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Nanodevices for Facing New Challenges of Medical Treatments: Stimuli-Responsive Drug Delivery Systems

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ABSTRACT

The administration of therapeutic agents for the treatment of diseases without inclusion in a pharmaceutical formulation has been rarely reported in the current literature. In this condition, drugs show poor biodistribution profiles, a lack of predictable therapeutic response, and possible toxicity. For overcoming this issue, delivery systems were developed to carry, release drugs that finally interact with target sites with accuracy. The advent of nanotechnology has encouraged the improvement of these devices for facing new challenges of medical treatments. Therefore, pharmaceutical formulations have evolved from dissolutions and powders towards nanosized-smart drug delivery systems. Consequently, in this review, they are shown the main applications of nanotechnology on the design and development of drug delivery devices such as niosomes, liposomes, lipid-based nanoparticles, polymeric micelles, polymer-based devices, liquid crystals-based systems, and nanocomposites; and their capability for responding to different external and/or internal stimuli and thus release their content in the specific site. Owing to the progress in drug (or another therapeutic agent) delivery system and those applied to the imaging diagnostics, a new subarea known as theranostic, have been launched. This strategy combines the diagnosis of diseases and their treatment in a one-step procedure through the application of external stimuli to a formulation that once administrated to the body can release their content for treating and also for following the progress of the disease. For that reason, theranostic therapy has also described in this text as another example of the evolution of formulations based on nanodevices.

Keywords: Nanotechnology based devices, stimuli-responsive systems, theranostic therapy.

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INTRODUCTION

The manipulation of nano-scale materials has led to humans to overcome big challenges and from its application to technology has emerged the nanotechnology. As a consequence of that, nanotechnology has changed the whole vision of how science is studied, taught and applied due to that the properties of materials such as melting point or chemical reactivity changes as a function of the size of the particle(1). The vision of nanotechnology begun in 1959 with the talk of Richard Feynman "There's Plenty of Room at the Bottom" at the annual meeting of the American Physical Society(2) but its definition was established in the United States at beginning of the 2000s(3). The National Nanotechnology Initiative has accepted a single definition that incorporates "nano" to words, science, and technology: "Nanotechnology is the understanding and control of matter at dimensions between approximately 1 to 100 nanometers. After that, another associated term has emerged, "nanomedicine". This term was established and has been used in specialized literature after the publication of the book of R. A. Freitas in 1999 named "Nanomedicine, Volume I: Basic Capabilities"(4). This book is an extensive description of how is possible the molecular manufacturing, the design of sensors at the nanoscale, and nanorobots (such as respirocite) which could be used for improving the health of human beings. Thus, nanoscience contributes to the improvement of technological devices in different areas from many years ago and at least, during many others.

One of the major areas where nanotechnology has focused on is pharmaceutical sciences; mainly, into the development of new formulations and devices for drug delivery. In this sense, any active component needs a formulation to be carried to the target site. There are very few references describing the administration of drugs without a dosage form. Formulations protect these compounds to degradation, improve their solubilization and decrease their toxicity. Pharmaceutical formulations have significantly evolved, but one of the major jumps in their evolution was due to the advent of nanotechnology. Thanks to this technology the pristine pharmaceutical formulations have become drug nano-carriers that have improved the effectiveness and accuracy in the diagnosis and treatments of diseases(5,6). These dosage forms have reached to be smart drug nano-carriers; and consequently, they can control the release of their content in the target site and decreasing the drug toxicity because they improve the cellular uptake of drugs with poor biodistribution profiles, offering considerable advantages over conventional therapies devices(7). The geometry and size of nanometric devices are one of their strengthening because they improve the efficiency of drug delivery more than the formulations formed by larger particles than 1000 nm (8).

The release of the content of a dosage form can be carried out by means of different strategies. Oral formulations are designed to be disintegrated depending on the different conditions of the gastrointestinal tract and the absorption of the drug is mainly produced at intestine(9). Values of pH play an important role both in the lumen of organs and inside the cells. Each tissue has its own pH values and additionally, healthy cells have different pH values than ill cells. In this context, cancer cells have a lower pH value than non-cancer cells of the same organ and this difference can be used as for targeting a drug against this diseased tissue(10). As a consequence of that, pH variation is the key to designing and developing stimuli-responsive carriers, however, it is not easy to achieve the pH-responsive based controllability owing to the complex biological environment. Nanometric-sized

carriers including for instance liposomes, micelles or polymer devices, have been designed and developed for improving the efficacy and decrease the toxicity of therapeutic agents; and in addition, their efficiency can be improved because they can be designed with stimuli-responsive properties. Therefore, in this review, we will provide a rational classification of these different devices and also their evolution along the time for becoming in smart drug delivery systems based on nanotechnology.

Thus, the review is divided into two main sections: the first section, nanodevices responding to internal stimuli for the treatment of diseases; and the second section, nanodevices responding to external stimuli for diagnostic and treatment (theranostic therapy). Therefore, within the first section, have been described drug delivery systems based on polymers (alginate, cyclodextrins, poly-co–glycolic lactic acid, chitosan and gelatin); surfactants as blocks of nano-assembly systems (liposomes, niosomes, micelles, liquid crystals-based systems); nanocomposites; and lipid-based nanoparticles (solid lipid nanoparticles and nanostructured lipids). Additionally, we will show some strategies for improving those devices and how they can be turned into internal-stimuli response systems. Additionally, it is important to remark that some of the pharmaceutical formulations addressed in this text have been approved by the health authorities and others are based on approved excipients but without the approbation of the formulation. The aim of this work is to show an overview of the present and possible future of (some) relevant formulations with nanometric size for the treating of different diseases. In the second section, theranostic therapy concepts will be displayed. Here, we will show how external stimuli such as magnetic fields, light, and ultrasound can be used for generating the release of a drug or a contrast agent from a specific nanoformulation and accordingly, it can be used jointly as an image diagnosis device and therapeutic.

In **figure 1**, a generic drug delivery system stimulus-responsive is shown. In this case, a lamellar liquid crystal-loaded with a lipophilic drug is shown as a model, and such as we will address in the text, an internal (pH variation) or external (light, ultrasound or magnetic fields) stimulus can be used to exert the release the drug from the formulation.

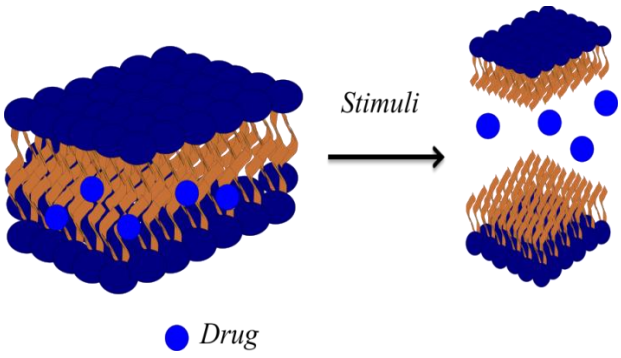

Figure 1: scheme of drug delivery system releasing the drug by application of stimuli.

DRUG DELIVERY SYSTEMS RESPONDING TO INTERNAL STIMULI BASED ON NANOTECHNOLOGY

The development of different pharmaceutical devices for ensuring the delivery of therapeutic agents to different target organs or tissues has been a challenge that scientists have taken for improving our health. Along this path, formulations have evolved, keeping their basic premises: improving efficacy, decreasing side and toxic effects(11). Therefore, this evolution of pharmaceutical formulations leads our attention to the application of nanoscience to this field.

Polymers for developing nanodevices

Synthetic, semi-synthetic, and also natural polymers have increased their relevance in the development of pharmaceutical formulations due to their vast possibilities of application in this field. The use of polymers in formulations is mainly conditioned by their biocompatibility, degradation (during the storage and into the body), and immunogenicity; and these own features of polymers can develop an important drawback in sensitive patients. There is another problem associated with these macromolecules, the lack of suitable mechanical properties; and for this reason, sometimes; they must be associated with other molecules or particles for generating crosslinked structures with certain applicability.

Based on polymers, supramolecular structures have been developed for delivering different active compounds from simple drugs to genes or macromolecules. Hydrogels are supramolecular arrangements formed by a type of biomaterial consisting of a solid three-dimensional network linked through non-covalent bonds, such as a hydrogen bond, hydrophobic interaction, and cation-π and π-π interactions(12). They can be designed for responding to a diversity of physical, chemical and biological stimuli; and hold enormous potential for developing drug-delivery systems. These stimuli can be coming from external sources such as light or internal when pH variation among tissues is produced or in illness states. Drug delivery systems based on polymers could be used as carriers for therapeutic agents as well as the scaffolds for bone, cartilage, cardiac, skin and tissue engineering and can be applied for the treatment of different pathologies such as cancer, diabetes, certain types of allergy, infection, and inflammation states(13). In this sub-section, we will focus on five types of biocompatible polymers widely used for developing nano-sized devices with a potential application on future pharmaceutical devices which respond to internal stimuli such as pH. The polymers included in this subsection alginate, cyclodextrins, polylactic acid (and its derivatives), chitosan and gelatin.

Alginate

Alginate is widely used polymer because of its water-solubility, biodegradability, thickening effect in certain conditions, and with the capability of forming hydrogels in situ. Additionally, after its degradation, non-toxic sub-products are evidenced. It holds high biocompatibility and shows good performance in cell bio-adhesion. In this context, it has been demonstrated that alginate-based composites are suitable for growing of osteoblasts and fibroblasts for improving periosteal regeneration(14). This polymer can also be used in composites combined with an inorganic matrix which would be suitable for developing drug delivery systems and additionally for filling large bone defects(15). Alginate holds a remarkable feature; it is a pH-sensitive polymer by itself. This behavior is due to the different tridimensional arrangements showed by

the polymer when the environment pH is modified and it is combined with divalent cations(16). The capacity of alginate-based devices to respond to environment pH modifications constitutes an appreciable advantage over to other biopolymers with need chemical modifications to reach this property and this feature can be exposed when it is combined with other structures, such as ceramics(15), octadecyltrichlorosilane(17) or it is applied alone. For example, natural cyclodextrins must be chemically modified and additionally be included in nanoparticles for obtaining a pH-responsive nano-sized structure such as was reported by He et al(18).

