnamic ester

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Recently, cinnamic esters have been combined with irreversible photocrosslinking to create nanocapsules. Yusa et al. conducted a study on this subject. Another form of irreversible photocrosslinking, using o-nitrobenzyl groups, was studied by Liu et al. who synthesized copolymers composed of ethylene oxide and o-nitrobenzyloxycarbonylaminoethyl methacrylate (POE-b-PNBOC). Upon self-assembly of the copolymer, vesicles were produced. However, UV irradiation at pH 7.4 did not lead to destruction of the blister, but rather an increase in the hydrodynamic radius of the vesicles. This phenomenon was attributed to the primary amine produced by photocleavage reacting with the esters and inducing crosslinking through an amidation reaction (Figure 34).

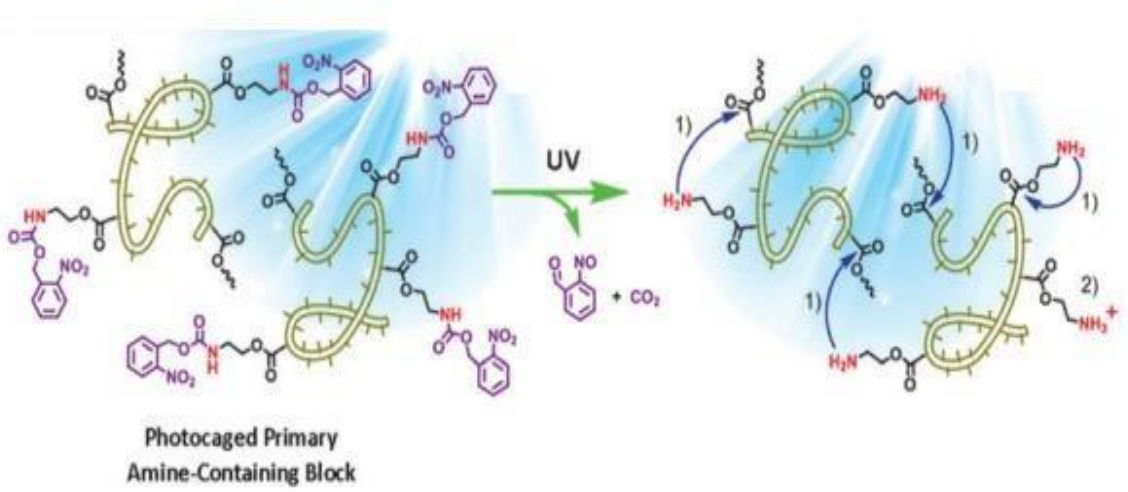

Figure 34: Irreversible photo-crosslinking of vesicles containing an o- carbamate nitrobenzyl

f) Multi-sensitive systems

The development of multi-sensitive nanovectors has enabled a wider range of applications for the vectorization of pharmaceutical agents (PAs). This new technology provides multiple triggers to precisely control the release of these agents, offering improved accuracy and reliability compared to conventional systems.

