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Microemulsion Based Nanostructures for Drug Delivery

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Most of the active pharmaceutical compounds are often prone to display low bioavailability and biological degradation represents an important drawback. Due to the above, the development of a drug delivery system (DDS) that enables the introduction of a pharmaceutical compound through the body to achieve a therapeutic effect in a controlled manner is an expanding application. Henceforth, new strategies have been developed to control several parameters considered essential for enhancing delivery of drugs. Nanostructure synthesis by microemulsions (ME) consist of enclosing a substance within a wall material at the nanoscale level, allowing to control the size and surface area of the resulting particle. This nanotechnology has shown the importance on targeted drug delivery to improve their stability by protecting a bioactive compound from an adverse environment, enhanced bioavailability as well as controlled release. Thus, a lower dose administration could be achieved by minimizing systemic side effects and decreasing toxicity. This review will focus on describing the different biocompatible nanostructures synthesized by ME as controlled DDS for therapeutic purposes.

Keywords: nanostructures, microemulsion (ME), drug delivery systems (DDS), emulsion synthesis, biocompatible materials

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INTRODUCTION

A drug delivery system (DDS) is the process that enables the introduction of a pharmaceutical compound though the body to achieve a therapeutic effect in a controlled manner (Tiwari et al., 2012). This method includes the administration, the release, and subsequent transport of its bioactive ingredients across the biological membranes to the site of action (Bassyouni et al., 2015).

However, intrinsic factors related to the nature of the pharmaceutical compound such as solubility, molecular weight, pKa, and affinity for the receptor, as well as extrinsic factors such as the physiological stage of the organism or enzymatic interaction with the surrounding environment, are being considered the major disadvantages of these DDS (Vega-Vásquez et al., 2020).These limitations make the bioactive compound susceptible to degradation or inactivation, decreasing its bioavailability (Chen F. et al., 2018). As a result, a higher frequency of drug administration must be needed, having a direct impact on the cost in addition to increasing the risk of side effects, which can be avoided by applying these processes in the pharmaceutical field (Kumar, 2013).

Nanostructures have been successfully applied in DDS due to their nanoscale particle size that leads to an exponential increase in surface area relative to volume which allows controlling the rate,

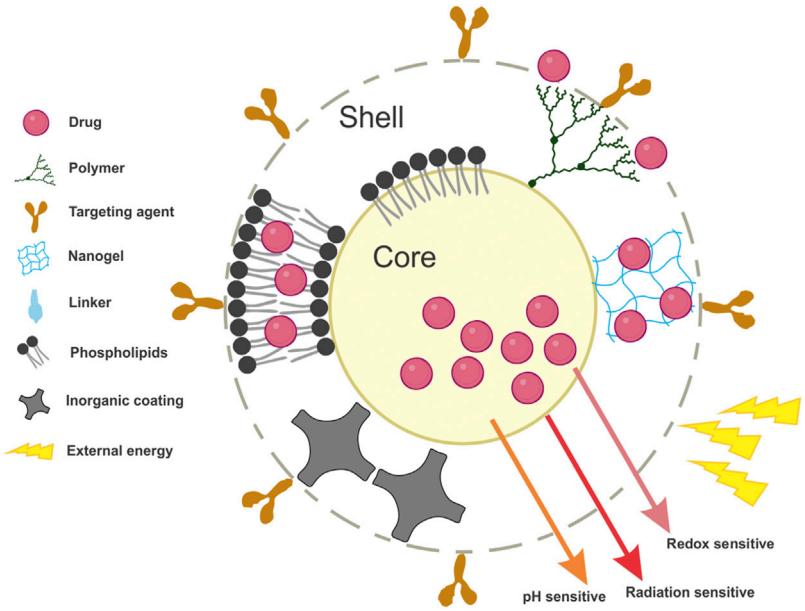

FIGURE 1 | Schematic representation of a nanostructure for drug delivery.

time, and place of the drug release in the body, improving in that way their effectiveness (Lu et al., 2016). Also, a variety of biodegradable polymeric materials such as proteins, polysaccharides, synthetic polymers, and inorganic metallic salts have been used for the nanostructure's synthesis, due to their biocompatibility as well as their mechanical properties that must provide prolonged protection to the pharmaceutical compound allowing chemical stability over time (Patra J. K. et al., 2018). Therefore, several methods such as phase separation (Reichheld et al., 2017), spray drying (Salama, 2020), and ME processes (Egito et al., 2020) are methods that have proven to be successful for nanocarriers synthesis.

ME-based methods are found to be a versatile route to synthesize a variety of nanostructures such as liposomes, nanocapsules, and dendrimers, to name a few (Agrawal and Agrawal, 2012). The manipulation of various components like surfactant or a mixture of surfactants, frequently in combination with a co-surfactant, involved in the formation of an ME enables the synthesis of nanostructures that can improve the target specificity and therapeutic activity of active compounds, and reduce toxicity of drugs, showing an enormous potential to be used as DDS (Fanun, 2012).

In this review article, we have attempted to describe the different nanostructures synthesized by ME techniques as a medium for generating new DDS for therapeutic purposes.

NANOSTRUCTURES AS DRUG CARRIERS

We can understand DDS as the modification of the environment around the drug, by creating an interface between the pharmaceutical compound and the microenvironment allowing to control drug interactions and that facilitates its delivery (Langer, 1998; Allen and Cullis, 2004). However, DDS have faced some challenges inherent to the size of the material used to modify the microenvironment of the drug, like poor bioavailability, *in vivo* stability, and poor solubility, absorption route in the body or issues with target-specific delivery. Over time, DDS had to adapt to new classes of therapeutics in order to enhance the aforementioned disadvantages, particularly improve drug targeting to specific tissues and diminish adverse effects of drugs (Martinho et al., 2011). Therefore, the application of nanostructures could be an excellent option to achieve new horizons to this field.

Nanostructures employed as DDS are complex nanoscale systems, composed of an external layer (shell), which may be functionalized with a variety of polymers and/or metal ions, and the internal layer (core), which is the central section of the nanostructure and chemically composed of different compounds (**Figure 1**). Therefore, the nanostructure-mediated strategy considered to entrap a pharmaceutical compound is possible in the core and shell, and the respective distribution depends on their physicochemical characteristics and also on the type of nanostructure (Mendes et al., 2018).

Nanostructures in the size range from 1 to 100 nm -even 300 nm-can be uptaken by cells in more effective ways compared with large particles ranging from 1 to 10 μm, henceforth, they can directly interact with desired cells with better efficiency and, therefore, reduce side effects (Kabanov et al., 2002; Mirza and Siddiqui, 2014). Also, these nanostructures are designed to respond to internal or external stimuli such as pH, temperature, light, and redox (Rudramurthy et al., 2016; Khan et al., 2019).

In this sense, nanostructures used as DDS must be safe, easily soluble, biocompatible, and bioavailable at the site of treatment. Also, they stay in the blood circulatory system for a prolonged

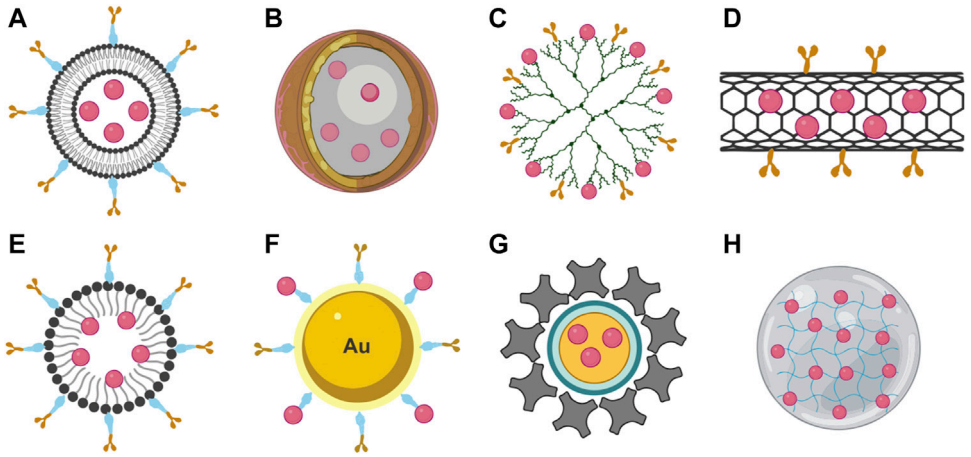

FIGURE 2 | Types of nanostructures used as DDS. **(A)** Liposome, **(B)** nanocapsule, **(C)** dendrimer, **(D)** nanotube, **(E)** polymeric micelle, **(F)** metallic nanostructure, **(G)** quantum dots, and **(H)** nanogel.

period and enable the controlled release of the drug at specific doses and also ensure action of the drug in the target location (Kumar et al., 2020).