Alginates are polysaccharides obtained from cell walls of different species of brown algae (natural sources). They allow significant variation of materials properties depending on the proportion of polysaccharides in their constitution(19).These anionic hetero-polysaccharides (the anionic character is provided by carboxylate groups) are composed of the α-L-guluronic acid (G) (pKa = 3.65) and the β-D-mannuronic acid (M) (pKa =3.38), both linked by a (1→4)-β bond(20) and the proportion of these segments results on variability in their physical properties(21).Typically, the concentration of alginate in aqueous solutions applied to formulations is between 1 and 2% w/v, and their viscosity of gels formed may vary influenced by its concentration, pH, temperature, and the presence of ions. As an example, their viscosity decreases above pH 10(22).

Several formulations were developed with this polymer but the most highlighted are hydrogels and nanoparticles. The relevant feature of these hydrogels is their adhesion to mucosal tissues such as buccal(23), ophthalmic(24), esophageal(25), and vaginal(26) ones. Alginate hydrogels have suitable properties for carrying sensitive hydrophilic active compounds such as proteins and peptides; among them immunoglobulin G (antibodies)(27), fibrinogen(28), insulin(29,30), melatonin(31), heparin(32,33), bone growth factors(34) and among others. On the other hand, the development of nanoparticles based on alginate (alone or combined with other polymers) for delivering drugs have resulted in a convenient strategy and an alternative to hydrogels. However, as in other nano-systems, alginate nanoparticles must be coated with other more hydrophilic polymers to do not capture by the mononuclear phagocytic system of the liver and spleen. Thus, alginate nanoparticles have been used for applying by different administration routes intravenous, ocular, pulmonary and others(35) and they have been used for drug delivery of antibiotics as vancomicyn(36), DNA(37), and anticancer drugs such as doxorrubicin(38).

Owing to their sensitivity to environmental variation of pH, pH-sensitive sodium alginate hydrogels grafted with polyglycidyl methacrylate are developed as a drug delivery matrix for riboflavin controlled release(39). Using this strategy, Abd El-Ghaffar et al have reported an increase of encapsulation efficiency of riboflavin and its release is controlled by the degree of polyglycidyl methacrylate grafted. In this context, another pH-sensitive drug delivery system, a composite material, has been designed by means of an in-situ formed hydrogel based on alginate and a calcium phosphate mineral matrix, brushite(40).This composite was actively loaded with ibuprofen during the crosslinking process between brushite and alginate. The crosslinking process has avoided the abrupt release of ibuprofen from the composite materials and as an opposed fact, an uncontrolled release of this drug is shown form conventional beads. However, the encapsulation efficiency of this composite material was exceeded by conventional beads. A similar composite material based on alginate and nano-sized hydroxyapatite has been designed by Benedini et al(15). These authors describe the formation of liquid crystals with different birefringence depending on environmental pH variations. At low pH (4.2) a higher birefringence was shown than high pH (7.4); and hence, better physical properties. However, at pH 6 no birefringence appears. Therefore, these systems could behave as a controlled delivery system for drugs due to the formation of different liquid crystals depending on the pH of their surroundings. All these foregoing systems show an encouraging alternative as drug delivery systems because they use the capability of alginate to modify the tridimensional structure when pH is changing and by this behavior modify the release profile of drugs or mechanical properties of the composites materials formed.

Cyclodextrins

Cyclodextrins (CDs) are synthetic and biocompatible cyclic hygroscopic oligosaccharides derived from starch which are formed by at least six D-(+)- glucopyranose units attached by α (1→4) glucoside bonds(22). Cyclodextrins show a truncated cone structure. They have hydrophilic out surfaces (hydroxyl groups of glucose) and lipophilic interior cavities (methylene groups); hence, by this condition, they are capable of interacting with a large variety of active molecules by forming non-covalent inclusion complexes, by working as solubilizing agents for poorly soluble drugs. These molecules are classified by their molecular weight and the size of their cavities from α to δ; and β-cyclodextrins are the most used(20). The smallest, α- cyclodextrin, has a cavity of 0.5 nm of diameter and a 1.3 nm of the total diameter. Additionally to natural cyclodextrins, around 1500 derivatives have been synthetized, hydroxyethyl, hydroxypropyl-, sulfobutylether-, and methyl-β-cyclodextrins among others(41). Cyclodextrins-based formulations have been developed to be applied in several administration routes. Those taken orally, such as tablets, have not shown any type of toxicity because their absorption in the gastrointestinal tract is negligible. Accordingly, these solubilizing agents are present in many types of formulations such as drop eyes(42,43), parenteral(44), rectal(45), and different solutions for carrying a wide variety of drugs (corticosteroids(42), anticancer-drugs(46), and others). In this context, Cameiro et al(47) have provided a detailed analysis of the biological performance of different drugs complexed with cyclodextrins and they have been described vitro and in vivo studies of those complexed and their bioactive efficacy. Additionally, they have shown that β-cyclodextrin (and some derivatives) is the main studied cyclodextrin which has been complexed with: albendazole, valdecoxib, meloxicam, amlodipine, limonene, and other essential oils. For this reason, the importance of cyclodextrins is based on that they can be administrated by different routes because of their safety and because they can be proposed as carriers for many types of drugs.

Cyclodextrins have shown some relevant properties in addition to their inherent feature as nanometric reservoir used for improving drug bioavailability. They can enhance the absorption through the membrane of cells and also, they can

stabilize biomolecules in physiological media by shielding them by means of non-specific interactions. Their interaction with biological membranes of cells produces the destabilization and permeabilization of molecules interacting cyclodextrins, affecting cell lipid distribution and cell signaling. For these reasons, cyclodextrins can improve the efficiency of gene delivery systems when they are added to the formulation(48,49). In this context, it has been demonstrated that the addition of a cyclodextrins solution to DNA-lipid formulation for the expression of a rat lung gene has increased 6-folds its expression. This effect of cyclodextrins to gene delivery systems has been also observed for viral vectors(50). The possibility to replace viral vectors for non-viral is an important step in gene therapy because the non-viral vector has been demonstrated to have improved the therapeutic perspectives compare to viral ones based on that they show less adverse effects (51).

Cyclodextrins and polymers can interact by forming supramolecular assembled structures. Owing to their ring shape, cyclodextrins have the ability to be threaded by certain polymer regions, either through its main-chain or lateral or side-chain, just like a thread goes through the eyelet of a needle(52). These systems have been loaded with cationic polymers for carrying plasmid genes; however, non-ionic surfactants can also be used. Due to their biocompatibility and rheological properties once injected, the system is diluted by the plasma and released genes are incorporated into cells by endocytosis(53). In this context, Davis et al(54) have reported the development of supramolecular complexes between cyclodextrins and siRNA linked by cationic oligomers for melanoma treatment. Thus, cyclodextrins can be used in combination with other molecules for developing a suitable carrier for very sensitive hydrophilic molecules such as DNA or RNA.

When stimuli-responsive systems based on cyclodextrins are designed, it must be taken into account some points for obtaining an accurate drug release. On the one hand, the changes in the properties of the drug that make guest molecules escape from the interior of cyclodextrins; and, on the other hand, the changes in physical-chemical properties of other materials of the carrier system(55). Therefore, a pH-sensitive device based on cyclodextrins can be designed in response to pH environmental variations. These types of systems use a passive-targeting strategy for reaching their target site. Meng et al(56) have developed a pH-sensitive anticancer device based cyclodextrins combined with polylactide for delivering doxorubicin dissolved in micelles. Another work also reports the use of doxorubicin, as an anticancer drug, combined to a plasmid gene into a supramolecular inclusion considered to be a high-efficiency drug-gene co-delivery system. In this context, Zhou et al.(57) have reported the synthesis of the co-delivery carrier based on oligoethylenimine-conjugated β-cyclodextrin and benzimidazole-modified 4-arms-polycaprolactone hyper-branched polyglycerol by forming a pH-mediated inclusion-complex between cyclodextrin and benzimidazole. The system showed the improved drug and gene delivery ability in vivo, and their cellular uptake and intracellular delivery. In this context, it has been demonstrated by in vivo studies that cyclodextrins have shown good performance for the proposed therapies and also show the versatility for carrying lipophilic and hydrophilic drugs with different approaches form drug delivery to transfection of genes including pH response capability.

Poly-co-glycolic lactic acid

During many years, poly-lactic acid has been applied to the development of nanoparticles for drug delivery systems through different methods: solvent diffusion, solvent evaporation, and salting-out method and solvent displacement(58). However, it has been displaced by poly-co-glycolic lactic acid, for the development of some formulations, due to that the first has shown low drug-loading capacity, low encapsulation efficiency, and terminal sterilization(59).

Poly-co-glycolic lactic acid is synthetic and relatively hydrophobic co-polymer molecule(60) formed by D and L poly-lactic acid and poly-glycolic acid where D- and L- lactic acid forms are in equal ratio(61).This polymer has become rapidly into a suitable molecule for developing drug delivery systems due to their excellent properties: lack of toxicity, biocompatibility, and biodegradability(62).Additionally, it has come for replacing petrochemical plastics, and for this reason, it is considered as renewable substance(63). Its physical-chemistry properties must be considered for design a better-controlled release system. This polymer has a glass transition temperature generally above 37°C, but it decreases with the lactide content in the co-polymer(64). In this context, poly-co-glycolic lactic acid has also been modified by co-polymerized with poly-ethylene-glycol (PEG) for adapting its properties to different routes of administration, methods of preparation, and types of loaded drugs through the formation of di or tri-blocks(65,66).