(i) Photo and temperature-sensitive systems

Jiang et al. investigated the development of temperature-sensitive micelles, comprising o-nitrobenzyl groups. To do so, they synthesized a diblock copolymer with a PEO block and a second thermosensitive block (ethoxytriacrylate (ethylene glycol)-o-nitrobenzyl co-acrylate). At temperatures above the LCST (25°C) of the thermosensitive block, the copolymer self-assembles into micelles. Under UV irradiation, the LCST of the copolymer increases to 36°C due to the transformation of the hydrophobic o-nitrobenzyl acrylate block into a hydrophilic acrylic acid block. In order to analyze the formation and degradation of photo-sensitive and heat-sensitive micelles, Nile Red, a fluorescent probe, was encapsulated in the core of the micelles. This probe is fluorescent in a hydrophobic medium and has a low fluorescence in an aqueous one. When exposed to UV radiation, the fluorescence of the micelles containing Nile Red sharply decreases, indicating the destruction of the micelles and the release of Nile Red. Additionally, an increase in the temperature of the medium leads to the reorganization of the formed PEO-b-poly (acrylic acid) copolymer, resulting in the re-encapsulation of Nile Red in the PEO/PAA micelles. To further study this phenomenon, Blasco et al. synthesized micelles from a star polymer composed of a photosensitive polymethacrylate modified with an azobenzene derivative (PAZO) and three thermosensitive poly (N, N-diethylacrylamide) arms (PDEAA) (LCST = 27 ° C). A study of these micelles performed by MET revealed that an increase in temperature up to 40 ° C caused the aggregation of the micelles, attributed to the polarity change of the micelles' crown (PDEAA), which became hydrophobic (Figure 35). These findings were further corroborated by DLS (Dynamic Light Scattering) that showed an increase in the size of the micelles from 31 nm to 53 nm when the temperature of the environment rose from 20 ° C (when the PDEAA crown is hydrophobic) to 40 ° C. Additionally, the researchers studied the photosensitivity of the micelles with the help of a UV lamp (9W) between 350 nm and 400 nm. During this process, a decrease in the π - π^* transition and an increase in absorbance at 450 nm, corresponding to the n- π^* transition, were observed, indicating photoisomerization of Azobenzene from the Trans to the Cis formAfter two minutes of irradiation, a photostationary state was reached and no further changes were observed in the UV-Visible spectra. The irradiated samples were then kept in the dark and, when analysed using UV-Visible after 24 hours, a reversible Cis-Trans isomerization was observed. Additionally, Nile Red was encapsulated in the core of the star polymers micelles during their self-assembly. At 40°C, the fluorescence intensity of Nile Red increased, confirming its successful encapsulation (Figure 35(b)). Conversely, a decrease in Nile Red fluorescence was observed at temperatures below the lower critical solution temperature (LCST) of the PDEAA (27°C), which was attributed to the decrease in micelle core hydrophobicity (Figure 35(a)). Lastly, upon irradiation, a decrease in the fluorescence intensity of the Nile Red was observed, due to the destruction of the micelles and subsequent release of the dye (Figure 35(c)).

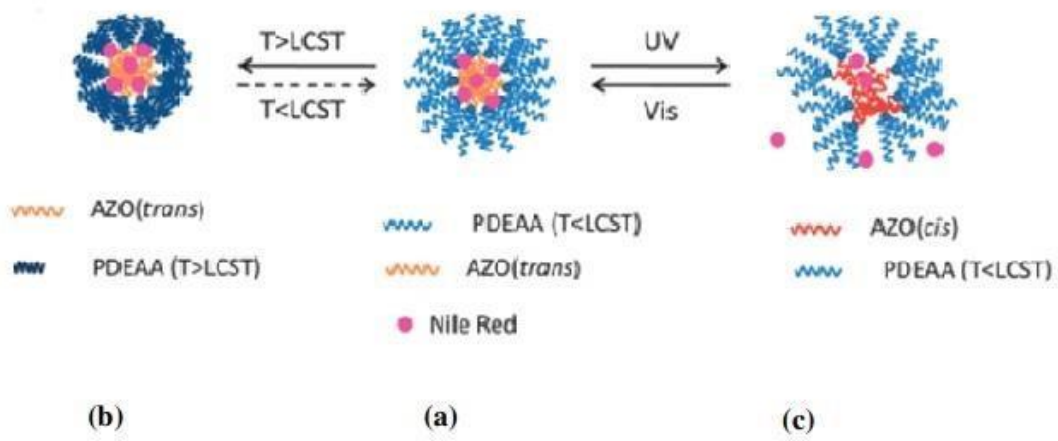

Figure 35: Schematic representation of the photo- and thermo-triggered release of the Nile Red at from Micelles

Recently, new thermo-photo-sensitive systems have been developed using crosslinked polymers such as poly (N-isopropylacrylamide-co-methyl methacrylate) , poly (ethylene glycol dimethacrylate) , and polyvinyl alcohol grafted with poly (N-isopropylacrylamide). These polymers can be used to fabricate stimuli-responsive hydrogels which have been shown to exhibit a range of properties in response to external stimuli such as light and heat. In the literature, other thermo- and photo-responsive systems have been described, such as triblock copolymer poly (TEGEA-co-NAB) -b PEO-b-poly (TEGEA-co-NAB) and triblock copolymer containing azobenzene groups and a poly block (N-isopropylacrylamide) . More recently, crosslinked polymers have been used to create stimuli-responsive hydrogels, such as poly (N-isopropylacrylamide-co-methyl methacrylate), poly (ethylene glycol dimethac

(ii) Photo and pH-sensitive systems

Meng et al. (2020) developed photo and pH-sensitive micelles for the transport and release of the anticancer drug Camptothecin. The micelles are formed through self-assembly of a chitosan-o-nitrobenzyl succinate glycol conjugate in water, and crosslinking of the crown chains is achieved through reaction of chitosan glycol and glutaraldehyde (Figure 36). The advantage of having pH-sensitive blocks in these micelles is particularly advantageous for treating infected cells due to their more acidic pH than that of healthy cells. Furthermore, UV irradiation of the micelles will result in their destruction and consequently rapid release of encapsulated PA.