ME is a promising technique employed to synthesize nanostructures in which certain properties can be controlled, such as size, geometry, morphology, homogeneity, and surface area (Orive et al., 2004; Razzacki et al., 2004). Therefore, the optimal selection of an ideal DDS depends on the drug properties, the synthesis of the nanostructure, and the method to obtain it, which determine the different properties and the release characteristics of the incorporated pharmaceutical compound (Kabanov et al., 2002). There is extensive research about the development of ME-based proposed as DDS such as liposomes, nanocapsules, dendrimers, and polymeric nanoparticles.

To this point, most of the ME based nanostructures approved for therapeutic use are polymer-based or lipid-based components, however, some non-polymeric nanoparticles, like quantum dots and metallic nanoparticles, are used in some clinical applications. In the further sections, we will summarize these different types of polymer- and non-polymeric based nanoparticles that are currently used as DDS (**Figure 2**).

TYPES OF NANOSTRUCTURES

Nanostructures can be categorized into polymer-, non-polymeric-, and lipid-based nanoparticles. To this point, most of the nanoparticles approved for therapeutic use are polymer-based or lipid-based components. However, some non-polymeric nanoparticles, like quantum dots and metallic nanoparticles, are being used in some clinical applications. In the further sections, we will summarize these different types of polymer- and non-polymeric-based nanoparticles that are currently used as DDS.

Lipid-Based Nanoparticles

Many bioactive molecules used for therapeutic purposes are non-soluble in aqueous systems. Lipid-based nanoparticles (LBNPs) such as liposomes, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC) constitute a broad and diverse group of nanostructures that can transport hydrophobic and hydrophilic pharmaceutical compounds, display very low or no toxicity, and increase the time of drug action by means of a prolonged half-life and a controlled release of the drug (García-Pinel et al., 2019).

Liposomes are one of the first lipid-based nanostructures investigated as a drug carrier that possess a spherical-vesicle structure composed of bilayers of phospholipids and steroids or other surfactants (**Figure 2A**). They can be synthesized through the hydration of dry phospholipids and form spontaneously when certain lipids are dispersed in the media where liposomes are prepared. The United States Food and Drug Administration (FDA) approved lipids used for the preparation of liposomal vesicles are 1,2-distearoyl-sn-glycero-3-pho sphoethanolamine, hydrogenated phosphatidylcholine from soybean lecithin, egg yolk phosphatidylglycerol, and 1,2-distearoyl-glycero-3-phosphocholine. Among all other techniques, the thin film hydration technique is the most suitable and feasible for the preparation of liposomes. Polyethylene glycol (PEG), chitosan, silk-fibroin, and polyvinyl alcohol (PVA) are generally used for surface functionalization and to avoid opsonization of the lipid vesicles.

The liposome can be prepared in different structures, size, and composition (Kumar, 2019). This nanostructure has been in sign the design of delivery systems because of their ability to fuse with cell membranes -inherent to their lipidic bilayer- and release their content into the cytoplasm. The outer shell diameter can range in size from 60 to 300 nm with a hollow core with a diameter of 50–100 nm where the molecule of interest can be loaded to further delivery (Daraee et al., 2016). Different types of liposomes can be synthesized, and they are classified according to the number of lipidic bilayers that compose the liposome. Unilamellar vesicles (can be small or large) possess an aqueous hollow surrounded by a single lipidic bilayer. It can be loaded with both hydrophilic and hydrophobic molecules due to their

structural properties; hydrophilic molecules can be loaded on the aqueous phase and hydrophilic molecules can be dissolved within the lipidic membrane (Oberholzer and Luisi, 2002). This feature is of particular interest since it allows us to load more than one drug within the lipidic or aqueous phases, which in turn allows that the different molecules can be released in sequence with the dissociation of layers from the outer shell to the inner core (Patil and Jadhav, 2014). Liposome formulations are used for delivering anticancer drugs, neurotransmitters, antibiotics, anti-inflammatory, antirheumatic, vaccines, gene therapy, and others.

In the cancer therapy field, recent studies have reported that liposomes integrated with different therapies may be beneficial in a broad range of tumors, not only facilitating antitumor effect but also modulating the tumor immune environment efficacy compared with monotherapy. In addition, adjusting the ratio mix of the pH responder and the lipid can optimize sensibility and specificity of the liposome. Recently, liposomes with matrix metalloproteinase-responsive behavior loaded with a programmed death ligand 1 (PD-L1) inhibitor and doxorubicin (DOX), a low dose achieved better anti-tumor efficacy than the components administered separately (Liu et al., 2019) or even changing composition of the outer shell, like tyrosine hydroxylase peptide-modified liposome, that protects antigen α-galactosylceramide (αGC) from the uptake in β-cells and trigger antitumor responses (Yang et al., 2016b). Interestingly, a combination of cancer therapies can be mixed and enhanced with designed liposomes. One approach is the combination of phototherapy and immunotherapy to deliver a photosensitizer molecule, when activated by light, produces reactive oxygen species to destroy cancer cells (Yang et al., 2016a; Kleinovink et al., 2017; Huis et al., 2020) and the later immunotherapy can improve the therapeutic index of these modalities by enhancing the stability and biocompatibility of cargos as well as reducing sides effects (Calixto et al., 2016; Zhu et al., 2017). In this sense, Li et al. (2018) reported the effectiveness of fluorophore-loaded liposomes (IR-7), a high near infrared region (NIR) absorbance, linked to a multivalent immunoadjuvant, hyaluronic acid-cytosine-phosphate-guanine (HA-CpG). This nanostructure can effectively regulate tumor microenvironment for synergistic photothermal therapy (PTT) and immunotherapy, by inducing the necrosis of cancer cells and promote the maturation of dendritic cells, realizing effective antigen presentation and activation of T cells to recognize and kill cancer cells. Recently, a liposome-based nanoplatform that encapsulated catalases, NIR photosensitizers, and DOX, improved the level of O_2 in tumors via catalyzing intratumoral H_2O_2 has been developed. The generated O_2 could further modulate immune cytokines to activate the immune system, enhancing tumor inhibition *in vivo* (Shi et al., 2020).

Recently, liposomal vaccine formulation showed a selective delivery of tumor antigen to the antigen-presenting cells through incorporation of gangliosides to the outer shell, a natural ligand of macrophages, resulting as an effective platform for cross-presentation and antigen-specific T cell activation (Affandi et al., 2020).

Outer shell modification or functionalization not only enhance targeting, they also can be used to produce liposomes that avoid the mononuclear phagocyte system uptake in order to increase circulation time (Mufamadi et al., 2011). In this sense, Oxaliplatin, a first-line chemotherapy for metastatic colorectal cancer, has been conjugated with a long-circulating liposome PEGylated thermosensitive based, that not only intensify the anti-tumor effect but also increase the retention time up to 24 h, achieving selective release at tumor sites, according to the report by Li et al. (2020).

As a vaccine delivery carrier, they protect antigens from degradation, carry simple or multiple hydrophilic and lipophilic antigens, control the release of the antigens, enhance cellular uptake, and improve antigen-specific immune response (Machhi et al., 2021). It suits different immunization routes including injection, topical administration, oral uptake, and inhalation (Trentini et al., 2014; Wang et al., 2014). Several lipids possess strong adjuvant activity, specially dimethyldioctadecylammonium bromide, a cationic lipid that showed the deposition of the antigen at the injection site, cellular antigen internalization, an antigen association (Anderluzzi et al., 2021). Another report shows that liposomes fabricated with tri-palmitoyl-S-glyceryl cysteine linked to a penta-peptide that carries mRNA for cancer immunotherapy triggers Toll-like receptors preventing tumor growth by increasing cytotoxic T lymphocytes (CTLs) population (Lee et al., 2020). In this sense, liposomes have gained much attention as a platform to deliver nucleic acid-based vaccines since they possess high loading capacity, sustainable release, no leakage, and easy manufacturing.

In response to the COVID-19 pandemic, SARS-CoV-2 mRNA vaccines were designed and produced by ModernaTX (Jackson et al., 2020) and Pfizer-BioNTech SE (Mulligan et al., 2020),which contain a synthetic SARS-CoV-2 mRNA inside a lipid-based nanocarrier to achieve a high-efficient delivery into cells after intramuscular injection by the lipidic nature of the liposome allowing endosomal release of the mRNA into cytoplasm, increase the half-life of mRNA and the latter, lead to a prolonged protein expression at the site of injection (Geall et al., 2012; Pardi et al., 2015) and the latter, development a synergistic effect for immune response against SARS-CoV-2 virus.

Nanocapsules

Nanocapsules are nanomaterials that consist of a liquid/solid core coated with a polymeric shell (Frank et al., 2019) that can be used as a DDS (**Figure 2B**). They provide a unique nanostructure that increases drug loading efficiency due to the reduced polymeric matrix content of nanoparticles (Raffin Pohlmann et al., 2002). Furthermore, encapsulated drug payloads can be protected from degradation or burst release by the polymeric shell that, also, can be functionalized to interact with certain biomolecules to target drug delivery (Zoabi et al., 2021).