Therefore, today, poly-co-glycolic lactic acid is used to formulate different systems for carrying a variety of drug from peptides and proteins such as leuprolide acetate, a luteinizing hormone-releasing hormone (LH-RH) agonist(67) to simple drugs such as sotalol (antiarrhythmic)(68) or salbutamol (bronchodilator)(69). Different types of biodegradable carriers to be applied by the intravenous route have been developed by using this polymer such as microparticles (microspheres, microcapsules), and nanoparticles (nanocapsules and nanospheres. It is important to remark that, as another possible administration route, both types of particles can be also implanted in the illness site. There are many techniques for preparing the first group: phase separation, solvent evaporation (or extraction) method and spray drying; and for preparing nanoparticles, the most common method used is emulsification-solvent-evaporation(61); however, they can be prepared by same methods than microparticles but the manufacturing parameters must be adjusted to reach to nano-size(70). Due to this text is addressed to nanosized systems, microparticles have not been discussed here. Owing to that the biodegradation of the polymer is produced by hydrolysis in aqueous media, pH values of its surroundings play an important role. High acid or alkaline pHs can increase its biodegradation(71) and; consequently, the kinetics of the release of the drug is increased and in extreme cases, lack of behavior as a drug release controlled system.

Additionally, both types of particles can be combined with other systems for highlighting some desirable features. Thus, Berg et al(72) have reported a stimuli-responsive formulation for treating periodontitis disease. In that work, nanoparticles based on poly-co-glycolic-lactic acid have been loaded with moxifloxacin and then included in a sol-gel internal-stimuli

responsive system. This device has shown an excellent drug release profile and a confined release in the periodontitis site.

Nanoparticles based on Poly-co-glycolic lactic acid are used not only for delivering drugs but also they are used to present antigens with adjuvants of vaccines and other immune-enhancing agents such as polysaccharides(73). In this context, Xu et al.(74) have reported the development of nanoparticles of poly(lactic-co-glycolic acid) as a formulation for improving the bioavailability of the immune-boosters, Astragalus polysaccharides. Additionally, this system has been carried out with ammonium bicarbonate to produce pH-responsive behavior. This device has shown low cytotoxicity and significantly enhanced mice splenic lymphocyte proliferation (CD4 and CD8) and consequently, its excellent immune-adjuvanticity has been demonstrated. The highest release of the adjuvant was observed at low pH (4.5) as a consequence of that, its release toward intracellular targets have been carried out more quickly.

Summarizing, poly(lactic-co-glycolic acid) based systems can be developed for delivering different types of active agents (including very sensitive as proteins) such as drugs for the treatment of diseases and also for preventing diseases when they are used as vehicles of vaccines. In both systems, the response to pH variations can be considered for improving the bioavailability of the active compound carried.

Chitosan

Chitosan is a natural cationic biopolymer formed by randomly distributed β-(1→4)-linked-N-acetyl-D-glucosamine and D-glucosamine which is obtaining from the partial deacetylation of chitin(22). The water solubility behavior of this polymer depends on the degree of deacetylation and pka; hence, it needs a deacetylation degree around 85% and pH value of the solution of 6.5 for dissolving in water. Additionally, its viscosity increase with an increase of the deacetylation degree and; on the other hand, by a rise of the ionic strength of the medium decreases the solubility of chitosan in aqueous solutions(75). Chitosan is a biodegradable, biocompatible and low-toxic polymer approved for wound dressing applications and is considered safe for human dietary use(76). Due to these mentioned properties and versatility it has been applied for developing formulations, it has been used in rapid release and also as a controlled drug delivery system, in mucoadhesive dosage forms, for improving peptide and gene delivery; administrated by different routes(22,77).

Chitosan has been modified for improving its properties for use in biomedical field. For this aim, the main modifications are N-acylation, N-alkylation, O-alkylation, and oxidation-Schiff base reaction(5). Additionally, this polymer can be formulated in nanoparticles and in this context, specific molecules can be anchored to the surface of nanoparticles for developing a targeting behavior against certain objectives(78) and stimuli-responsive systems such as those pH-sensitive drug delivery systems(5). Therefore, as an example of a combination of chemical modification and active targeting, we found N-tri-methyl chitosan nanoparticles for oral administration loaded with the nucleotide analog, gemcitabine, for treating the breast cancer. The peptide CSKSSDYQC was anchored to the surface of the nanoparticles as an active targeting strategy. This formulation has improved 60% of the biodistribution of the therapeutic agent with a decrease of 3 to 5 folds of the tumor in mice models(79).

Nanoparticles based on chitosan have shown many applications in non-parenteral drug delivery additionally to the treatment of cancer such as gastrointestinal diseases, pulmonary diseases, drug delivery to the brain, and also ocular infections(76). Another promising device for delivering an anticancer drug-loaded onto pH-responsive nanoparticles of chitosan was proposed by Vivek et al(80). In this system, tamoxifen is released from the device much more rapidly at pH 4.0 and 6.0 than at pH 7.4. This is a desirable feature for tumor-targeted drug delivery; due to that tumors have lower pH than normal tissues. In this work it has been demonstrated, that tamoxifen-loaded nanoparticles have induced remarkable improvement in anticancer activity against human breast cancer MCF-7 cells, and therefore have induced apoptosis in a caspase-dependent manner, indicating that drug-loaded nanoparticles work efficiently.

Cui et al(81) have reported the development of pH-sensitive nanoparticles of carboxylated tri-methyl chitosan grafted with poly(methyl methacrylate) for oral delivery of insulin. The system has shown low release of insulin at low pH, but its release is higher when pH is increased above 6 in mice models.

Additionally, Barbosa et al(82) have also reported another pH-sensitive system based on chitosan for oral delivery of quercetin as a functional food. In this work, through the polyelectrolytic self-assembly method, fucoidan-chitosan polymeric nanoparticles were carried out. Three parts of fucoidan per a part of chitosan have been necessary to achieve suitable stability of the formulation, the pH-sensitivity, and an appropriated release of the antioxidant after oral administration. With this ratio (fucoidan-chitosan) there is a low release at low pH which is increased when pH is increased and due to that fact, the antioxidant properties of quercetin are conserved.

Gelatin

Gelatin (as a generic term) is a biodegradable, hydrophilic, biocompatible, and non-toxic polymer, which is obtained by controlled hydrolysis of proteins and collagen, which are the major components of skin, bones, and connective tissue of cattle and pigs. Due to its versatility has been widely used in the pharmaceutical industry for carrying active principles in different pharmaceutical dosage forms such as biodegradable matrixes, implantable delivery systems, and the most common formulation, capsules(22). With the advent of nanotechnology and due to its properties, it can serve as a candidate for the preparation of colloidal drug delivery systems such as nanoparticles(83).

The main types of gelatin found commercially are named type A and B. Both are obtaining from collagen but the first is obtained under treatment with acid while second, is obtained by alkaline treatment(20). Gelatin has a triple helical structure which is defined by its high content of the amino acids' glycine, proline (mainly as hydroxyproline), and alanine. Pharmaceutical formulations based on gelatin have some stability drawbacks related to increased temperature and moisture. These problems can be overcome by inter or intramolecular cross-linking(83) or chemical modifications.

Owing to its low toxicity and immunogenicity, gelatin can form hydrogels for injectable administration. However, this molecule cannot be administrated by that route without modifications or cross-linking. For this aim, it must be functionalized with certain groups or molecules such as vinyl

groups or acrylic acid, respectively(84). Through this strategy, novel mucoadhesive pH-responsive systems based on gelatin co-polymerized with acrylic acid for potential oral delivering of protein for active drugs such as insulin have been reported by Oh et al(85). In this work, these formed co-polymers have shown a negligible swelling at a pH lower than 5 but the swelling increases when the pH is increased. This effect establishes a release of insulin in the gut but not in the stomach when it is administrated orally and in this way is protected of degradation. In this context, due to its capability of responding to the change of pH and its mucoadhesive feature, this polymer combined with glycerin has been proposed for applying benzydamine by the vaginal route(86). It is important to notice due to the state of health or illness the pH of the vagina can vary and the adaptation of this device to both conditions will be desirable. In this work, the in vitro studies have been successful results.

Gelatin has been also used for development nanogels. Some of those systems have been coated with stem cells forming a membrane for generating a biocompatible drug delivery system with tumor-targeting property(87). Among these systems, those reported by Gao et al(88) for delivering doxorubicin, as an antitumor drug, have shown excellent properties of stability and tumor-targeting ability in vitro and in vivo studies. Additionally, to the efficient anti-cancer activity, the absence of side effects in the tissues of the heart, liver, spleen, lung, and kidney in animal models have been displayed. Another work based on nanogels has been reported by Curcio et al(89). The authors have developed pH-responsive nanospheres based on gelatin, N, N′-ethylene bisacrylamide, and sodium methacrylate for the delivery of diclofenac. This system has shown non-toxicity on human bone marrow mesenchymal stromal cells. These nanogels have shown a lower release of diclofenac at pH=1 because the groups of the co-polymer remain in neutral form and therefore, the gel is not swelled but at pH=7.4 the swelling is carried out because increase the repulsion of the groups and the drug is released.

Surfactants as blocks of nano-assembly systems

Surfactants (is the short form of surface-active agent) have been used from the ancient as cleaning agents but today, they have a more diversified present. Owing to their main property, the reduction of the surface tension between water (or a polar phase) and a non-polar phase, they decrease the imbalance of forces at interphase; and consequently, the system is stabilized(90). For this reason, they have an important role in the development of pharmaceutical formulations either being part of their structure, as an assembly containing the active ingredients, or acting as enhancers for improving the penetration in different tissues(91). Therefore, surfactants are used as solubilizes, antifoams substances, emulsifiers, and many others; by generating stability through different organizational structures. There are many types of surfactants, but they generally share a basic structure and they can be divided into two regions. On one hand, a polar region, or head, that could have an ionic character (anionic, cationic or zwitterionic) or not (uncharged surfactants); and on the other hand, a non-polar region(92). Consequently, due to the essence of their structure, they can place between two phases with different features by harmonizing their relationship. Non-ionic surfactants have are not ionized in solution, so they are insensitive to pH variations and have high compatibility with most surfactants(93).