Jin et al. have designed a poly (ethylene oxide) -b polymethacrylate copolymer of (2- (diethylamino) ethyl-co-6-methacrylate of (4-phenylazophenoxy) hexyl) [PEO-b-P (DEAEMA-co-PPHMA)], which can self-assemble into vesicles in an aqueous solution at pH 8. By decreasing the pH to 3, the vesicles transform into micelles. The same transformation can be induced by keeping the pH constant at 8, but by adding β-cyclodextrin to the medium. Additionally, when exposed to alternating UV and visible light in the presence of β-cyclodextrin, a reversible transition of micelles into vesicles occurs, due to the Trans-Cis transition of azobenzene groups (Figure 37).

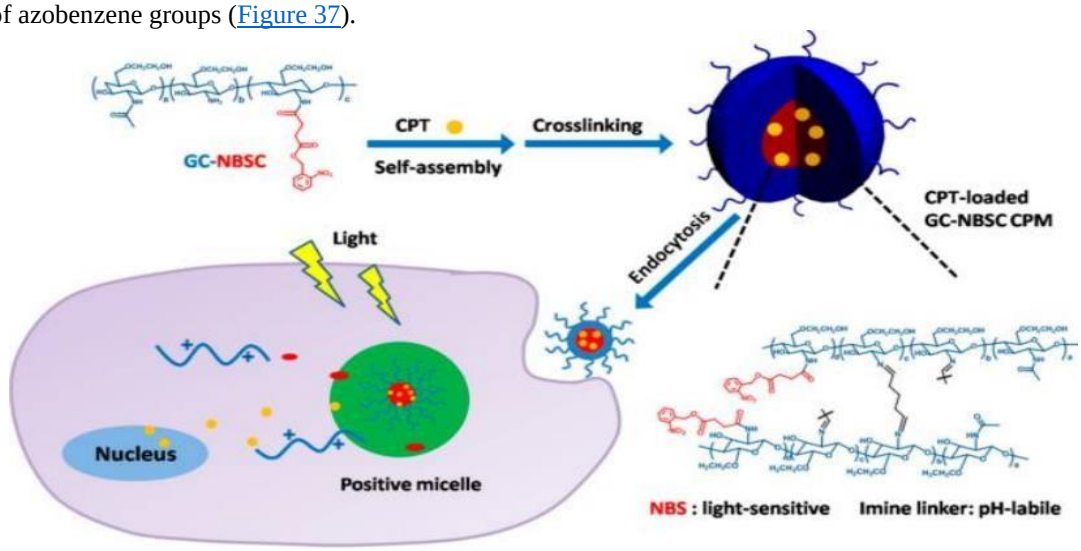

Figure 36: Preparation of photo- and pH-sensitive micelles containing camptothecin and Induced release of this PA

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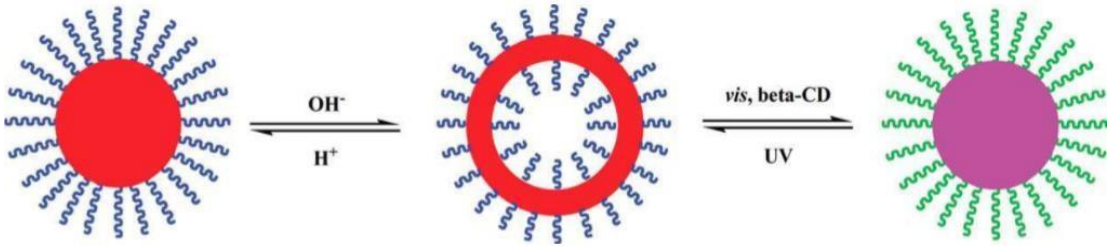

Figure 37: Schematic representation of reversible transitions from micelles to vesicles

Photo- and pH-sensitive systems have been the subject of several studies in the literature. Among the works we can mention the work carried out by Wei et al. and Lin et al. dealing with diblock copolymers consisting of a poly(ethylene oxide) hydrophilic block and a hydrophobic polymethacrylate block comprising photosensitive azopyridine groups.