Shell materials are critical in the development of nanocapsules, since properties of selected polymers to synthesize them exerts significant influence on stability, encapsulation efficiency, release profile, and biodistribution (Deng et al., 2020). PEG and PVA are the most used biocompatible polymers to synthesize nanocapsules due to their ability to assist drug release by

diffusion and, also, they can be removed from blood via the reticuloendothelial system (Shastri, 2005; Almeida et al., 2011). However, various polymers can be used to formulate the nanocapsule shell to comply with application requirements, and they can be classified as natural or synthetic polymers.

Polysaccharides have been broadly used to synthesize nanocapsules, since they possess highly desirable properties like high biocompatibility. One of the common natural polysaccharides used is the chitosan due to their gelation conditions, mucoadhesive properties, and cationic charge that allows the shell to have electrostatic attractive interactions. Also, it can be endogenously metabolizable into degradable products (Li et al., 2008; De Matteis et al., 2018). Chitosan-based nanocapsules have been used as a delivery system to infectious diseases since cationic charge on the surface improves interactions with bacteria membranes (Jeon et al., 2014; Anversa Dimer et al., 2020). However, the cationic charge of the chitosan shell can induce aggregation of the nanoparticle, protein adsorption, and fast removal from blood circulation. Therefore, anionic polymers can be used to counteract this undesirable feature (Cafaggi et al., 2007; Chen et al., 2010; Shagholani et al., 2015; Belbekhouche et al., 2018). Some research groups explore the possibility of formulating new types of bactericides using this kind of nanostructure enhancing antibacterial activity by increasing the number of chitosan layers. By this approach, Belbekhouche et al. (2019a) developed a chitosan (cationic)-alginate (anionic) nanocapsule that prevents the development of *Escherichia coli* and *Staphylococcus aureus* through membrane dysfunction and denaturation of cellular components due to flexible conformation of the nanomaterial.

Additionally, other polysaccharides have been employed to prepare nanocapsules as drug carriers for different applications, such as poly(cyclodextrin), that have been used to elaborate nanocapsules to efficient encapsulation and deliver 4-hydroxy tamoxifen to podocytes for the treatment in hyperplasia of the breast (Belbekhouche et al., 2019b). Also, heparin-based nanocapsules have been formulated for intracellular release of artesunate in malaria therapy, achieving a high release of the load and an extended half-life, facilitating the intracellular release (Ismail et al., 2019). Hyaluronan nanocapsules have been developed for the intracellular delivery of hydrophobic anticancer drug (docetaxel), enhancing their cytotoxicity -due to its encapsulation- and show to be more stable during storage (Oyarzun-Ampuero et al., 2013).

It has been proposed that protein-based polymers can be used to produce polymeric shells for nanocapasules due to their biocompatibility (by its nature) and tunable properties (De Frates et al., 2018). One example is the use of human serum albumin, which reduces the immunogenicity of the nanoparticle, also serves as a targeting ligand for albondin receptors, which in turn are overexpressed on endothelial cells of tumor blood vessels, providing an excellent drug targeted system. Gaber and collaborators exploited this approach when reporting the development of an albumin-shell oily-core nanocapsule loaded with a combination of exemestane and hesperidin for targeted breast cancer therapy, demonstrating an enhanced internalization onto breast cancer cells leading to a significant reduction of tumor. Overall, this approach offers a promising platform for cancer treatment (Gaber et al., 2019), Also, synthesized materials present certain advantages over natural material since they can be tuned with different chemicals to gain different properties, like ionic, mechanical, solubility, or degradability, according to the application needs (da Silva Júnior et al., 2017). In this sense, poly(ε-caprolactone)-based nanocapsules are an excellent option since they have a low cost and are more suitable for long-term delivery systems compared to other synthetic materials (Gomes et al., 2019). Recently, a poly(ε-caprolactone)-based nanocapsule was developed to load pilocarpine, a glaucoma therapy, increasing the payload and achieving a long-term release for almost 42 days after administration (Lee C.-H. et al., 2017).

Dendrimers

Dendrimers are synthetic polymeric nanostructures characterized by a large number of branching points, a spherical-shaped structure, and monodispersity (**Figure 2C**) (Tomalia et al., 1985). These polymer systems have three well-defined chemical structures: the core, a central nucleus of a single atom or group of atoms; the branches, repeating building blocks, known as "generations," attached to the core that grow and give size to the dendrimer; and functional groups on the surface, which have the capacity of being tunable, according to the application given to the dendrimer (Zhu et al., 2019).

The dendrimers synthesis contemplates divergent and convergent methods. The divergent approaches are from the core to the shell, generation by generation, first with the activation of functional surface groups, and second, with the addition of branching monomer units (Fana et al., 2020). This method can modify the surface of dendrimer molecules by changing the end groups at the outermost layer. However, the formation of defective dendrimers that arise from incomplete growth and side reactions is the main disadvantage of this method (Rai et al., 2016).

In the convergent approach, compounds are constructed from the periphery to the core, involving two stages, first branching units are grown and connected to other groups; second, when the growing branches, called dendrons, are large enough, they attach to a core for the formation of a complete dendrimer (Hawker and Fréchet, 1990). This method allows better structure control of dendrimers because of the low possibility of side reactions. However, the production of high generation dendrimers can be a problem because steric barrier occurs in the reactions of the dendrons and the core molecule (Caminade et al., 2006).

Hence, the most important difficulty in a dendrimer synthesis process is to ensure the full substitution of all reactive groups to avoid structure defects. To overcome those problems, other methods like "hypercores" and "branched monomers," involving the pre-assembly of oligomeric species to hasten up the rate of dendrimer synthesis (Chavda, 2007); "double exponential," allowing the preparation of monomers in either the divergent and convergent growth from a single starting material (Kawaguchi et al., 1995); and "lego" and "click chemistry," leading a higher growth in the number of terminal

surface groups in few reactions (Arseneault et al., 2015), are being developed with the intention to minimize the number of reaction steps, the starting materials, the reaction time, and the cost associated with the dendrimers production (Kesharwani et al., 2014).

In addition to the dendrimers physicochemical properties mentioned before, polyvalency, precise molecular weight, increased solubilization, control over macromolecular growth, internal cavities available to host small molecules, biocompatibility, and absence of immunogenicity provide them the ability to be used as a novel DDS (Sandoval-Yañez and Rodriguez, 2020).

Poly-(amidoamine) (PAMAM) and polypropylenimines (PPI) are the most dendrimers polymers evaluated for their efficient drug delivery due to the availability of a great density of amine groups on their surface Also, the dendrimers structure determines the number and type of bioactive molecule in a DDS, which can be covalently conjugated to the dendrimer terminal groups or enclosed within the core by hydrogen bonding, electrostatic interaction, or hydrophobic linkages (Nikzamir et al., 2021).

In this sense, dendrimers, as carriers of different drugs, should be nontoxic, non-immunogenic, permeable, able to target specific structures, have the ability to extend the circulation time of the drugs, and protect them from the environment (Chauhan, 2018). In oral drug delivery, the dendrimers have been shown to improve the drug solubility due to their capability to decrease non-specific interactions with protein of food, leading to increase the drug absorption via intestinal epithelium (Sadekar and Ghandehari, 2012). Fourth generation PAMAM dendrimer covalently linked to ibuprofen (PAMAM-G4-OH) were synthesized by Kolhe et al. (2006). These authors suggested that the dendrimer improved the drug efficacy by enhancing cellular delivery compared to pure ibuprofen. In ocular drug delivery, dendrimers are an ideal carrier system due to non-irritating, biocompatible, sterile, isotonic, and biodegradable properties (Raj et al., 2020). Viewed in this way, Vandamme and Brobeck (2005) improved the bioavailability of the pilocarpine increasing the resident time in the eye of the drug by using PAMAM dendrimers. These nanostructures have been shown to be efficient as a transdermal delivery system of non-steroidal anti-inflammatory drugs (NSAIDs). Several researchers have indicated that the PAMAM dendrimer complex with NSAIDs can increase the permeation of drugs through penetration enhancers (Manikkath et al., 2017). In pulmonary delivery drugs Conti et al. (2014) developed inhalable generation four amine-terminated PAMAM dendrimer (G4-NH2) siRNA complexes (dendriplexes) by spray drying technique using mannitol and an emulsification diffusion method using chitosan-g-lactic acid. The results showed that the approach of encapsulating siRNAG4-NH2 by emulsification diffusion has superior potential as a pulmonary delivery system. Finally, dendrimers have emerged as versatile carriers as targeted delivery drug systems by passive as well as active routes, which is achieved by the branching units and surface groups of dendrimers (Agrawal and Agrawal, 2012). This approach is particularly effective in treating fatal disorders like cancer as reported by Quintana et al. (2002), who synthesized folate conjugated dendrimers for targeting anticancer bioactive tumors. Since the folate receptors are overexpressed on the surface of different types of cancer cells such as ovarian and breast cancer, hence folate conjugated dendrimers can efficiently target anticancer bioactive cancer cells.