The capability of surfactant molecules to adopt different tridimensional arrangements under certain conditions, have peaked the attention due to the diversity of structures (micelles with different shapes, liposomes, niosomes, liquid crystals, and others) and sizes obtained. The sizes of these assemblies are between 1 and 1000 nm and hence, they belong to structures known as colloids(94). However, there are some exceptions such as large multilamellar niosomes, which be even bigger(95). The application of colloidal structures to pharmaceutical science dates from many years ago(96) and currently, these structures have become more sophisticated being able to respond to internal conditions of the environment such as pH variations and oxidative atmosphere, and for targeting selectively to a particular tissue(97–99). However, because we are describing nanosized devices; those larger to 100 nm will not be considered. In this sense, some of the most relevant drug delivery systems responding to pH variations of their application environment based on surfactants are shown in the following subsections.

There are two important parameters of surfactants that distinguish the development of assembled structures and their interphase behavior: the critical packing parameter (CPP or INM index) and the hydrophilic-lipophilic balance (HLB) and for this reason they will briefly described first. Not all surfactants are spatially arranged in the same way. A set of surfactant molecules has a spatial behavior conditioned by the shape of these molecules even though more precisely, by the relationship between their different portions. This relation was defined by Israelachili, Mitchel, and Ninham (INM) as critical packing parameter or IMN index(100). The authors have established the following relation:

$$CPP = \frac{v}{a_0 l_c}$$

Where, a_0 *is* area of the hydrophilic head, v is the volume of their hydrocarbon chain, and l_c is the maximum length of chains (critical chain length). Therefore, when molecules of surfactant are added in an aqueous solution and the packing parameter is known, it is possible to predict the type of arrangement formed (this behavior is shown under certain conditions of concentration and temperature). For example, when the parameter is close to 1, molecules organize into lamellar structures, if it is >1, inverted micelles are favored. Values lower than 1/3, indicate a conical shape of molecules and consequently, a strong tendency to form spherical micelles. Finally, molecules with a parameter between 1/3 and 1/2 form cylindrical micelles(100–102).

The other parameter is useful for choosing a surfactant depending on its solubility. Therefore, depending on the HLB, it is possible to predict the distribution of phases. The HLB parameter is a dimensionless number that ranges from 0 to 20. Consequently, low values of HLB (<9) refers to a lipophilic surfactant (oil-soluble) and a high HLB (>11) to a hydrophilic surfactant (water-soluble). Thus, surfactants can act as emulsifiers: when the value is between 3 and 8, it works as a water-in-oil (W/O) emulsifier and when it ranges from 8–18, it works as an oil-in-water (O/W) emulsifier(95).

The main pharmaceutical formulations based on surfactants described in this review are summarized in figure 2.

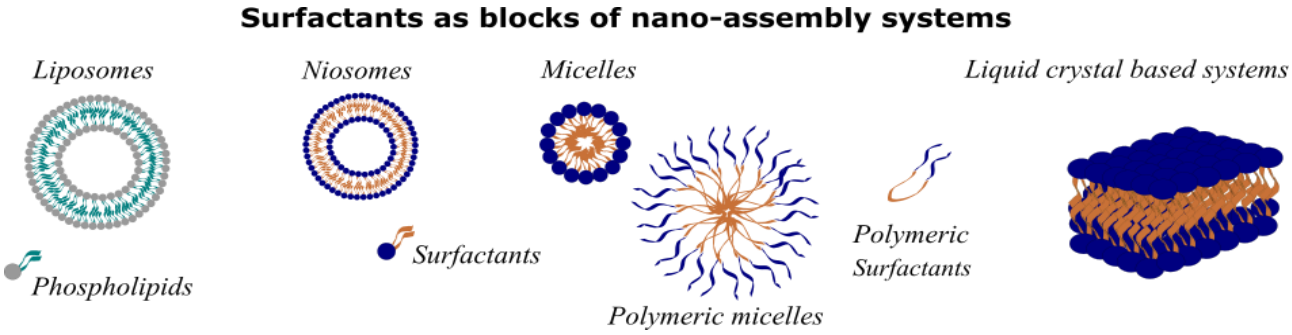

Figure 2: Surfactants as blocks of nano-assembly systems.

Liposomes

The liposome-based drug delivery systems are used to treat a wide variety of diseases and they also promote the enhancing of the therapeutic index of different types of drugs(103). Liposomes are one of the first surfactant-based systems that rapidly became on drug carrier systems; unlike micelles, that they were used jointly in very different fields of investigation and development(92). Liposomes were discovered in 1965 by A. D. Bangham(104), and they can be defined as closed single vesicles. As every substance used for human medicine, they are formed by a non-toxic type of surfactant molecules, phospholipids, which are stacked forming bilayers. The lack of stability and the contamination by bacteria are some of the main drawbacks of liposomes. For these reasons, lipids are not alone, other molecules might be used for improving their stability, increase the load capacity or modifying any other properties such as their electrostatic potential (used for stabilizing and also, for establishing particular interactions); and for avoiding the contamination preservative substances can be used.. As is it was mentioned by many authors (105–109), liposomes can also be defined as a self-closing lamellar liquid crystal matrix (the liquid crystal phase will be explained in the next **section 2.2.4** of this review, and it is another type of aggregation structures used as drug delivery systems). Finally, we can describe liposomes as a supramolecular lipid matrix ordered in a smectic mesophase(110).

Liposomes can be classified, basically, by considering size, the number of lamellas, and type of structure or composition. According to the size are divided on smalls, middles, larges, and giants. Their size ranges from 20 to 1000 nm for small to large liposomes; however, giant unilamellar liposomes (GUVs) can reach to bigger sizes. According to lamellarity, they can show one or more than one bilayers(111). It is important to remark that liposomes are formed by at least one bilayer there are no monolayers such as in micelle systems or single emulsions; therefore, their external surface and the internal one has polar character. In depends on composition we can mention ethosomes (containing ethanol), proteasomes (derived from bacteria) or immunosomes (when glycoproteins are anchored onto their surface), among others. However, both parameters are not crucial for reaching a long-circulating and avoiding the clearance by the mononuclear phagocyte system (MPS) in the liver and spleen. In the beginning, it was demonstrated that smaller liposomes had more circulating time than larger ones(112), the unilamellar more than multilamellar ones(113) and by using saturated phospholipids with compared to the unsaturated phospholipids, the circulation time was also improved. However, the modification that launched to liposomes to the clinical application was the incorporation of polyethylene glycol (PEG) to their surface(114,115). This hydrophilic molecule generates and steric boundary and, hence, the proteins of plasma cannot bind to liposomes and the MPSs cannot uptake them. These liposomes were called "stealth liposomes" and doxorubicin was the first drug loaded into them that reach to the market as Doxil(116). This formulation was approved by Food and drug administration (FDA) in 1995 and in the following year non-PEGylated liposomes for delivering daunorubicin citrate (DaunoXome®) were also approved. Both formulations are still used for Kaposi´s sarcoma treatment in acquired immune deficiency síndrome (AIDS)(3). These last liposomes have shown a lower toxicity profile than free daunorubicin, with increased capability to overcome the blood-brain barrier, and additionally, they have shown more efficacies against multidrug-resistant cell lines. For that reason, they have also been propose for treating relapsed meningeal acute myeloid leukemia(117).

Liposomes have been loaded with different types of molecules for a wide variety of treatments. This is due to hydrophilic drugs can be loaded into the core (aqueous) of liposomes and the hydrophobic ones can be dissolved within the lipids of the membrane. There are many hydrophilic drugs applied to the treatment of diseases; however, some of these molecules have a rapid clearance generating an unfavorable biodistribution with low cell-target penetration and; therefore, low therapeutic efficiency(118). Encouraging results have been achieved by the search of the suitable lipid composition (mix of lipids), preparation method of liposomes and their load process. Ciprofloxacin has been loaded in liposomes reaching to promising results, loading about 90% using ammonium sulfate gradient method(119). Other liposomes have reached suitable stability parameters for diclofenac. Additionally, using the calcium acetate-gradient method almost 100% of the drug has been loaded into these vesicles(120). Doxorubicin and daunorubicin are two other weakly ionic hydrophilic drugs that have reached a good percentage of entrapping efficiency (> 95% and 100%, respectively) in liposomes based-formulations using pH gradient method as loading strategy(121,122). Additionally, doxorubicin has reached lower entrapping results (90%) using the ammonium sulfate

gradient method(123). However, the most currently relevant hydrophilic active agents considered for loading in liposomes are those used for gene therapy. DNA (cyclic(124) or linear(125)) and interference RNA(126) or silencing RNA (siRNA)(127,128), are some of the most significant active molecules for the regulation of genetic and epigenetic expression in somatic and germinal cells(109).

One of the main hydrophobic drugs carried by liposomes is amphotericin B (systemic antifungal)(129); and many of these formulations have been launched in the market(130). There are many formulations approved by FDA based on liposomes and they have shown different sized. For example, Ambisome® has liposomal dimensions between 45 and 80 nm, but Amphocil®, has ~ 100 nm(130). Due to the reduction and/or by avoiding solvents with some risk for health due to their side effects, these liposomes have shown as a suitable alternative as systemic antifungal systems. Cationic liposomes loaded with another hydrophobic drug, paclitaxel, have been a good option for avoiding the adverse effects produced by solvents (cremophor and ethanol(131,132)) used for dissolving this molecule into the formulation.