VI. CONCLUSION

This article is dedicated to examining colorectal cancer and presenting the different treatment modalities currently offered to patients (surgery, chemotherapy, chemoradiotherapy, radiotherapy and targeted treatment). As an extension of this biological study, the development of nanocarriers for the vectorization of PA as an anticancer drug was presented. These systems are able to protect PA over time and space by selectively targeting a tissue or cell and controlling its release . These vectors have reduced the side effects of cancer treatment, reduced the amount of AP consumed, and increased their bioavailability . Although these carriers can have different morphologies depending on their chemical nature and structure (liposomes, micelles, nanocapsules, nanospheres, and dendrimers), NP polymers are an important topic of current research.These NPs can be prepared by different processes: (i) polymerization of monomers (interfacial polycondensation and polymerization in dispersed medium) or (ii) from preformed polymers (nanoprecipitation, evaporation of organic solvent emulsions, diffusion of organic solvent emulsions, emulsion/release). , emulsion/coacervation and dialysis).

DECLARATION

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Ethical Approval and Consent to Participate	No, the article does not require ethical approval and consent to participate with evidence.
Availability of Data and Material/ Data Access Statement	Not relevant.
Authors Contributions	All authors have equal participation in this article.

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AUTHOR PROFILE

Dr. Nasser Thallaj, Assistant professor PhD in Chemical Sciences, , Member of American Chemical Society (ACS) E-mails: nasserthallaj@gmail.com

2020- presente time: professor in the biomedical Science program.
2020- Present time: *Assistant professor* position. Faculty of pharma *alrashed university*, Damascus, syria
From 15 june 2019 – 31 July 2020: President Of *AlJazeera University*, Damascus, Syria.
From Abril 1st 2019 – 15jun: vice president for scientific affairs and Dean of Faculty of pharmacy AlJazeera University, Damascus, Syria.
From October 1st 2018-15 march 2020: Dean of Faculty of pharmacy *AlJazeera University*, Damascus, Syria.
2017-31 July2020: *Assistant professor* position. Faculty of pharmacy, *AlJazeera University*, Damascus, Syria
- 2015-2017: *Assistant professor* position. Faculty of pharmacy, *Syrian Private University*, Damascus, Syria
- 2015- 2016: Consultant in Ugarit Education Group: foundation of *AlManara University*.
- 2014-2015: vice president for scientific affairs (in charge), *University of Kalamoon*, Dier Attieh, Syria.
- 2014-2015: In charge of higher education affairs, *University of Kalamoon*, Dier Attieh, Syria.
- 2012-2014: Dean of Faculty of applied Sciences, *University of Kalamoon*. Dier Attieh, Syria.
- 2010-2013: Head of Department of Chemistry. Faculty of applied Sciences, *University of Kalamoon*. Dier Attieh, Syria
-2008: *Assistant professor* position. Faculty of applied Sciences, *University of Kalamoon*. Dier Attieh, Syria
2007-2008 : Post-Doctoral position. *Laboratory of NanoOrganic Chemistry, and Supramolecular Materials*, thesis title : *drug delivery system Department* of Chemistry. *University Notre Dame de la Paix*. Namur, Belgium.

Dania Hani ali Hamad, Undergraduate student . A student in the group of Prof. Dr. Nasser Thallaj in research for the graduation project, to obtain a license in pharmacy and pharmaceutical chemistry from the Faculty of Pharmacy at Al-Rasheed International University for Science and TechnologyE-mail : alhyatlhn107@gmail.com

Naseem Ahmad Batieh, Undergraduate student .A student in the group of Prof. Dr. Nasser Thallaj in research for the graduation project, to obtain a license in pharmacy and pharmaceutical chemistry from the Faculty of Pharmacy at Al-Rasheed International University for Science and Technology. E-mail : nasimbatia1820100@gmail.com

Gheed Ahmad saker, Undergraduate student. A student in the group of Prof. Dr. Nasser Thallaj in research for the graduation project, to obtain a license in pharmacy and pharmaceutical chemistry from the Faculty of Pharmacy at Al-Rasheed International University for Science and Technology.E-mail : gheedsaker.99@gmail.com