Nanotubes

Carbon nanotubes (CNTs) are cylindrical molecules made of carbon atoms. They are graphene sheets rolled into a seamless cylinder that can be open ended or capped, having nanometric diameters and a length of several micrometers (Elhissi et al., 2012) (**Figure 2D**). CNTs have physicochemical properties, such as electrical and thermal conductivity, strength, stiffness, toughness, and low density. Also, their small size, high surface area to volume ratio, and their ability to be functionalized give them exceptional properties to be used in the medical field (Kushwaha et al., 2013).

CNTs are divided into two categories: single-walled carbon nanotubes (SWCNT), which consist of single layer of cylinder graphene; and multi-walled carbon nanotubes (MWCNTs), which contain multiple layers of graphene sheets (Figure 3). Both, SWCNTs and MWCNTs, are capped at ends of the tubes with a hemispherical arrangement of carbon networks called "fullerenes" wrapped up by the graphene sheet (Iijima, 1991).

CNTs have hydrophobic surfaces in which a functionalization process of these nanostructures has been proposed as a solution to this problem. Functionalization is a chemical synthesis process in which desired functional groups can be introduced onto the CNTs walls (Kaur et al., 2018). Due to the above, the process of functionalization imparts high solubility with enhanced biocompatibility to the CNTs, being highly suitable for encapsulation of therapeutic molecules for multimodal targeted delivery. There are two methods through which the functionalization process can be carried out: covalent (chemical bond formation) and noncovalent bonding (physioadsorption) (Beg et al., 2018).

Covalent bonding between nanotubes and the attached molecule involves the polymerization of monomers from surface-derived initiators on CNTs or the addition of preformed polymer chains, respectively (Madani et al., 2011). In order to achieve this type of functionalization, CNTs are subjected to treatment with chemical and high temperature reflux conditions. The oxidation of CNTs is the most common technique used for generating covalent functionalization, in which a concentrated acid such as nitric or sulfuric are sonicated and heated, allowing the side-wall covalent functionalization; that results in the attachment of carboxylic acid groups, rendering CNTs water-soluble (Jahangirian et al., 2017). In DDS, the covalent functionalization of drug molecules to CNTs surface has been less reported. However, for therapeutic biomacromolecules, such as proteins, peptides, DNA, and siRNA, covalent functionalization has been widely practiced (Chen et al., 2011).

The noncovalent bonding involves the attachment of therapeutic drug molecules onto the surface of CNTs by adsorption mechanism. The hydrophobic and π-π stacking interaction force between the chains of adsorbed molecules

and the surface of CNTs helps in the functionalization on the surface (Tang et al., 2012). The hydrophobic interaction is the more widely used method in drug delivery and it can be carried out by coating CNTs with amphiphilic surfactant molecules or polymers creating a micelle-type structure. On the other hand, the π-π stacking interaction force between the chains of adsorbed pyrene molecules and the surface of CNTs can help in the functionalization on the surface. However, this process was shown to be unstable, as it is cleaved by nucleases, limiting the biologic applications (Liu et al., 2010).

Functionalized CNTs have some potential advantages over other delivery systems, such as an exceptionally high drug loading capacity due to their high surface area and the possibility for incorporating additional therapeutic and diagnostic moieties, either on the surface or their inner cavity (Yadav and Mohite, 2020).

The applications of CNTs in drug delivery through the oral route have been used in tablet coating with hydrogels such as ethyl cellulose, cellulose acetate, and hydroxypropyl methylcellulose for achieving the desired sustained release profile of drug delivery. In 2012, Madaeni and collaborators (Madaeni et al., 2012) reported a carboxyl functionalized MWCNT for sustained therapeutic action of indomethacin. In targeted drug delivery, the cylindrical CNTs shape enable a transmembrane penetration into the target cell; due to the above, choriocarcinoma, carcinoma of cervix, breast cancer, prostate cancer, brain gliomas, and testicular tumors, are some of the disorders in where the CNTs have the potential for delivery of anticancer agents (Dineshkumar et al., 2015). In this sense, Bottini et al. (2011) have reported that the generation of poly(ethylene glycol) (PEG)-modified CNTs have favorable pharmacokinetic and toxicology profiles, i.e., SWCNTs functionalized with PEG and conjugated with the monoclonal antibodies are able to selectively target the CD20 cell surface receptor present on β-cells, with little nonspecific binding to negative T-cells. This approach has proved to be an alternative way in targeting drug molecules to the cancer cells. The potential of CNTs has also been used for ocular drug delivery, due to the advantage of enhanced retention ability in the retinal site to release the drug molecules (Chaurasia et al., 2015). However, the ocular route has not been explored much in this regard.

Polymeric Micelles

Polymeric micelles (PMs) are other nanostructures, which have gained attention for encapsulating and delivering hydrophobic drugs (**Figure 2E**). PMs, with diameters ranging from 10 to 100 nm, are self-assembled nanostructures formed in aqueous solutions characterized by a core–shell structure; the inner core is composed of the hydrophobic regions which encapsulates the poorly water-soluble drug, whereas the outer shell or corona of the hydrophilic block of the copolymer protects the drug from the aqueous environment (Xu et al., 2013).

Hence, PMs always contain a nonionic water-soluble compound and an ionic compound that can be neutralized by an oppositely charged surfactant to form a hydrophobic core. The electrostatic interaction between the ionic segment of the block polymer and the surfactant group changes these segments from water-soluble to water-insoluble, leading to a hydrophobic core in the micelles (Ahmad et al., 2014).

Self-assembled PMs have special characteristics as delivery systems, such as high loading capacity and improved solubility of drugs, decreased systemic unfavorable effects, enhanced permeability and retention effect, and their possible modification of physicochemical characteristics (Vonarbourg et al., 2006).

The PMs carriers for the purpose of drug delivery are synthesized under three distinct designs: the micelle-forming polymer–drug conjugates, in which the drug incorporation within the micellar carrier is achieved through the formation of hydrolysable chemical bonds between the functional groups of the polymeric backbone and the drug (Girase et al., 2020); the polymeric micellar nano-containers design, which can be achieved only if the block copolymer and the drug are water soluble. In this system, the formation of hydrophobic interactions or hydrogen bonds between the micelle-forming block copolymer and drug provides the basis for the solubilization of drugs in the polymeric micelles (Shahin and Lavasanifar, 2010); and, finally, the polyion complex micelles, in which the incorporation and delivery of different therapeutic moieties that carry charge are needed to promote the electrostatic interactions between oppositely charged polymer and drug combination (Chen W. et al., 2018).

The drugs get released from PMs by two major pathways: dissociation of the micelle followed by the separation of the drug from monomers and drug–polymer bond breakage within the micelle followed by diffusional escape from the delivery system (Aliabadi and Lavasanifar, 2006). Also, it is important to know that the incorporation efficiency of PMs depends on the initial amount of drug added. After maximum loading capacity, the drug is precipitated. In this sense, the drug loading efficiency also depends on the aggregation number of the PMs. Micelles with high aggregation number cause more solubility of the given drugs in the inner core (Lee et al., 2012).

Polymeric segments composed of poly(ethylene oxide) (PEO) (Iurciuc-Tincu et al., 2020) and biodegradable polymers like polyesters like PEG (Xu et al., 2019) are employed to form the hydrophilic outer shell of PMs. Other authors have reported the use of poly(acryloylmorpholine), poly(trimethylene carbonate), and poly(vinylpyrrolidone) (Zhang et al., 2006; Nagarwal et al., 2011) (Gjuroski et al., 2019), respectively. For the hydrophobic core of PMs, poly(glycolic acid), poly(D-lactic acid), poly(D,L-lactic acid), copolymers of lactide/glycolide, and poly(e-caprolactone) are some of the most commonly used polyesters (Bassyouni et al., 2015).

One of the most important applications of PMs is in oral chemotherapy, because most anti-tumor drugs are not orally bioavailable (Feng et al., 2011). As a result, the absorption improving mechanisms by PMs may involve different membrane permeating behavior, inhibition of efflux transports as well as bioadhesive properties (Gong et al., 2012). Paclitaxel is a significant anti-tumor agent and has been shown to exhibit high activity against various solid tumors, including ovarian, breast, non-small cell lung cancers, and head and neck carcinomas. Jing and co-workers developed a PM from paclitaxel/mPEG–PLA

block copolymer prodrug. The antitumor activity of this PM was evaluated by MTT assay against human liver cancer H7402 cells and the results indicated that paclitaxel can be released from the conjugate without losing cytotoxicity (Zhang et al., 2005). In targeted drug delivery, (Kabanov et al., 1989) showed that the neuroleptic activity of intraperitoneally administered haloperidol is increased by more than two orders of magnitude after its incorporation into poly(ethylene oxide) –poly(pro-pylene oxide) –poly(ethylene oxide) (PEO–PPO–PEO) micelles coupled with brain specific antibodies. The enhancement of drug efficacy was attributed to specific targeting and increasing the drug permeability through biological membranes given by the polymeric amphiphiles.