The development of liposomes based formulation of cyclosporine A has shown an important decrease in the toxicity of compared to those using cremophor as a surfactant but the pharmacokinetic behavior has not been modified significantly(133). Propofol (another hydrophobic drug) has been carried by means of liposomes and, due to its small size has a higher entrapping efficiency than bigger drugs such as rifampicin(134,135). The application of a combination of drugs for addressing two different treatments or to potentiate the effect of a drug has been reported. In this context, Benedini et al(136) have shown how two hydrophobic drugs amiodarone and ascorbyl palmitate can be loaded in liposomes simultaneously. In this case, amiodarone was loaded because of its cardiologic effect and the ascorbyl for decreasing phospholipidosis effect producing by the first drug and as membrane stabilizer. Additionally to that, the lipophilic anticancer prodrug such melphalan has been successfully including into the layer of 100 nm liposomes obtaining better performance than the commercial product Alkeran®(137).

It is important to remark that there are many strategies to enhance drugs encapsulation in liposome. The most important considerations are composition of lipid of liposomes, charge, and the addition of other molecules for changing the rigidity (cholesterol, for example). Encapsulation and preparation methods are also very important, and consequently, liposomes can be classified through the preparation method such as dried reconstituted vesicles, reverse-phase evaporation vesicles, vesicles produced by extrusion technique, and many others but they will not be addressed in this text. For this information, it must be consulted the following references(109,138,139).

Liposomes were conceived for the delivery of poor pharmacokinetic profile drugs, or/ with high toxicity or sensitive to the exposed environmental conditions once administered. By using this last property, sensitive-environmental liposomes were designed and developed; and hence, and stimuli-responsive liposomes appeared. These liposomes can be classified as responding to internal stimuli (or physiological-dependence release) or as external stimuli-responsive. The main example of the first class is represented by pH-sensitive liposomes. In general terms, this targeting strategy is focused on the release of the therapeutic agent in cancerous or inflammatory tissues, due to that tissues have a slight decrease of pH. Therefore, if the pH of blood is around 7.4 and in the inflammatory tissue is 6, the system must keep stable in the first pH and be degraded in the second releasing the drug(140).In this sense, Li et al(141) have reported the development of pH-sensitive liposomes that have anchored onto their surface a peptide (glutamic acid-alanine-leucine-alanine) by acting as a fusogenic system. At normal pH, the peptide has hydrophilic character but at low pH, it becomes hydrophobic and promotes the fusion between the liposome membrane and that of illness cells and releases its content. Additionally, Monteiro et al(142) have reported the development of other pH-sensitive liposomes loaded with paclitaxel. These liposomes release their content inside the tumor because they suffer a destabilization depending on the pH of the environment. Another recent development of pH-sensitive liposomes is based on the formation of a cleavable binding between polyethylene glycol molecules and lipids. This system reaches a good accumulation of chemotherapeutic agents in MIA PaCa-2 line cells depending on the pH conditions(143).

Accordingly, liposomes are formulations formed by a bilayer (or more) of phospholipids dispersed in an aqueous solution. They can additionally be composed of other molecules for improving their stability and drugs for providing a therapeutic activity. Furthermore, liposomes can be designed to behave as stimulus-responsive systems. Applied rapidly to therapeutic formulations, they will remain to be chosen for developing advanced drug delivery systems.

Niosomes

In the nanotechnology research field, there are systems based on non-ionic surfactants that have been purposed for the delivery of multiple therapeutic agents. Among these systems, we can find to niosomes. It is known that non-ionic surfactants are best-tolerated surfactants; however, the concentration used must be carefully controlled because they can develop irritation and in some cases (by intravenous route) adverse severe reactions but if this concentration is controlled, they can be applied by this mentioned route. There are many approaches to the utilization of niosomes as drug delivery systems. In their review, Thakkar and Brijesh(144), have purposed that they can be utilized to package old drugs for improving their efficacy. These authors propose replacing the search of new drugs by this strategy.

Niosomes are vesicles formed by non-ionic surfactants and, in many cases, additives as cholesterol can be added. These structures are structurally related to liposomes and share many properties with them. Both have been conceived for protecting drugs and improving their therapeutic performance in the body. This last concept implies that the bioavailability, biodistribution, the effect on target cells and retard the clearance of drugs are really enhanced. Additionally, both types of vesicles can be loaded with hydrophobic and also hydrophilic drugs(145). The first type of drug is included in the membrane and the second ones are dissolved into the core. However, niosomes have certain advantages compared to liposomes, they show higher chemical stability, longer storage time. Due to that different types of hydrophilic heads can be used, there is a wide possibility for modifying them and consequently, their surface properties and behavior can be

customized. Furthermore, they show lower immunogenic reactions than liposomes owing to the properties of non-ionic surfactants(95,146).

Such as liposomes, these systems can be classified as uni or multilamellar and in small or large. Small unilamellar niosomes size is between 10 to 100 nm, and large unilamellar form 100 up to 3000 nm. Bigger sizes than 3000 nm can be reached by large multilamellar niosomes(95); however, in this text, only unilamellar niosomes (under 100 nm) will be described.

There are three main families of non-ionic surfactants used in the development of niosomes: tweens, spans and brijs; however, other molecules such as carbopol (carbomer) or cellulose derivatives can be also used(146). Additionally, cholesterol and charged molecules also plays an important role in physical-chemistry stability of niosomes. Many formulations based on these carriers have been described by using a vast combination of these types of surfactants and active compounds. In this context, Terzano et al(147) have demonstrated that niosomes formed by tween-20 and cholesterol increase the permeation rate of beclomethasone dipropionate through a mucosal barriermodel. Encouraging results with a similar system have been later reported by Marianecci et al(148). In this last work, it was also evaluated the cellular tolerability and cytotoxic on primary culture of human lung fibroblasts. Both studies have focused on the treatment of for the treatment of obstructive pulmonary disease. The pulmonary route was proposed by Moazeni et al(149) for the delivery of ciprofloxacin. In this work, the authors have use niosomes formed by a mix of span 60 and tween-60 added with cholesterol. In all of these formulations, cholesterol is used as another important component. Through the interaction with surfactants, cholesterol influences the physical properties of niosomes, just as it does in liposomes. This molecule decreases the fluidity of the membrane(150). However, there is another type of behavior occurring in nisosomes. In some systems, the formation of vesicles only appears after the addition of cholesterol between 30 and 50% and this proportion depends on the HLB value of the surfactants. Higher proportions of cholesterol are needed when the HLB of surfactants is above 10 but there is not a rule and its addition must be evaluated case by case depending on the physical-chemical characteristic of surfactants and loaded drugs(146,151).Therefore, as can be seen, niosomes are very closely related to liposomes because of the use of surfactants and cholesterol in their preparation and additionally, charged molecules and PEG can also be incorporated. Charged molecules such as dicetyl phosphate and phosphatidic acid (negatively charged) or stearylamine and cetylpyridinium (positively charged) are commonly used for preventing aggregation; however, their concentration must be under 25% because they disfavor the aggregation process of surfactants and consequently the formation of niosomes(152,153).

Niosomal carriers have been proposed for delivering many types of drugs through different administration routes. For example, formulations formed by tween-20, span-60, and cholesterol for delivering ibuprofen(154) and meloxicam(155) were proposed for applying by dermal route. Particularly, the formulation carrying ibuprofen has incorporated a fusogenic compound. This molecule can undergo a phase transition under acidic conditions, such as in the skin. Therefore, pH-sensitive niosomes can be destabilized when the external pH conditions are changing, and the formulation can deliver their content when is applied to the skin. Additionally, Carafa et al(154), in their work, realize an in vitro permeation studies by using rat skin obtained from 6–8-week-old hairless male animals

Rinaldi and coworkers(156)have reported the design and development stimuli-responsive niosomes for the delivery of ibuprofen and lidocaine. These structures based on polysorbate (tween-20) and other functionalized with glycine (tween-20/glycine) were proposed as an anti-inflammatory and anesthetic pH-sensitive system. They also demonstrated the lack of toxicity using in vitro tests and additionally, in vivo compatibility and good results of their therapeutic effect using murine models. Through a similar (tween-20/glycine) system, Marzoli et al(157)have reached a successful delivery of ibuprofen in mice models by the development of pH-sensitive niosomes.

Using span-20 as a non-ionic surfactant, Pereira et al(158) have designed and developed pH-sensitive niosomes of 80–90 nm in diameter. Furthermore, they have added cholesterol (50 mol%) and a low pH Insertion Peptide (L-pH-IP) (5 mol%)conjugated with DSPE lipids(1,2-dioleoyl-sn-glycero-3-phosphoethanolamine-N-[4-(p-maleimidophenyl) butyramide] sodium salt (DSPE-maleimide)) (DSPE-L-pH-IP). In this work, the peptide is used for coating niosomes because it works as an acidity sensitive targeting moiety. The authors demonstrated that L-pH-IP coated niosomes sense the extracellular acidity of cancerous cells. These niosomes were tested in mice models obtaining a significant accumulation in tumors (2–3 times higher than PEGylated niosomes) and a very low in organs such as kidney, liver, and muscles after intravenous injection. This is an excellent example of an active targeting system for drug delivery.

Micelles

Micelles are arrangement formed by surfactants, under certain conditions, in aqueous solution. They are classified as direct when oily-portion of molecules form a liquid nucleus and polar groups are forming the surface; and as indirect, when non-polar groups go outside(101). First, when molecules of surfactants are added into an aqueous solution, they are placed at the surface (liquid-air) (or interphase, when a liquid-liquid system is considered). This behavior decreases the surface tension or interphase tension until a point where the continuous addition of the surfactant does not modify the surface tension value. Accordingly, this point or this range (better) of concentration is known as critical micelle concentration (CMC) or Kraft point(159) and it depends on the type of surfactant (ionic or not), the temperature, and presence of ions. Such as it was mentioned in **section 2.2** the shape of these micelles is conditioned by the spatial shape of the surfactant, and consequently, depends on the packing parameter. Owing to this parameter micelles can adopt spheres forms or rods-like. However, in some cases, spherical micelles can become into rods by increasing the concentration or by modification of other parameters(100,101).

