Chapter

Novel Drug Carries: Properties and Applications

Luis Jesús Villarreal-Gómez
and Graciela Lizeth Pérez-González

Abstract

Conventional drug administration has several issues and challenges such as full doses absorption and efficient targeting, some generate undesirable secondary effects and promote damage to organs and tissues such as the liver and kidneys, and others trigger inflammation and immune responses. Hence, drug carriers help to promote drug absorption, enhance targeting, avoid or decrease secondary effects, possess the ability to camouflage drugs from immune cells and proteins, and permit controlled release to provide prolonged drug delivery to maintain its blood concentration within therapeutic limits. Drug carriers have gained importance thanks to their various properties such as biocompatibility, biodegradability, mechanical properties, and high surface area, among others. Drug carriers are getting crucial to avoid or diminish secondary effects and improve the targeting of the administered drugs incrementing their effectiveness. Hence, this book chapter aims to introduce some drug carriers (electrospun nanofibers, aptamers, micelles, and liposomes), describing the properties and polymers used. It is observed that fast dissolving administration is the most recommended strategy for the use of drug carriers, where more evident therapeutics benefits can be appreciated.

Keywords: aptamers, drug delivery, drug carriers, nanofibers, micelles, electrospinning, nanogels, liposomes

1. Introduction

Presently, drug carriers can be incorporated in several systems that are available in the market in different presentations such as tablets, syrups, and shots that the patients swallow, chew, or are inoculated administering specific doses of the medical compound. However, children, geriatrics, and patients with specific conditions have still difficulty obtaining the recommended doses through these administration routes and medical presentations [1–4]. Until now, oral administration has been the preferred administration route for its easiness of administration [5–7].

Innovative drug carriers can include several micro and nanostructures such as micelles, nanoparticles, liposomes, emulsions, and nanofibers, among others [8]. The most important technical advantages of drug carriers can be reported as the high stability, high carrying capacity, the feasibility of several administration routes, and

the capacity to be used with hydrophilic and hydrophobic molecules. The intention to use drug carriers is to control the drug release using these polymeric matrices and reduce or avoid secondary effects [9].

One of the main properties needed for a drug carrier is biocompatibility, which is the absence or decrease of adverse tissue reactions against the implanted or administered biomaterials avoiding immune response. Biomaterials can include natural and synthetic polymers, ceramics, metals, and a combination of them [10]. However, biomaterials that are applied as a drug carrier need to develop a bioactive role in the tissue such as to respond to chemical, physical, or external stimuli and possess a therapeutic effect [11].

Drug carriers can include nanogels, micelles, mucoadhesives, bacteriophages, magnetic nanoparticles, graphene, dendrimers, carbon-based materials, viral-based nanoparticles, nanofibers, liposomes, films, bacterial vesicles, metal-organic frameworks, and carbon nanotubes, among others [12]. **Figure 1** shows some examples of nanocarriers.

For all the above, this chapter discusses the electrospun nanofibers' properties applied as drug delivery systems, some characteristics of the main polymers used, describing their advantages and disadvantages. Some electrospinning strategies are also compared.

2. Electrospun nanofibers

Electrospun nanofibers (**Figure 2**) are polymeric-based structures that possess diverse customary properties that make them interesting to be used as drug carriers [13], these characteristics include biocompatibility [14, 15], biodegradability [16, 17],