Metallic Nanostructures

Metallic nanostructures have a highly potential use in targeted DDS. These metal-based nanoparticles are generally made from gold, silver, gadolinium, and iron oxide, which are delivered in a colloidal form and hold the potential to carry large drug doses increasing their therapeutic index (Ahmad et al., 2010). Drug loading on this type of nanostructure can be achieved through non-covalent interactions, where no specific bond cleavage is required for drug release and only alteration in native physical forces is required. Several functionalization methods for this type of nanomaterial are currently used, like oligo or PEG, BSA, amino acids or tailored peptides, to name a few, which each of them possesses unique features to make them suitable for their biological application (Lee et al., 2008; Lipka et al., 2010; Rink et al., 2010).

The gold nanoparticles have been widely used as drug and gene delivery vehicles (**Figure 2F**). They can be synthesized in a variety of forms such as rod or dot, with sizes ranging from 0.8 to 200 nm, that make them easily detectable within micromolar concentrations, warranting their favorable optical applications (Wang L. et al., 2017). Recently, there is a new trend in metallic nanostructure synthesis where microorganisms like bacteria, fungi, algae, yeast, or even plants can form the nanoparticle intra- or extracellularly by mixing an adequate growth media with metal precursor solution (Metz et al., 2015; Moghaddam et al., 2015). Using this synthesis approach, there are several reports of gold, silver, cadmium sulfide, and titanium dioxide-based nanostructures synthesized using different bacteria, like *Escherichia coli* or *Bacillus subtilis,* and surprisingly, they still possess all the aforementioned characteristics (Iravani, 2014).

With regard to biocompatibility, cells have been shown to intake gold nanoparticles without cytotoxic effects (Fadeel and Garcia-Bennett, 2010). Hirsch and collaborators reported that intra-tumoral injection of gold-nanoparticles resulted in irreversible tissue damage upon exposure to low doses of near infrared light (Hirsch et al., 2003).

Also, metallic nanoparticles have been used as new carriers in cancer treatment due to the significant advantages they possess, such as increased stability and half-life as drug carriers in circulation, required biodistribution, and passive or active targeting into the required tumor site (Mody et al., 2010). The development of tumor-targeted gold nanoparticles encoded with a Raman and further encapsulated with a thiol-modified PEG coat was reported by Qian et al. (2008). Additionally, to specific targeted tumor cells, the pegylated gold nanoparticles were then conjugated with an antibody against epidermal growth factor receptor, which is sometimes overexpressed in certain types of cancer cells. The results obtained suggested a high specific recognition and detection of human cancer cells, as well as active targeting of epidermal growth factor receptor-positive tumor xenografts in animal models.

Recently, a ferric-ferrous mixture of nanoparticles (5–20 nm) were conjugated with erythropoietin (EPO) to deliver it to injured sites in the central nervous system with EPO receptors, increasing the amounts of EPO available for neuro-protective action. More interesting was the fact that the nanostructure can be guided using magnetic control without displaying neurotoxicity in the form of a particle or solution (Nguyen et al., 2020).

Quantum Dots

Quantum dots (QDs) are a particular category of nanoparticle characterized by a crystalline structure. There are core-QDs, which have uniform internal composition, and core-shell QDs, which had different molecules as core and shell that cover it (**Figure 2G**). In this sense, the basic structure of QDs is made up of a semiconductor core, a shell, and a cap. The shell acts as a protective block for the core —which controls their overall properties— and is responsive for capping ligands coat the core and the caps provide solubility in aqueous media. Cadmium sulfide and cadmium selenide QDs are among the most popular core materials for these nanostructures (Juzenas et al., 2008), since they provide noble optical characteristics, nevertheless, cadmium is probably toxic to human cells (Mo et al., 2017).

Their diameter typically ranges from 1 to 50 nm, which is a desirable property that had made them a tool in biomedical research, especially for multiplexed, quantitative, and long-term fluorescence imaging and detection that are not available for individual molecules or bulk semiconductor solids. One of the most important emerging applications of QDs is like traceable drug delivery, because of the potential to elucidate the pharmacokinetics and pharmacodynamics of drugs (Probst et al., 2013). The combination of using DD and diagnose in a single application is known as *theranostics*, a field in which QDs have been widely exploited.

As pointed out by Zhao and Zhu (2016), a quintessential QD nanocarrier material for DD should possess the following properties: should not react with payload drug, high drug capacity and encapsulation efficiency, appropriate preparation and purification method, good biocompatibility and low cytotoxicity, mechanical strength and stability, appropriate particle size and shape, and longer residence time *in vivo*. Recently, they gained research interest as DD since their surface can be modify *ad hoc* (attached through COOH groups) with tailored peptides, folate, or any other biological molecules to targeted delivery to specific organs (Heyn, 2016; Khodadadei et al., 2017) therefore reducing systemic toxicity.

In this sense, Wang et al. (2017) engineered a QD NIR fluorescence indium phosphate core and a zinc acetate shell,

whose cytotoxicity are less compared with cadmium-based cores, with EGFR nanobody (low weight protein derived from heavy-chain antibody) conjugated onto the surface in order to target EGFR-overexpressing tumor cells and deliver aminoflavone. This study shows a successful strategy in which a nanobody surface modification can target specific cells and improve the cellular uptake and cytotoxicity.

Recently, graphene QDs have positioned in the sight of researchers because they possess good solubility, large surface area, easily functionalized edges, and present excellent biocompatibility. Interestingly, graphene QDs alone, without functionalization, are transported through a biological membrane by a lipid raft-mediated mechanism (Wang et al., 2015), where the smaller the size of QD, the higher the apparent membrane permeability is. More recently, Du et al. (2020) used graphene QDs as an oral DD for vanadium compounds, which are anti-diabetic agents. They tested this nanocarrier in a type 2-diabetic mice model (*db/db*) and they observed a delayed glucose lowering profile but more profound effects on insulin enhancement and β-cell protection after 3 weeks of treatment. One interested observation was that they report that QD alone could effectively lower blood lipid levels on the aforementioned mice model.

There are two main techniques used to synthesize QDs: top-down processing methods and bottom-up approach. Top-down processing method consists of making a bulk semiconductor thinned by electron beam lithography, reactive-ion etching, and/or wet chemical etching. On the other hand, bottom-up or self-assembly techniques implies precipitation methods (wet-chemical method) which are generally microemulsion methods, sol-gel, competitive reactions, to name a few (Valizadeh et al., 2012). Other techniques are those based on the vapor-phase method to produce QDs that begin with processes in which layers are grown atom by atom; these methods are mainly used to produce QDs from III-V semiconductors and II-IV semiconductors (Bera et al., 2010).

Nanogels

Nanogels are three-dimensional networks formed of hydrophilic polymers cross-linked by either physical or chemical bonds (**Figure 2H**). The natural polymeric macromolecules used to form these nanostructures include chitosan, dextran, and sodium alginate in which the presence of numerous polar groups such as –OH, –COOH, $–CONH_2$, and $–SO_3H$ distributed along the polymer chain gives the hydrophilic nature to nanogels. Also, synthetic polymers include poly(N-isopropylacrylamide) (PNIPAm), poly(ethylene oxide) (PEO), poly(ethyleneimine) (PEI), and cholesterol-bearing pullulans are considered to form nanogels despite the risk of the presence of toxic compounds within their structure (Cuggino et al., 2016).

Nanogels have been promoted to use as carriers of bioactive molecules due to their advantageous properties such as nanoscale particle size, great stability, large inner surface area, biocompatibility, and good permeation capability. Also, these nanostructures are designed to respond to internal or external stimuli such as pH, temperature, light, and redox (Soni and Yadav, 2016).

The synthesis of nanogels by ME is especially used to control their particle size. In this method a colloidal suspension of the polymer is made by the homogeneous nucleation of water-soluble monomers that are used to synthesize stabilized nanogels. Nanogels of smaller particle size can be synthesized by adding an ionic surfactant, which also increases the colloidal stability of the formulations. As the surfactant concentration decreases, particle size increases in the nanogel formulation (Sharma et al., 2016).

According to their properties as DDS, nanogels are classified in two different types. Nanohydrogels, which can carry a variety of low and high molecular weight drugs, can absorb a large quantity of water or biological fluids within its structure acting as a filter for the diffusion of solutes, while preserving its arrangement. The second type of nanogels is nano-organogels, which have the capability to hold oily bioactive compounds, forming aggregates in contact with water while enfolding their hydrophilic regions at the center (Suhail et al., 2019).

Nanogels thus have the unique capability to encapsulate more than one bioactive compound in the same carrier which is not feasible in other nanostructures such as dendrimers, PMs, or liposomes (Hajebi et al., 2019). Considering these properties, a nanogel loaded with nanovesicles as an efficient topical delivery of drug can be a feasible approach. In this sense, Abdel-Rashid (2019) developed an ocular surfactant-based nanovesicle carried in mucoadhesive chitosan-based nanogel for topical delivery of acetazolamide (ACZ) to lowering intraocular pressure, which results are significantly prolonged in comparation to ACZ tablets alone.