Direct micelles have the potential to dissolve non-polar drugs into their core and due to that fact, they can improve their bioavailability because enhancing their permeability for crossing the physiological barriers and consequently, they improve the biodistribution profile of the drugs and their toxicity is reduced(98). Owing to their small size (from 5 to

100 nm), micelles work through a selective mechanism of penetration, known as passive-targeting; by demonstrating a spontaneous penetration into weakly junctions' vasculature.

Polymeric surfactants can act as micelle forming systems such as low molecular weight surfactants but with a very low CMC (1.10^{-7} to 1.10^{-9} M) and bigger micelle sizes (100 to 200 mn). Polymeric surfactants have hydrophobic and hydrophilic portions or blocks and micelles formed by them possess high stability both in vitro and in vivo.

The use of polymeric micelles for carrying hydrophobic drugs for applying by the ophthalmic route is widespread. In this context, dexamethasone, a steroidal anti-inflammatory drug, has been delivered efficiency for ocular via by using a combination of polymeric micelles based on pluronic F127 and a chitosan(160). Bigger micelles (129 nm) composed of linear and branched poly (ethylene oxide)-poly (propylene oxide) were reported by Shamma et al for the application of non-steroidal anti-inflammatory, lornoxicam, by the same route. Thus, non-ionic surfactants have demonstrated to be harmless vehicle formers for ophthalmic applications(160). Anti-inflammatory drugs are not the only hydrophobic molecules included in polymeric micelles. Alpha-lipoic acid, an antioxidant indicated for the treatment of diabetic keratopathy and retinopathy, was incorporated in polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol copolymer for enhancing its effects on the corneal residence time(161).There are many other hydrophobic molecules carried by polymeric surfactants forming micelles. Paclitaxel, doxorubicin, cisplatin and cyclosporin A, are some examples of anticancer drugs carried by these systems. Additionally, the first three drugs were also loaded in pH-responsive polymeric micelles for improving their efficiency. The carrier for delivering paclitaxel was prepared through binding of poly (2-methacryloyloxyethyl phosphorylcholine) block and poly (D, L-lactide) biomimetic micelles(162)In this system, the release of the drug is triggered by acidic conditions at the tumor site yielding in improving the utilization of the drug, and the antitumor efficacy is facilitated. The doxorubicin-carrier device was fabricated from a mixture of two block copolymers based on poly(L-histidine)-b-PEG -folate and poly (L-lactic acid)-b-PEG-folate (relation 3:1). This system has shown 90% of cytotoxicity for doxorubicin tumor resistant cells(163). The pH-responsive polymeric micelle system for the delivery of cisplatin was developed with methoxypoly(ethylene oxide)-block-poly-(α-carboxylate-ε-caprolactone). These micelles of 50 nm size were prepared through complexation, perhaps through coordinate bonding. In this work, micelles were characterized using dynamic light scattering measurement and the in vitro release of cisplatin at different pH values was evaluated. The in vitro cell uptake and cytotoxicity of the system were evaluated against two breast cancer cell lines obtaining encouraging results(164).

Liquid crystal-based systems

Liquid crystals or mesophases can be defined as another state of the matter. Formed by surfactants under certain conditions, they are specific tridimensional arrangements. In **section 2.2** and **subsection 2.2.3**, we have described how surfactants behave when are dissolved in water and their concentration is increased. Therefore, we will start at the last point. When a micelle system appears, by means of an increase of concentration of surfactants, and micelles are formed in solution, they can change their form or can develop liquid crystals. This mesophase shares the properties of liquids, fluidity, and the crystals, order or periodicity. Accordingly, they show orientational and positional orders but in some dimensions(109). These systems can be classified as thermotropic or liotropic. The firsts can be divided into nematic (chiral or not), smectic (A or C) and discotic. The seconds are cubic, hexagonal, bicontinuous cubic and lamellar. It is important to remark that cubic and hexagonal phases are very closely related because they formed by one layer of surfactant, i.e., they are formed by spherical micelles and cylindrical or rods micelles in a cubic and hexagonal arrangement, respectively. However, bicontinuous cubic liquid crystals and lamellar are formed by bilayers (although some bicontinuous cubic may not be) and consequently, are closely related to liposomes. Detailed information can be found in the following reference(165).

Accordingly, due to their properties, liquid crystalline phases or mesophases can be conceived as drug delivery vehicles for both hydrophobic and hydrophilic drugs which could be administered by different routes; because these types of formulations can enhance the solubility and improve the profile release of drugs. Hydrophilic drugs will be located in the aqueous environment or close to the polar head of the surfactant; lipophilic drugs will be located in the lipid bilayer, and amphiphilic drugs at the interface. In this context, liquid crystals as drug vehicles can be classified into two categories: bulk mesophases (cubic and hexagonal, among others);and liquid crystal nanoparticles such as cubosomes and hexosomes(166).

Cubic mesophase has great versatility for delivering drugs with different properties such as polarity, size, solubility and using various concentrations. This phase can behave as a sustained-release system because of its high viscosity. Among drugs carried by these systems, we find aspirin, vitamin E, chlorpheniramine maleate and propranolol HCl, insulin, metronidazole and more. The most common surfactants used for cubic phase developing are the monoolein and glyceryl-monooleate but other lipids such as monoelaidin, phosphatidylethanolamine, and phospholipids (PEGylated or not) were also used(167). Oleylglycerate and phytanylglycerate were used as a reverse hexagonal phase former in excess water. Boyd et al have reported their behavior compared with that of glycerylmonooleate. In this work, the matrices were loaded with a series of model hydrophobic and hydrophilic drugs, such as paclitaxel, irinotecan, glucose, histidine, and octreotide and were demonstrated that oleylglycerate matrix has released the drug faster than the phytanyl glycerate matrix and; additionally, their stability was also assayed in vivo. It is important to mention that from those glycerate surfactants used for the development of hexagonal phases it could be formed hexosomes at physiological temperature(168). Hexosomes are nanostructures that remain hexagonal mesophase. In 2001 Spicer and Hayden(169) have reported a method for obtaining a new cubic mesophase, cubosomes. Both cubosomes and hexosomes are formed from cubic and hexagonal phases (respectively) as a consequence of an infinite swelling phenomenon. Oleylglycerate and phytanylglycerate can produce hexosomes and cubosomes; and additionally, they can be carried out by glyceryl monooleate. Both systems show a 200 nm size particle. Boyd et al(170) have reported irinotecan-loaded hexosomes for

injectable administration. In this context, cubosomes loaded with flurbiprofen, odorranalectin, diazepam and dexamethasone have also reported by Lakshmi et al(171).

The stability of these systems depends on concentration, temperature, type of surfactant, ionic strength, and pH. For this reason, the development of pharmaceutical devices based on liquid crystals must be carefully designed and tested because the modifications of the aforementioned parameters can rise up a lack of stability with negative consequences (burst release of the drug).

In this context, and using the pH-responsive property of liquid crystals, Negrini and Mezzenga(172) have reported a system capable of responding to pH variations with a reversible switch in both the structure and physical properties. The system is composed of monolinolein and linoleic acid in the presence of excess water at 37°C. For simulating physiological conditions, ionic strength of 150 mM was used. Therefore, in those conditions, the system changes from a reverse bicontinuous cubic phase to a reverse columnar hexagonal phase when pH is changing from neutral (pH 7) to acidic (pH 2) values. The system has also shown an efficient controlled-release delivery of a hydrophilic drug, phloroglucinol.

Nanocomposites

Nanocomposites are formed by a combination of multiple (dissimilar) materials at the nanoscale to get improved properties. These formed devices can be used as biomaterials such as wound dressing, tissue fillers, and additionally they can be tailored with properties for delivering drugs. Nanocomposites are mainly formed by an inorganic structure combined with phospholipids, polymers and/or other materials of organic nature. (173,174).

Autologous bone graft still remains the gold standard for the addressing of bone defects. However, there are some drawbacks associated with this strategy. Some of these problems could be solved using an association of ceramics materials and polymers. Ceramic materials such as hydroxyapatite (calcium phosphate and carbonate) have shown interesting properties because of their hierarchical structure and lack of toxicity. These materials also provide good osseointegration, biocompatibility, osteoconduction, lack of immunogenicity and drug loading capability. For improving their properties, hydroxyapatite can be formulated with polymers as alginate. As we previously mentioned, alginates can form hydrogels by interacting with divalent ions of hydroxyapatite increasing their viscosity and consequently develop scaffold systems for applying in bone tissue engineering because they increase cell attachment at the interior portion of the bone matrix(15,175). We have already mentioned the pH-sensitive behavior of alginates in **section 2.1.1** and, as a consequence of that, composites materials developed with this polymer and hydroxyapatite can behave like a smart device under different pH conditions. In this context, Benedini et al.(15) have reported the development of a hierarchical scaffold from synthetic nano-sized home-made hydroxyapatite of 50 nm length and sodium alginate with potential application as bone filler. The authors have demonstrated that at a pH 6 and low ionic strength, the device looks amorphous, but when these conditions are modified (an increase of pH at 7.4 of decrease pH at 4.2) it generates liquid crystal phases. Thus, such we have mentioned in **section 2.2.4** (liquid crystals based systems) the emergence of these types of arrangements could additionally be used as a carrier of analgesics, anti-inflammatories, and/or antibiotics which can modify their release reliant on pH and ionic strength of the environment.