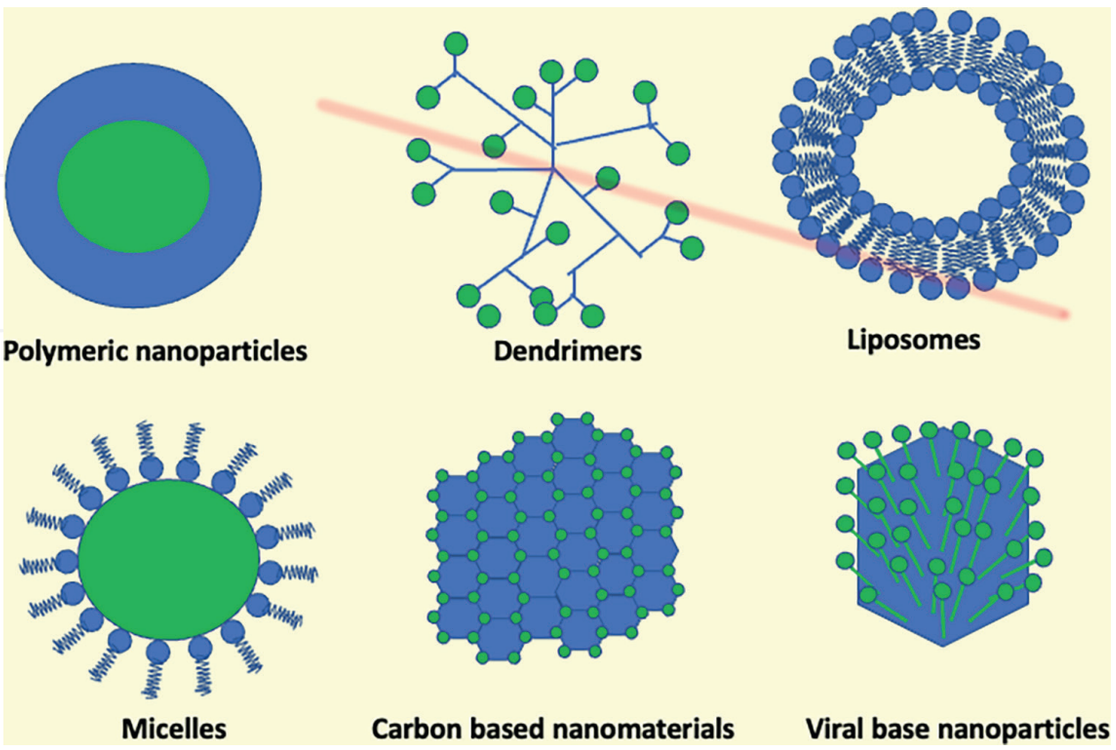

Figure 1.
Some examples of drug carriers.

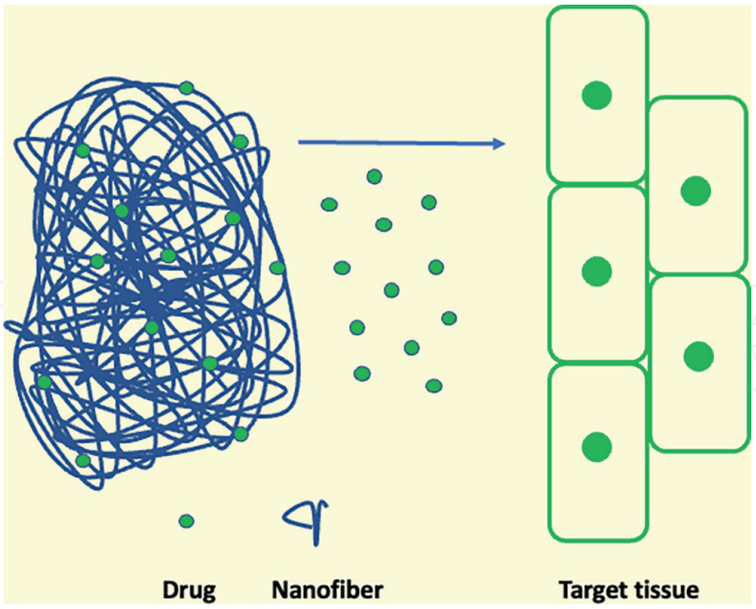

Figure 2.
Electrospun nanofibers as drug carriers.

high surface area [18, 19], adequate mechanical properties [20, 21], highly customizable fiber diameter and structure [22, 23], excellent porosity connectivity [24, 25], ease of handling [26, 27], functionalization [28, 29], and the ability to encapsulation of a diversity of bioactive molecules [30, 31].