Great potential has been shown by nanogels in many fields including delivery of genes, chemotherapy drugs, targeting of specific organs, and several others. Nanogels are used in the treatment of cancer as carriers of low-molecular weight drugs such as doxorubicin, cisplatin, 5-fluorouracil, and heparin, to name a few (Jayakumar et al., 2012). Synthetized doxorubicin loaded chitin nanogels showed a relatively higher toxicity on prostate, breast, lung, and liver cancer cells. As an example, Shi and collaborators (2017) developed a selectively intracellular delivery pH and reduction dual-responsive polypeptide nanogel as a hepatoma chemotherapy; this nanogel maintains structural integrity and minimal doxorubicin release in the circulatory system and shows on-demand cell uptake via endocytosis, accumulation in tumor tissue, cell proliferation inhibition, tumor suppression activity, and low cytotoxicity in off target cells. In the same way, Sahu and collaborators (2019) synthesized a chitosan-based pH responsive biodegradable nanogel loaded with 5-fluorouracil as a topical chemotherapy of aggressive melanoma in mice. This nanogel shows a sustained drug release kinetics and induce apoptosis on target cells at low drug doses by an endocytosis mechanism. They report that payload releases at slightly acidic microenvironment resulting in selective accumulation on tumor site, which they state to be a promising platform for efficient and sustained delivery of chemotherapy agent.

TABLE 1 | Selected nanocarriers synthetized by ME and their applications

Nanocarrier and particle size	Payload	Disease/condition	Features	Reference
Liposome (119–137 nm)	Doxorubicin	Leukemia	BAT1-Liposome endocytosed by CXCR4-overexpressing cells. Show increasing selective uptake of payload, reducing bystander toxicity	McCallion et al. (2019)
Liposome (84–114 nm)	Quercetin	Lung cancer	Functionalized surface with T7 peptide for targeting TFR-overexpressing cells. Displays enhanced cellular uptake, cytotoxicity, and apoptosis	Riaz et al. (2019)
Liposome (10–125 nm)	*Slug* miRNA	Triple negative breast cancer (TNBC)	tLyp-1 peptide-modified functional liposomes uptaken through NRP-dependent internalization on tumor cells. Shows long duration of circulation, accumulate at the tumor site	Yan et al. (2019)
Liposome (137.93 nm)	Paclitaxel	Breast cancer	Estrone-conjugated liposomes targeting cancer cells overexpressing estrogen receptors. Exhibits high-efficiency, low-toxicity, long-term circulation, reduced side effects of payload and tumor accumulation	Han et al. (2020)
Liposome (111–449 nm)	Berberine	Hypercholesterolemia	1,2-Distearoyl-sn-glycero-3-phosphoglycerol and hydrogenated soy phosphatidylcholine-based liposome that present pH-dependent extended drug release behavior with aims to advance the oral bioavailability of payload	Duong et al. (2021)
Nanocapsule (~200 nm)	Docetaxel	Lung cancer	Hyaluronic acid-based nanocarrier able to enter cancer cells providing intracellular drug release, stability during storage, reconstitution of freeze-dried nanocarrier and improve pharmaceutical effect of payload	Oyarzun-Ampuero et al. (2013)
Nanocapsule (221–249 nm)	Pilocarpine	Glaucoma	Poly(ε-caprolactone) based nanoparticle with high encapsulating capability. Displays long-term drug release by the low diffusion of the payload from the hollow nanostructure	Lee et al. (2017a)
Nanocapsule (157–173 nm)	Exemestane and hesperetin	Breast cancer	Albumin-shell nanocarrier, loaded with a combination of hydrophobic drugs. Targets cancer cells. Passive and active targeting of the payload to the tumor site, reducing tumor volume and promoting necrosis; limited multiple drug resistance through the co-delivery of both drugs to the same cell; formulation showed stability over 3 months of storage	Gaber et al. (2019)
Nanocapsule (112.1 nm)	Artesunate	Malaria	Artesunate-heparin conjugate based nanocapsule that showed auspicious colloidal stability and effective release of parent drug in simulated physiological acidic microenvironment. Heparin coating led to extended circulation in bloodstream	Ismail et al. (2019)
Nanocapsule (20–30 nm)	Rituximab (Anti-CD20 mAb)	Tumor metastasis into the central nervous system (CNS) and lymph nodes (LN)	Neutral polymer based nanocarrier that allows penetration of payload into selected tissue (CNS and LN) by systemic delivery through a single intravenous injection; sustains payload in circulation and release it in controlled fashion *via* hydrolysis under physiological pH conditions	Qin et al. (2020)
Dendrimers (20–30 nm)	Ibuprofen	Anti-inflammatory therapy	PAMAM dendrimer with high drug payload for enhanced cellular delivery through fluid phase endocytosis by non-specific interactions and localizes predominantly in the cytoplasm, achieving high intracellular concentration of the drug at site of action minimizing systemic side effects	Kolhe et al. (2006)
Dendrimers (143–302 nm)	AT1R siRNA	Cardiovascular disease	Cell penetrating peptide linked to PAMAM "tadpole" dendrimer that regulate siRNA complexation and endosomal escape; displays improved targeting, internalization, and efficient siRNA delivery in cardiomyocytes	Liu et al. (2013)

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TABLE 1 | (*Continued*) Selected nanocarriers synthetized by ME and their applications

Nanocarrier and particle size	Payload	Disease/condition	Features	Reference
Dendrimers (4–11 nm)	Doxorubicin	Lung cancer	G3NH2-PAMAM based dendrimer that showed modulable release and local delivery of payload to lungs; achieve nuclear colocalization and therefore enhances time-dependent cell kill	Zhong and Da Rocha, (2016)
Dendrimers (202–219 nm)	Apoptin pDNA	Hepatocellular carcinoma	Ornithine conjugated PAMAM dendrimer that releases payload into cytosol through endocytosis; showed very low cytotoxicity, cell viability, enhanced transfection efficiency, and intracellular uptake, and could induce apoptosis *via* the mitochondria-mediated pathway	Bae et al. (2017)
Dendrimers (Not reported)	Nitric oxide	Chronic rhinosinusitis (CRS)	Star copolymer consisting of the b-cyclodextrin (b-CD) core and seven PAMAM-G3 arms, with high drug payload carrier and high cytotoxicity in bacteria	Liu et al. (2021)
Carbon Nanotube (d = 50 nm; l = < 500 nm)	Gemcitabine	Lung and pancreatic cancers	Single-walled carbon nanotubes functionalized through carboxylation, acylation, amination and PEGylation, with high loading capacity, low cytotoxicity and afford higher efficacy in suppressing tumor growth. Uptake mechanism was possibly due to the tubular and nanoneedle shape, which could passively penetrate the cells to the later accumulates into the tumor cells and released GEM at a high concentration level	Razzazan et al. (2016)
Carbon Nanotube (~180 nm)	Dexamethasone	Rheumatoid arthritis	PEG coated carbon nanotube conjugate with payload that improves intracellular drug delivery via increased caveolin-dependent endocytosis and suppressed the expression of major pro-inflammatory cytokines and shows high drug uptake and efficient drug release from endosome, even with low-dose of the drug	Lee et al. (2017b)
Carbon nanotube (d = 30–70 nm, l = 100 nm–2 μm)	Doxorubicin	Tumor cells	Folic acid (FA)-modified multiwalled carbon nanotubes that show active targeting and pH-responsive for delivering the payload drug to tumor cells overexpressing FA receptors and inhibit their growth. Importantly, payload side effect decreased	Yan et al. (2018)
Carbon nanotube (d = 1 nm)	Amphotericin B	Visceral leishmaniasis	Amine-functionalized carbon nanostructures that doesn't alter the viability of intracellular targets because of their uptake by lymphocytes and macrophages; these are nontoxic to macrophages, and they show inhibition of the intramacrophage parasite at very low concentrations	Gedda et al. (2020)
Carbon nanotube (200–400 nm)	TLR9 Stimulator (unmethylated cytosine and guanine dinucleotide)	Colon cancer	Carbon nanotubes conjugated with CpG complex that displayed a significant antitumor effect, also TGF-ß induced epithelia-mesenchymal transition was effectively blocked, increasing survival rates	Jin et al. (2021)
Polymeric micelle (not reported)	Paclitaxel/mPEG–PLA block	Hepatocellular carcinoma	Monomethoxy-poly(ethylene glycol)-b-poly(lactide) based polymeric micelle that is covalently connected to payload, slowing down the release rate of the drug without losing cytotoxicity. Relace kinetics may be adjusted by poly(lactide) block biodegradation. Show antitumor effect and their cytotoxicity on cancer cells depends on the drug concentration	Zhang et al. (2005)
Polymeric micelle (24–816 nm)	Quercetin	Breast and ovarian cancer	Pluronic polymers-based micelles thar exhibited sustained release of payload drug. Showed increased in cytotoxicity in breast, ovarian and multidrug resistant cancer cells and also exhibited an enhanced antioxidant activity compared to free drug	Patra et al. (2018a)

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TABLE 1 | (*Continued*) Selected nanocarriers synthetized by ME and their applications