Another pH-sensitive system based on hydroxyapatite has been reported by Placente et al(176). In this case, authors have developed a multi-drug delivery formulation combining this ceramic material based on hydroxyapatite coated by a lipid membrane mimetic. This device loaded with ciprofloxacin and Ibuprofen (antibiotic and anti-inflammatory, respectively) has shown an efficient release of drugs depending on environmental pH and good biocompatibility behavior. This type of system can be proposed as a potential bone filler material in pathologies where bone mass is lost. Additionally, due to their therapeutic activity, they could decrease the inflammatory status because of the presence of ibuprofen, and they could prevent an infection in situ due to their antibacterial activity. In the same sense, another system sensitive to pH variations based on acrylamide-co-acrylic acid hydrogels cross-linked with N,N'-methylene bisacrylamide (forming a hydrogel) and chitosan decorated with carbon nanotubes (used to reinforce the structure) has been reported by Bellingeri et al(177). These materials have shown good biocompatibility properties when was tested against Madin Darby Canine Kidney cell lines and 3T3 cell lines (derived from embryo fibroblast of Mus musculus) with a viability of 100% after 48 h of incubation. Additionally, they have displayed efficient pH-response, at low pH (2) they have experienced a lower swelling than at higher pH values. This type of property is important in the drug release process. However, in this work, the antibacterial activity was tested against *Staphylococcus aureus* (ATCC 29213) and it is due to the chitosan, no drug is released. However, good pH-responsive properties have become them into a suitable tool for potential drug delivery based on pH environmental modifications.

Lipid-based nanoparticles

This group is formed by lipid nanoparticles and nanostructured lipids. Both systems have demonstrated effectiveness and safety for carrying different types of drugs, showing excellent drug targeting and physical stability, providing suitable flexibility in their release profiles. The main difference between solid lipid nanoparticles and nanostructured lipid carriers is that the core of first is solid and the second has a core containing a mix of state lipids, liquid and solid. Both systems with a mean diameter between 40 and 1000 nm, have been developed for the potential treatment of many diseases acute and chronic as cancers and infectious diseases; and they can be applied through different administration routes such as ocular, lung, hepatic, intravenous and other. However, in this text, the upper limit of the size of the described systems will be ~100 nm.

Basically, solid lipid nanoparticles are formed by a solid lipid (wax, triglycerides) and a surfactant, polymers or a mix of them can be used for stabilizing the system(178,179). Owing to the nature of the core, these systems are mainly focused on the delivery of hydrophobic drugs; however, certain salts of the hydrophilic ones could be loaded or by generating an inverse mini-emulsion system(180,181). The basic production method of these nanoparticles is based on the dissolution of the drug in the lipid (5-10 °C above its melting point) and then,

the system is stabilized by surfactants. However, there are several production techniques such as high-pressure homogenization, solvent emulsification /evaporation, supercritical fluid extraction of emulsions, ultrasonication or high-speed homogenization, spray congealing and spray drying(178,179). In dependence on the production method, the drug into solid lipid nanoparticles can be incorporated by two models: solid solution model and core-shell model. In the second model, the drug can be included in the core or into the shell; consequently, they are named: drug-enriched core or drug-enriched shell, respectively(179).

Paclitaxel has been loaded into these lipid nanoparticles reaching a high concentration in the brain, liver, and kidneys. This formulation has been developed as a stealth system and also as non-stealth, and there was no difference in drug accumulation in organs between both systems. Additionally, corticoids, for an intra-joint application, have been also carried by these nanoparticles.

Doxorubicin has been loaded into ~100 nm pH-responsive solid lipid nanoparticles. This pH-responsive system was developed using cholesterol-polyethylene glycol adduct-coating for forming nanoparticles. Additionally, this system was capable of overcoming the multidrug-resistance system in breast cancer cells. The in vitro drug release profiles have displayed a pH-controlled drug release behavior and the accumulation of the drug into the tumor tissue was also demonstrated. The authors of this work have proposed that this increase in the concentration of the drug was produced by the enhanced permeability and retention effect into the tumor(182). Another anti-cancer drug, camptothecin, has been also loaded in lipid nanoparticles. However, its derivative, 10-hydroxycamptothecin, has been loaded in a pH-sensitive system based on nanostructured lipids and this system has been reported by Sun et al(183). In this work, N-Arginine-N-octyl chitosan, as a pH-sensitive system, was synthesized by grafting l-Arginine onto carboxymethyl chitosan and then, this molecule has been used to modify the surface of nanostructured lipids to generate pH-sensitive charge-reversal lysosomolytic nanocarriers. At pH 7.4 the particles are negatively charged but when pH is decreased (as in tumor environment) the surface potential shifts to positive which improves the cell internalization of the device. Therefore, these modified nanostructured lipids have gained a positive surface charge necessary to release the drug into the cytoplasm. The modification of the surface in that system has become possible an improvement of pharmacokinetic profiles and the distribution through tissues in mouse tumors models and it has reached an improved antitumor activity compared to nanostructured lipids systems without modification of their surface.

Up to this point, it has been discussed about systems with a certain sensibility internal stimulus such as to pH changes, which generate the release of drugs loaded on them, or their physical or mechanical properties are modified. Additionally, to that, in the following section we will discuss systems based on the same type of formulations, such as liposomes, responding to external stimuli.

THERANOSTIC THERAPY: DRUG DELIVERY SYSTEMS RESPONDING TO EXTERNAL STIMULI BASED ON NANOTECHNOLOGY

The term "theranostic" has emerged in 2002(184) and as we can infer; this term encompasses two parts: therapy and diagnosis. All medical treatments need necessarily the diagnosis for eventually after, the respective treatment. However, these events occur in two steps but in theranostic therapy, they are carried out at the same time. When it is talked about diagnosis, in this therapy, we don´t have to ignore the uses of diagnostic imaging devices and additionally, contrasts agents. However, in theranostic, these agents could act as contrast or/and as therapeutic drugs. In addition, there are other types of molecules forming these formulations for example molecules with particular properties such as magnetic nanoparticles. Therefore, theranostic therapy is a merge of a diagnostic imaging procedure that can release the therapeutic agent by means of different stimuli depending on the physical properties of the applied technique. The agent used in this procedure can behave both, as a contrast agent and as a drug; and all the procedure is carried-out in one-step (184–187).

One of the main advantages of these types of therapies is that they can overcome undesirable differences in biodistribution that can occur between imaging agents and therapeutic ones. Another challenge overcome by theranostic is its capability to be monitoring the ill tissue when it is treated with the therapeutic agent; consequently, you are obtaining an "image of the treatment". Additionally, it is possible to establish the kinetics delivery profile of drugs and the assurance that it has got into the target tissue and once inside it you could tuning the amount of drug released modifying the stimuli(188).The guarantee that a drug may be released into the target site has great relevance, this is due to the main drugs used in theranostic are chemotherapeutic agents and; consequently, they generate serious adverse effects in normal tissues(189). As a consequence of that, the need for patients with cancer to have a personalized therapy and eventually, a reduction of the adverse effects of the anticancer agent (due to in situ release), additionally to the decrease in the time between diagnosis and treatment, it has turned the theranostic therapy into a suitable and promising strategy for these patients(3). Therefore, in this section, we show a brief description of different sources of exogenous stimuli used in this therapy: ultrasound, light and magnetic stimuli. It is important to remark that there are many formulations for applying in this therapy and their general properties have been already described in their respective section such as liposomes, nanoparticles, and others. Therefore, in this section, their specific features related to the external stimuli will be addressed.

Exogenous stimuli

Targeting of actives molecules for the treatment of diseases is a widespread strategy and it can be divided into passive and active. In the first, molecules are not guided to the target site but when the site is reached, they are retained because they are designed to respond to a particular feature of this specific tissue or cell. However, in an active targeting, formulations or devices are guided to the specific target sites through molecules onto their surfaces which interact with specific receptors of target cells. Certain types of theranostic therapy procedures could be considered as an active targeting strategy, but in those cases, this targeting is produced when an external stimulus (magnetic field, light or ultrasound) releases the

active compound (diagnosis agent or drug or both) into the target site.

This type of therapy has many advantages that will be described in the following section, but they also have some drawbacks that must be overcome. Among these problems that must be face form today to obtain a safe product to human health are the high toxicity of some devices and we propose as the main challenge, the lack of validation of nanoscale integration, between therapeutic and imaging. For that reason, more evidence is necessary to carry these products from laboratory scale to a commercially viable product.

In the next subsection, three main strategies for releasing the drug from the pharmaceutical formulation applied in theranostic are summarized in **figure 3**.

Ultrasound stimulus

The application of this technique in theranostic is based on the use of gas-filled devices due to that they generate the echogenicity which is related to the generation of the image for diagnosis and it is used, for example, for studying blood perfusion and its flow. When a high-intensity ultrasound is focused on cancer tissue, an increase of temperature in this zone is shown and the tissue is destroyed by heating. Therefore, an improved pharmacological response can be achieved by the design of pharmaceutical formulations such as liposomes and bubbles (nano-bubbles) loaded with therapeutic agents such as paclitaxel (chemotherapy) with the capability to respond to ultrasound stimuli(190). For reaching this aim, the formulations must include a certain percentage of gas in their interior(191). The local release of the content of these devices is produced by the expansion of the gas inside the system by ultrasound waves pulse. Some of the main advantages of ultrasound over other imaging techniques are its deep penetration and high-resolution real-time view of the observed organ. Additionally, it has low cost, portability, broad availability. However, one of the main advantages is that patients are not exposed to ionizing radiation(192). It is important to notice that when this type of stimuli is applied in a whole-body the intensity range of this stimulus is between 720 mW/cm^2 and 105 W/cm^2 (power/body area)(191). However, for cell lines cultures (MiaPaCa-2, Panc-1, MDA-MB-231, and AW-8507 cell lines) the ultrasound pulse must be reduced to 1 W/cm^2.