Electrospinning is a versatile technique that has expanded through time, where the objective of this technique is to fabricate fibers or particles in the nanoscale range [32] creating a tridimensional scaffold that has wanted characteristics with potential use as drug carriers such as the large surface area, where this property permits a high drug loading capacity in a reduced volume range [33], low cost [10], and adaptability [33]. The electrospinning technique uses a high-voltage electrical field that charges a polymer solution breaking its surface tension when is injected with a specific rate, this polymeric solution is attracted to a conductive collector creating a liquid jet yielding nanofibers (~10–1000 nm) where the solvent evaporates in the air [18, 34].

There are different types of electrospinning techniques that help to incorporate bioactive molecules or drugs into the fibers or over their surface [35, 36]. The objective is to release the loaded drug at the target zone through the polymeric degradation of the fibers controlling its delivery rate depending on the polymer used [37]. Among the reported electrospinning techniques can be listed the blending, coaxial, emulsion, and surface modification electrospinning, each of them has a different strategy for drug incorporation. The advantage of this strategy is that improves the equilibrium between the mechanical and physicochemical characteristics of the functionalized resulting fibers. Moreover, it permits the adjusting of the proportion used of the bioactive component by altering the concentration added to the final solution [38].

One of the advantages of electrospinning is that is a one-step method because the loaded biomolecules or drug solution is dissolved or dispersed directly into the polymeric solution. In this method, it is important to choose correctly the polymeric matrix because its characteristics will determine the efficiency in the drug encapsulation, dispersion in/on the fibers, and delivery rate. It is reported that the equilibrium between hydrophilic and hydrophobic functional groups in all components of the

system (drug, polymer, solvent) will improve the optimal functionalization of the resulting fibers [39]. It's important to note that due to the hydrophobic properties of some polymers, lipophilic drugs are easier to dissolve and create a homogeneous solution and vice versa. Such is the case of the polyester's polymers, which are hydrophobic and interact very well with the hydrophobic drug rifampicin and paclitaxel, and gelatin, poly (ethylene glycol), and poly (vinyl alcohol), which are hydrophilic polymers, can dissolve hydrophilic drugs such as doxorubicin [40].

The disadvantage of this method is that some metallic bioactive molecules tend to aggregate in the polymer solution and in the resulting fibers [34]. Moreover, with this process, pharmaceutical drugs that are insoluble in water cannot be encapsulated using hydrophilic polymers [41]. To avoid this issue, cyclodextrins are used to improve the solubility of the insoluble drugs in the polymeric solution [42]. The main advantage of fibrous scaffolds proposed for drug delivery systems is that they possess a high surface area to volume ratio, which can permit high dose load and promote the solubility of the drug in an aqueous environment improving the drug efficiency [43].

3. Aptamers

Aptamers are also used as interesting drug carriers; these molecules are composed of short nucleic acid oligomers. Many pieces of literature have reported the use of aptamers as drug carriers and diagnostic's approaches [44–47]. Aptamers are important because they can be designed and predicted to become a drug carrier for even general drugs and theragnostic drugs for specific pathologies such as Alzheimer's disease and cancer, among others. Since they can be designed, they are able to bind to various important targets such as lipids, nucleic acids, proteins, small organic compounds, or entire organisms. Thanks to their binding specificity, these specific drug carriers have shown less toxicity [44].

Kanwar, et al., 2011, discussed that aptamers can bind to a wide range of targets, which are called epitopes, which possess a high affinity and specificity. Aptamers can be used in chemical biology, therapeutic delivery, diagnosis, research, and monitoring therapy in real-time imaging. As mentioned before, aptamers are interesting for their low immunogenic reaction and also can mimic monoclonal antibodies that are proposed for research, diagnostic, and therapeutic [48].