Nanocarrier and particle size	Payload	Disease/condition	Features	Reference
Polymeric micelle (~60 nm)	Myricetin	Ocular anti-inflammatory treatment	Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer polymeric micelles to increases aqueous solubility, stability, and corneal permeability to promote payload efficacy in eye. showed high storage stability, micelle solution had no significant cytotoxicity and displayed high cellular uptake	Sun et al. (2019)
Polymeric micelle (196 nm)	Cabazitaxel	Prostate cancer	PEG-cholesterol block based polymeric micelle that targets matrixmetaloproteinase-2, which is overexpressed in tumor microenvironment of prostate cancer; displays high drug loading, high entrapment efficient and very low critical micelle concentration; showed high cellular uptake, inhibition on tumor growth and the drug release depends on cleavage of PEG on micelle	Barve et al. (2020)
Polymeric micelle (220 nm)	Berberine	Skin diseases/antimicrobial treatment	Thiolated pluronic polymer micelles that's binds to keratin through a disulphide bond, to produce epidermis retention but did not penetrate to deep skin layer; shows safety profile with no potentially hazardous skin irritation and transdermal administration and reduced the amount of drug that entered the systemic circulation	Niu et al. (2020)
Metallic nanoestructure (8–11 nm)	Usnic acid	Medical device-related infections/ antimicrobial treatment	Surface-engineered manganese iron oxide nanostructure coated with two different polymers, were able to load the drug and bind to the negative bacterial cell membrane causing an alteration of cell wall integrity and promoting the penetration of the released significant drug amounts into the cell membrane	Taresco et al. (2015)
Metallic nanoestructure (70–80 nm)	Docetaxel	Breast and cervical cancer	Hyaluronic acid-cleavable peptide-gold nanoparticles show selective delivery of the payload, show greater cytotoxicity and higher tumor suppression efficacy in tumor; induced cell death via apoptosis by targeted delivery of the drug in the mitochondria	Gotov et al. (2018)
Metallic nanoestructure (39 nm)	Resveratrol	Liver cancer	Nano-gold particle that showed a high payload carry capability and locate in mitochondria; show stronger effect on inhibiting cell proliferation and promoting apoptosis in tumor tissue. No observable toxicity was found on non-tumor cells	Zhang et al. (2019)
Metallic nanoestructure (850 nm)	Erythropoietin	Central nervous system (CNS) injuries	Ferric–ferrous based nanostructure coated with alginate that can pass through the lung capillaries with showing the high coating efficiency and high cellular uptake to target site. Controlling the alginate degradation rate could potentially control the payload release rate applying a magnetic field to the target area	Nguyen et al. (2020)
Quantum dots (7–17 nm)	Methotrexate	Breast cancer	Nitrogen-doped graphene quantum dots that shows good biocompatibility and high drug loading capacity; payload slowly diffuse in and out of the cancer cells, resulting in lower cytotoxicity than payload alone in short times, but cytotoxicity behavior is inverse on prolonged exposure times	Khodadadei et al. (2017)
Quantum dots (3–5 nm)	Aminoflavone	Triple negative breast cancer (TNBC)	A quantum-dot based micelle conjugated with an anti-epidermal growth factor receptor nanobody engineered for EGFR-overexpressing cancer cells; show accumulation in in tumors at higher concentrations, leading to more effective tumor regression; there was no systemic toxicity	Wang et al. (2017b)

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TABLE 1 | (*Continued*) Selected nanocarriers synthetized by ME and their applications

Nanocarrier and particle size	Payload	Disease/condition	Features	Reference
Quantum dots (d = ~4 nm)	Doxorubici	Fibroblast cells (Cos-1 cells)	Maltose binding protein-CdSe/CdS/ZnS quantum dots that, once delivered to the cellular cytosol, could be triggered to release its payload by the addition of maltose to the extracellular medium; temporally controlled maltose-induced drug release is ideal for the triggered release of cytosol-targeted drugs that require tight regulation of their bioavailability by the systemic delivery of an extracellular effector molecule	Field et al. (2018)
Quantum dots (5 nm)	Bevacizuma and ranibizuma	Age -related macular degeneration	Graphene quantum dots coated with β-cyclodextri showed enhanced solubility and enables drug loading with controlled release on cell target; pH sensitive drug release rate	Qian et al. (2018)
Quantum dots (2.5–3.5 nm)	Vanadium compounds	Type 2 Diabetes	Graphene quantum dots that exhibited membrane permeability with reduced cytotoxicity; showed improved pharmacokinetic performance; is transported across the cell membrane via lipid raft-mediated transcytosis, nanocarrier alone effectively lower the blood lipid levels of mice model	Du et al. (2020)
Nanogel (~120 nm)	Doxorubicin	Hepatoma	Selectively intracellular delivery pH and reduction dual-responsive polypeptide nanogel that maintains structural integrity and minimal drug release in the circulatory system and shows on-demand cell uptake via endocytosis, accumulation in tumor tissue, cell proliferation inhibition, tumor suppression activity and low cytotoxicity in off target cells	Shi et al. (2017)
Nanogel (65–75 nm)	Shikonin	Osteosarcoma	Peptide-decorated disulfide-crosslinked polypeptide nanogel targeting and kill VIM-overexpressing cells by inducing RIP1- and RIP3-dependent necroptosis; efficiently suppressed tumor growth and reduced pulmonary metastasis; showed low systemic toxicity and high cytotoxicity in cancer cells due increased cellular uptake by endocytosis and high accumulation	Li et al. (2018b)
Nanogel (~290 nm)	Acetazolamide	Glaucoma	Chitosan–sodium tripolyphosphate based nanogel shows controlled released profile with minimal irritation effect; prolonged residence time of payload in target site by diffusion mechanism	Abdel-Rashid et al. (2019)
Nanogel (100–180 nm)	5-Fluorouracil	Melanoma	Chitosan-based pH responsive biodegradable nanogel with sustained drug release kinetics; induce apoptosis on target cells at low drug doses; nanocarrier penetrate by endocytosis mechanism; payload releases at slightly acidic microenvironment resulting in selective accumulation on tumor site	Sahu et al. (2019)
Nanogel (~21 nm)	Diflunisal	Rheumatoid arthritis	Xanthan gum-based nanogel with increased drug bioavailability and high drug release profile; ensured a modulate and localized drug effect by maintaining higher degree of retention of payload therefore providing a prolonged effect	Bashir et al. (2021)

Nanogels composed of a polysaccharide pullulan backbone with cholesterol hydrophobic moieties (cholesterol-bearing pullulan) as an artificial absorber of amyloid proteins can be used to inhibit the aggregation of amyloid β-protein, represents a promising approach for therapy of Alzheimer's disease (Kousalová and Etrych, 2018). Also, nanogels have proven to be an efficient DDS to pulmonary tissue since these particles avoid fast renal clearance and the phagocytosis by macrophages. In this sense, previous studies have shown that an engineered trypsin-responsive and neutrophil elastase-responsive polymeric nanogel can be an easily exchanging enzyme-responsive crosslinkers, releasing the payload after

enzymatic degradation and, therefore, therapeutic nanoparticle can reach the smallest capillary vessels and penetrate pulmonary tissues to treat acute and chronic pulmonary diseases (Mejías and Roy, 2019).

Also, a xanthan gum-based nanogel was designed and formulated as DDS for diflunisal (DIF) for topical anti-inflammatory activity to treat rheumatoid arthritis. This nanogel showed an increased drug bioavailability and high drug release profile, ensured a modulate and localized drug effect by maintaining a higher degree of retention of payload, therefore providing a prolonged effect (Bashir et al., 2021). Hence, this approach can be an attractive alternative compared with conventional topical formulation or even a promising substitute to oral DDS.

MICROEMULSIONS AS A SYNTHESIS METHOD FOR DRUG DELIVERY SYSTEMS

The design and development of new DDS that enhance the efficacy of existing drugs is an ongoing process in pharmaceutical research. Since there are many types of DDS that have been developed, ME have provided a great potential for achieving the goal in drug targeting. In this sense, they can be used to formulate and synthesize new DDS such as liposomes, nanocapsules, dendrimers, polymeric micelles, metallic nanostructures, quantum dots, and nanogels (Fanun, 2012). Selected examples of nanostructures synthesized by ME are represented in **Table 1**. Nanostructures as colloidal systems with a nano-scale organization as well as high surface area to volume ratio enable penetration of entrapped therapeutic agents across tissues allowing us to increase the residence time of bioactive molecules while the frequency of drug administration is reduced (Albanese et al., 2012).

In this sense, the implementation of efficient synthesize methods are needed in order to preserve the properties of nanostructures used as DDS. Therefore, ME has been proposed as a versatile technique that allows us to control the particle size, morphology, homogeneity, and surface area of the nanostructures used as DDS (Malik et al., 2012).

ME are defined as thermodynamically stable and isotropic dispersions of two immiscible liquids, where a surfactant stabilizes micro-domains in combination with a cosurfactant (Lawrence and Rees, 2012). These self-aggregated colloidal systems, with an average droplet diameter of 10–140 nm, could be classified as water-in-oil (W/O) ME, where the water is dispersed homogeneously in an organic media; oil-in-water (O/W) ME, where oil is dispersed in water, and bicontinuous ME, consisting of water and oil nanochannels separated by flexible surfactant monolayer (Fanun, 2009).