Light stimulus

The light incidence can be confined to a target site; the light-based theranostic therapy provides high selectivity and specificity. Basically, in this type of therapy, we are seeking that an active compound is released from its formulation by means of the physical changes produced by absorption of light of a photosensitive molecule. Photodynamic therapy, fluorescence, and photo thermal therapy are the three main processes occurring when a formulation containing light-sensitive molecules is irradiated. In photodynamic therapy, photosensitizers agents in the formulation are impacted by the light generate singlet oxygen (from oxygen) and therefore, the death of the tissue is produced. In photothermal therapy, the energy of the light can be transferred to other forms by non-radiative relaxation of molecules; and finally, in fluorescence, the energy is produced by the emission of light due to radiative relaxation of molecules. This last principle is mainly applied for diagnosis(193).

Photodynamic therapy involves two main components, the photosensitizing agent or photosensitizer (or a dye) and a source of light with a suitable wavelength. The important point is that both components are non-toxic separately. Near-Infrared light (700-100 nm) has significant advantages in phototherapy over UV and visible light because it generates suitable images of deep tissues. However, visible light (700-400 nm) is widely used(194). Porphyrins are one of the main photosensitizing agents used in this therapy. This strategy is based on the skin photosensitization caused by the disease, porphyria. Other molecules such as tetra-hydroxyphenyl-chlorin, benzoporphyrin derivatives, and radachlorin are also used(195). For example, visudyne, a benzoporphyrin derivative, is under clinical trials for treating pancreatic cancer, brain cancer, basal cell carcinoma, brain and central nervous system tumors. Additionally, gold and silica nanoparticles, and other devices containing photosensitizer agents such as liposomes, ceramic, polymeric carriers have been reported for applying in photodynamic therapy(193).

In photothermal therapy, the damage into the tissue is produced by an increase of temperature (45- 300℃) which is obtained by the application of visible wavelength light and near-infrared. This type of therapy uses photo-absorbable molecules for generating the increase of temperature when the light in impacted on them (no-reactive oxygen species are produced). Photodiagnostic and phototherapeutic strategies for the detection and treatment of tumors and infections have achieved by non-photobleaching plasmonic metal nanoparticles. The development of gold nanoshells has further enhanced the efficacy of phototherapy because they absorb in near-infrared(196). There are many photothermal nanotherapeutic systems such as noble metal nanostructures, nanomaterials based on transition metal sulfide/oxides, nanocarbons, inorganic nanomaterials (form mesoporous silica nanostructures) and others(197). Finally, it is important to consider that both photothermal and photodynamic therapies can be applied simultaneously for synergically objectives of diagnosis and treatment.

Magnetic stimulus

Nuclear magnetic resonance is one of the favorite techniques for diagnosis due to it is a no-invasive technique and it produces high-resolution images through non-ionizing radiation. It is applied to clinical diagnosis of soft tissues such as the brain, heart, abdominal organs, and more. The procedure for obtaining the image is based on the application of a magnetic field and an electromagnetic pulse. The application of a magnetic field in theranostic procedures is based on the capability that this stimulus can generate heat when it impacts on magnetic nanoparticles. If these particles are inside a tumor the heat can induce the death of cancer cells. Additionally, these particles can be used as contrast agents.

When anticancer therapy is addressed, tumor cells and their stem cells must be destroyed.

The use of specific ligands for binding to overexpressed or abnormally activated molecules in tumor cells is a strategy of active targeting against tumors; however, cancerous stem cells are sometimes devoided of those molecules on their surface for interacting with the anticancer device. Consequently, cancerous stem cells can keep growing and differentiating and a new treatment for killing them must be started. Super paramagnetic iron oxide nanoparticles can produce magnetic

hyperthermia decreasing significantly cancerous stem cells. Iron, nickel, cobalt and their conjugates and derivatives such as oxides, can be used for as magnetic nanoparticles; however, the most commonly used are iron ones because of their biocompatibility. The combination of monoclonal antibodies, for interacting specific antigens on cells of the tumor, with paclitaxel loaded iron oxide magnetic nanoparticles could be an encouraging strategy against cancer stem cells activity in multiple myeloma and will lead to a significant reduction of tumor growth(198). This specific strategy can be carried out through multilayer platforms such as multi-functioning nanoparticles. In these devices, an iron oxide nanoparticle is working as a contrast agent forming the core which can be coating by layers containing the drug and specific molecules anchored to their surface to interact with receptors of the tumor. This type of system can be also loaded with nucleic acids for gene therapy. Therefore, the application of a magnetic pulse for releasing the therapeutic or contrast agents in a specific site avoids the accumulation of drugs in healthy sites, and hence, adverse side effects. Another strategy for applying magnetic treatments is to encapsulate the magnetic nanoparticle (loaded with a drug or not) into other nanometric systems such as liposomes or micelles for treating cancer and other diseases, and they can be administrated by different routes. For example, an aerosol containing magnetic nanoparticles can be inhaled for the treatment of lung cancer but also in other non-malignant pathologies such as chronic obstructive pulmonary disease, cystic fibrosis, and respiratory infections(199). An increase of a drug concentration in the tumor can be achieved by using magnetic-responsive nanoparticles, but also these devices can reveal the tumor itself by magnetic resonance imaging. In this context, a macromolecular platform or liposomes(200) carrying chlorotoxin and a contrast agent, Gd, has been developed to target certain types of cancers such as glioma or liver tumors in mice models(201).

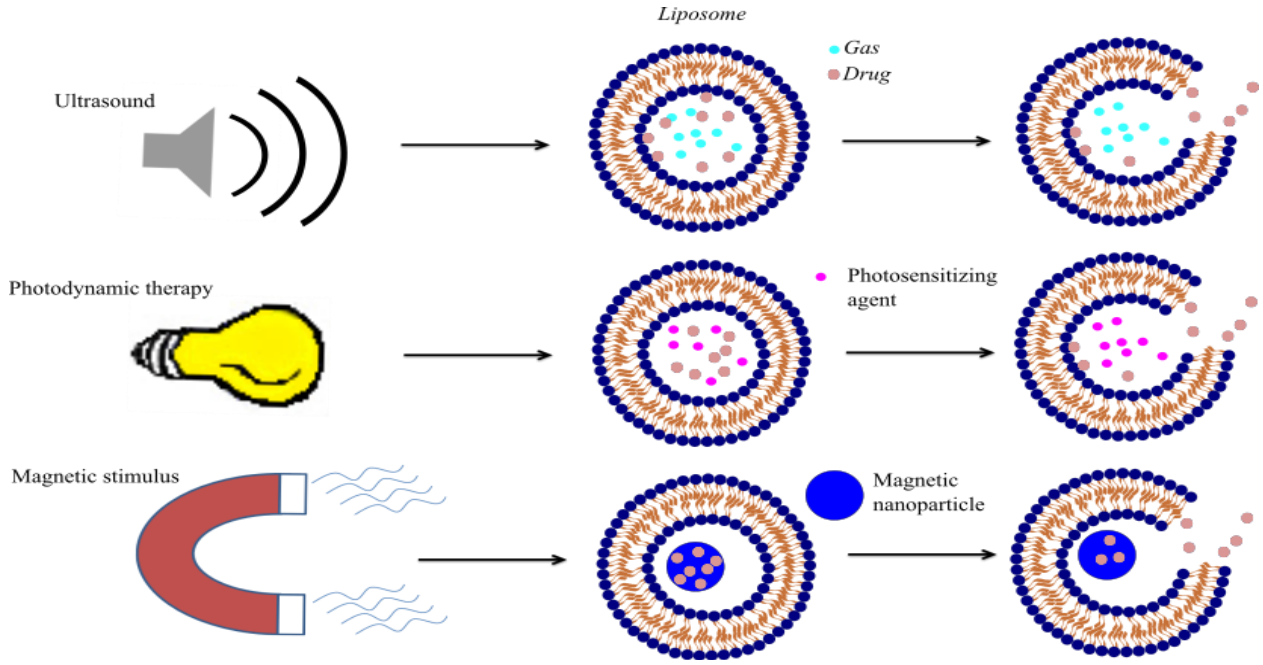

Figure 3: main strategies applied to theranostic therapy.

PERSPECTIVES

As time passes, many problems base on toxicity, lack of bioavailability of drugs, or the need for improving their release profile have emerged, and therefore, new perspectives have arisen in the field of pharmaceutical science and at this time we are not outside that logic. The application of nanotechnology for facing these issues has achieved encouraging results but new challenges have arisen. The use of nanodevices has reached wide the horizon because of the development of devices that respond to stimuli internal and/or external, and for this reason, the adaptation of future therapies to the different physiological conditions has enormous value. The reach of nano-sized systems has improved the biodistribution and consequently, the bioavailability of the drugs. Additionally, lower concentrations of drugs are needed if they are carried by these devices. Nowadays it has been increased the strategies for improving the pharmaceutical devices through the application of nanotechnology, but we should not forget that these devices must be safe for human health. For this reason, the main effort of the scientific community must be centered on that point. Many incredible pharmaceutical formulations have been proposed with the expectancy for improving the lives. Therefore, we must guarantee the safety of these devices to accomplish this objective.

CONCLUSION

Nanotechnology has set the way in many areas including pharmaceutical sciences. It is overwhelming the ability of nanoscience for carrying out improvements in existing formulations and for giving rise to new ones. This technology has led dosage forms to a higher level of specificity for the treatment of different diseases and has decreased their side effects. In this text, we have described and discussed different

formulations based on nanodevices and that respond to internal stimuli. Among these devices, we have mentioned systems based on polymers, based on surfactants, nanocomposites, and based on lipids. Additionally, we also discussed formulations that respond to external stimuli used for theranostic therapy. This therapy has been addressed as a new combined strategy for diagnosis and treating a disease in one-step. Therefore, we conclude that this review provides an overview of different pharmaceutical formulations which could be potentially used for the treatment of diseases, and for both diagnosis and treatment jointly, based in nanotechnology. Finally, we consider that this technology constitutes an essential tool for overcoming some drawbacks associated with drug administration.

CONFLICT OF INTEREST

The authors report no interest conflict.

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