Ganji et al., 2016, mentioned that aptamers can be generated from libraries of single-stranded nucleic acids against different molecules. The authors discussed that aptamers can be used for dendritic cell targeting, in order to improve immunotherapy in the treatment of allergies and cancers. In this scenario, dendritic cells use several receptors to stimulate the adaptive immune response through the antigen presentation route in naïve T cells [49].

Aptamers are single-stranded oligonucleotides that fold into defined architectures and bind to targets such as proteins. In binding proteins, they often inhibit protein-protein interactions and thereby may produce therapeutic effects (**Figure 3**) [50].

4. Micelles

Micelles have been importantly positioned as a drug carrier [51]. Micelles, which are commonly synthesized from polymers, have been proposed in preclinical studies

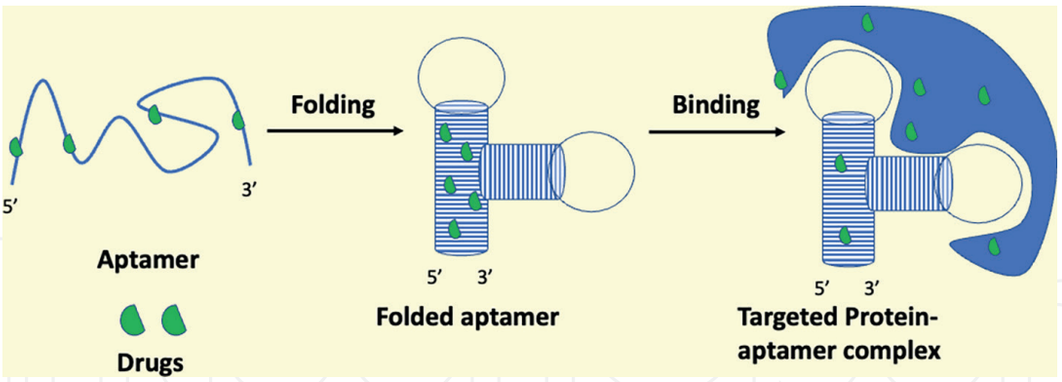

Figure 3.
Aptamers as drug carrier.

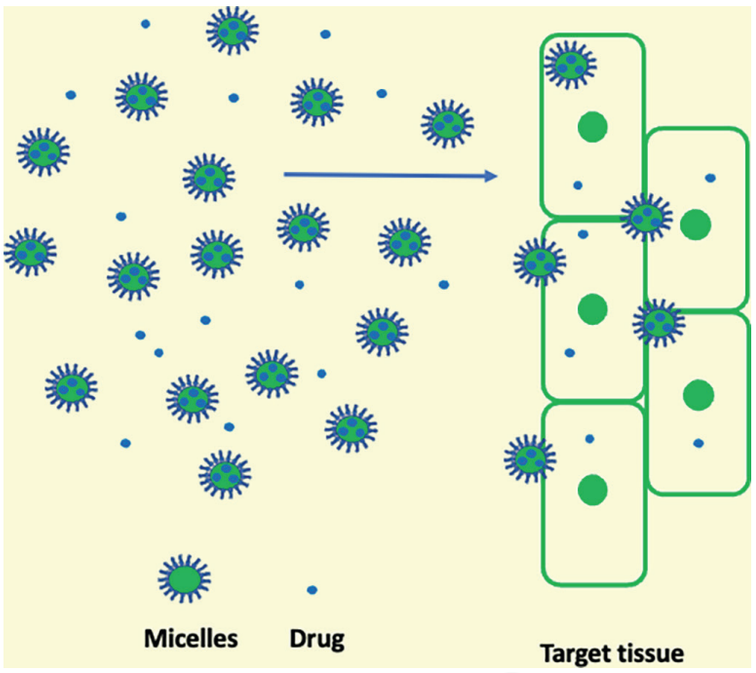

Figure 4.
Micelles as drug carrier.

for the drug release of poorly soluble chemotherapeutic agents in cancer. Polymeric micelles are created via the self-assembly of amphiphilic polymers [52].