The synthesis method by ME offers unique properties such as ultralow interfacial tension, large interfacial area, thermodynamic stability, and the ability to solubilize otherwise immiscible liquids, making it feasible to be used to produce nanostructures as delivery platforms (Muzaffar et al., 2013).

Different routes of delivery that include transdermal, oral, ocular, parenteral, and others have been the focus of the medical research.

Transdermal

Transdermal drug delivery is viable for administering low molecular weight drugs that are susceptible to the first-pass metabolism. Furthermore, this route provides a non-invasive route of administration, prolonged drug release, and reduced side effects.

Transdermal drug delivery directly depends on the structure, physiology, and barrier properties of skin. Therefore, the carrier attributes the increased absorption of drugs in transdermal applications by the enhancement of penetration through the skin. In this sense, the use of ME has been widely implemented as a strategy to improve the transport into and across the skin barrier (Kogan and Garti, 2006).

Taking this into account, liposomes are an excellent option for transdermal drug delivery, since phospholipids (as the main component) are amphiphilic molecules that can be used to encapsulate hydrophilic and hydrophobic drugs. The latter, liposomes can be absorbed onto the skin and fuse with the lipidic bilayer of the most superficial layer of the epidermis (stratum corneum), where the lipids facilitate drug permeation into skin (Yu Y.-Q. et al., 2021). Recently, a wide variety of anti-inflammatory drugs have been loaded onto liposomes for localized transdermal delivery, like diclofenac (Sacha et al., 2019) or baicalein (Kim et al., 2019), to name a few.

In 2020, Pandey and collaborators (Pandey et al., 2020) formulated a repaglinide loaded nanostructured lipid carrier-gel (RG-NLCs-gel) system to improve the bioavailability of this anti-diabetic drug by transdermal route. The RG-NLCs ME was prepared by high-speed homogenizer technique. The *in vivo* pharmacokinetic study showed two times improvement in the bioavailability in comparison to marketed oral tablets in a rat model.

Taking aside the advantage of transdermal nanocarriers, the main disadvantage is that to date it is still difficult to overcome the skin barrier, uncontrolled drug release, limited penetration, and lack of specific targeting, focusing on localized delivery. However, functionalization and surface modification strategies can help to overcome these main issues (Yu Z. et al., 2021).

Oral

The most common route of drug administration for systemic or local drug delivery, for the gastrointestinal (GI) tract, is the oral route. This route of drug administration presents desirable advantages for patients since it is non-invasive and has ease of use, however, it may not be favorable to use during an emergency since it possesses a slower absorption compared to other routes (Homayun et al., 2019). Despite the aforementioned advantages to patients, oral drug delivery possesses a number of challenges like poor drug stability, solubility, and low permeability across mucosal barriers, since these parameters are affected by the physiological environment of the GI tract (Hua, 2020).

More than % of new chemical entities exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery. Due to

the above, ME can significantly improve the oral bioavailability of hydrophobic drugs (Fanun, 2012).

However, the shortcomings related to the formulation of ME used as oral delivery systems include inadequate solubility in lipidic constituents, lower drug loading ability, and higher risks of GI irritation due to the presence of high quantities of surfactants (30–60% w/w) (Ohadi et al., 2020).

As a solution to the above, it has been proposed the use of biosurfactants such as lipopeptides and glycolipids in ME formulation instead of surfactants to increase the safety and minimizes toxicity and gastric irritation typically associated with the surfactant use. Hence, ME techniques using an O/W biosurfactant mixture are useful in the production of the stable and uniform nanoparticles (Ohadi et al., 2018). The development of a novel ME that contained oleth-5 as a surfactant to enhance the oral absorption of all-trans retinoic acid (ATRA) was reported by Subongkot and Ngawhirunpat (2017). This ME significantly improved the intestinal absorption of ATRA. Also, the intestinal membrane cytotoxicity of the ATRA-loaded ME did not differ from fish oil.

Ocular

The ocular drug delivery can be achieved by multiple routes of administrations, where the topical via, like eye drops, guarantee high compliance by patients. Topical ocular drop delivery is an efficient administration route for the treatment of anterior segment illness but inefficient to treat posterior segment of the eye since multiple ocular barriers make it inefficient to drug delivering (Rodrigues et al., 2018; Kim and Woo, 2021).

Thus, nanoparticles offer a particular benefit to overcome the limitations mentioned above due to the large surface area and their capability to support many surfaces functional modifications to improve drug delivery (Jacob et al., 2018). As an example, there are reports of formulation and characterization of ME composed of oleic acid, non-ionic surfactants between 20/60, 1-propanol and phosphate buffer, where the authors uncovered that the drug is entrapped between the oxyethylene groups of hydrophilic shells of ME and its stability was enhanced for ocular application (Peng et al., 2011; Rashid et al., 2019).

Furthermore, ME are highly stable, possess low toxicity and irritation, and improved drug bioavailability, making them a great option as a DDS in ocular drug delivery. It is important to mention that, after topical application of ME to the eye, this is absorbed through the cornea, where the ME prolonged the contact time between the drug and the corneal epithelial cells (Damiani et al., 2019).

Parenteral

The parenteral route of administration is highly recommended to deliver poorly water-soluble molecules that can exhibit erratic absorption characteristics and low systemic bioavailability (Kolluru et al., 2021). In this sense, parenteral drug delivery route allows us to overcome the limitations mentioned above by bypassing the GI tract.

ME have evolved as a novel vehicle for parenteral delivery of the hydrophobic drugs. Kale and Patravale (2008) evaluated a lorazepam (LZM) ME for compatibility with parenteral fluids, globule size, *in vitro* hemolysis, and stability of the drug using a Capmul MCM as an oily phase. LZM ME were compatible with parenteral dilution fluids and the *in vitro* hemolysis studies indicated that ME were well tolerated by erythrocytes. Nanoparticles used to DDS had the advantage of reducing side effects and helping to protect the drug from being rapidly cleared from the body (Kolluru et al., 2020).

CHALLENGES OF MICROEMULSION-BASED NANOSTRUCTURES

Since there are many types of nanostructures that have been developed as DDS, the synthesis method by ME has provided a great potential to achieve drug targeting through these nanoscale structures (Fanun, 2012).

ME are composed of polar and non-polar phases stabilized with an amphiphilic agent decreasing the interfacial tension between these two components. This chemical structure provides to ME an excellent thermodynamic stability being one of its major advantages (McClements, 2012). Due to the above, ME has shown great potential in terms of producing DDS with increased bioavailability of pharmaceutical compounds, particularly those as poorly water-soluble (Ohadi et al., 2020).

Nevertheless, the shortcomings related to ME-based nanostructures include inadequate solubility in lipidic compounds, lower drug loading ability, and higher risks of GI irritation by the presence of high levels of surfactants (30–60% w/w) as well as poor storage stability (He et al., 2010).

Hence, the use of biosurfactants, a group of diverse amphipathic metabolites produced by several microorganisms, has been proposed as an alternative instead of surfactants for ME synthesis. Generally, lower molecular weight biosurfactants including glycolipids such as rhamnolipids, and lipopeptides such as surfactin, have excellent surface-active properties due to their relatively simpler chemical structures provide them thermodynamically stability. Therefore, their isotropic systems are considered to be very promising in the development of nanostructures for DDS increasing the safety and minimizing toxicity and gastric irritation specifically for oral or parenteral routes (Rodrigues, 2015).

Due to the above, more studies focused on complex interactions between the pharmaceutical compound and the physiological environment need to be performed to facilitate the use of ME for the formulation, stability, and packaging of drug delivery nanostructures.

CONCLUSION

In this review, we discussed the different types of nanomaterials synthesized by ME methods and their applications as a DDS to target specific areas or even the use for delivery of vaccines since it has been in the spotlight recently. Nanomaterials have been widely used to enhance the penetration of large and/or hydrophilic fractions of therapy molecules and can be

composed by different polymers or lipids. Nowadays, nucleic acid-based therapies use nanomaterials as delivery systems since they facilitate targeting and penetration. Additionally, cancer therapies have shown certain predilection for nanocarriers, however, chronic and large-scale toxicity tests in humans must be done, only *in vitro* studies have been reported. It should be noted that the selection of a type of nanomaterial mainly depends on the pharmacological properties and application purpose. Regardless of the type of the nanomaterial selected, the general idea of using nanomaterials as a DDS is to enhance bioavailability of the drug, reduce side effects, and improve target-tissue delivery of payload reducing harmful effects to tissue environment. We give an overview of the different routes of administration and drug delivery medicinal areas like oral, pulmonary, and cancer cells above others as targeted drug delivery based on biocompatible nanomaterials. Despite the potential progression achieved in the nanotechnology area, highlighting the need to test all the new development biocompatible nanomaterials in suitable *in vivo* models and compare with products that are already in the market to demonstrate the suitability for clinical trials or even improve production scale-up process to develop an industrial-scale model to be cost-effective is feasible.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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