Many polymers have been proposed to produce micelles including poly(lactide) (PLA), poly(caprolactone) (PCL), poly(lactide-co-glycolide) (PLGA), polyesters, poly (amino acids), lipids, poly (ethylene glycol), poly(oxazolines), chitosan, dextran, and hyaluronic acids, among others. Micelles can be prepared on a nanoscale enabling the enhanced permeability and retention (EPR) effect (**Figure 4**). Moreover, the stimuli (pH, hypoxia, enzymes) sensitive breakdown offers the micelles an efficient drug release. These micelles can be degraded using light, ultrasound, and temperature among other external stimuli to perform a controlled release of the drug [52].

Soleymani Abyaneh et al., 2015, prepared a block copolymer micelle containing methoxy poly (ethylene oxide) (PEO) as a shell layer, poly (lactic acid) (PLA) of different stereo-chemistries as the outer core, and poly (α-benzylcarboxylate-ε-caprolactone)

(PBCL) or poly(ε-caprolactone) (PCL) as the inner core. The micelles were used as drug carriers of the hydrophobic drug nimodipine, which is a drug used to treat symptoms from a ruptured blood vessel in the brain [53].

5. Liposomes

Liposomes can be defined as spherical vesicles, which involve one or more layers of phospholipids. These drug carriers can be used to load hydrophilic drugs in the inner core and/or lipophilic drugs in the double layer of phospholipids [54].

The main advantages of liposomes are their augmented stability and decreased toxicity of the encapsulated drug, capacity to be fused directly with the target cell membranes (**Figure 5**), biologically inert, non-antigenic, and non-pyrogenic, increased efficacy and therapeutic index of several drugs (actinomycin-D, amphotericin B, Taxol, Daunorubicin), improved stability via encapsulation, nontoxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations, reduce the toxicity of the encapsulated agent, help reduce the exposure of sensitive tissues to toxic drugs, site avoidance effect, flexibility to couple with site-specific ligands to achieve active targeting [55].

On the contrary, the main issues of liposomes are linked to their production; several methods have been developed, but industries prefer to use batch-mode methods, which are characterized by low repeatability. Moreover, raw materials employed are particularly non-economic, low-solubility, with short half-life, sometimes phospholipid undergoes oxidation and hydrolysis-like reaction, leakage and fusion of encapsulated drug/molecules, the production cost is high, and fewer stables [54].

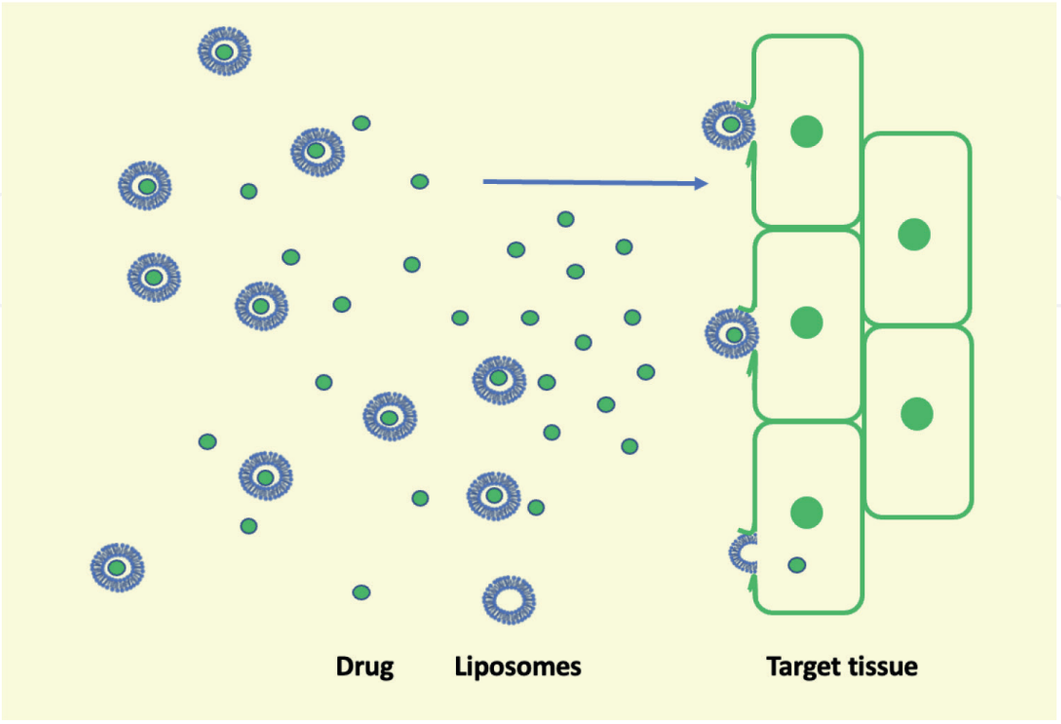

Figure 5.
Liposomes as drug carriers.

6. Carbon-based nanomaterials

Carbon-based nanomaterials (CNBs) possess a singular structural dimension, which gives them special physicochemical properties interesting for several applications including as drug carriers [56]. CNBs can be classified as graphene, carbon nanotubes, mesoporous carbon, nanodiamonds, and fullerenes. All these structures differ in their excellent optical activities and multifunctional surface area, but all of them have demonstrated a high capacity for drug loading, biocompatibility, and low immunogenicity [57].

One of the principal areas of application of CNBs as drug carriers is in the treatment of several kinds of cancer, due to their excellent supramolecular π-π stacking, high absorption ability, and photothermal conversion capacity, among others [58]. Unfortunately, the use of CNBs in cancer therapy comes with undesirable secondary effects related to the cytotoxicity of healthy tissues [59].

Respecting their role as drug carriers, single-walled carbon nanotubes (SWCNTs) have been loaded with paclitaxel, doxorubicin, and isoniazid increasing the capacity of drug delivery, incrementing drug action, improved bioactivity in the destruction of bacterial cells [60–62]. Another example of CNBs such as fullerenes can be loaded with hydroxyurea, ibuprofen, chloroquine, doxorubicin, and N-desmethyl tamoxifen, giving them a better delivery efficiency of these pharmaceutical drugs [63–65].

7. Viral-based nanoparticles

In the case, the viral-based nanoparticles are reported to be useful for photodynamic therapy due to their simple manufacturing and good safety profile [66], also they have interesting characteristics such as to possess great diversity in their structural uniformity, functionalization, expression, and self-assembly. Viral-based nanoparticles are mostly seen as therapeutics adjuvants or excipients that promote, improve, start, and attenuate or avoid the toxicity of the loaded pharmaceutical drug or bioactive compound [67].

Alemzadeh E et al., 2018, discussed that viral-based nanoparticles possess several advantages over other drug carriers, which include biodegradability, biocompatibility, known structure in atomic level, capacity to attach to ligand with high control on structure, accessibility for genetic and chemical alteration and malleable methods of preparation [68].

Several RNA viruses have been used as drug carriers such as *Brome mosaic virus* (BMV), *Red clover necrotic mosaic virus* (RCNMV), *Cowpea mosaic virus* (CPMV), *Cucumber mosaic virus* (CMV), *Hibiscus chlorotic ringspot virus* (HCRSV), *Tobacco mosaic virus* (TMV), *Potato virus X* (PVX), which have icosahedral and helical symmetries, from the pharmaceutical drugs loaded in these particles can be included doxorubicin, proflavine, DAPI, propidium iodide, acridine orange, polystyrene sulfonic acid, polyacrylic acid, phenanthriplatin, Herceptin, among others [68, 69].

7.1 Types of polymers used as drug carriers

Not all polymers can be used for drug carriers, these polymers have to possess specific characteristics such as biocompatibility, biodegradability, permit drug loading, permit mass transfer, and respond to certain stimuli, among other characteristics [70]. Some examples of these polymers and their properties can be listed in **Table 1**:

Polymers	Advantages	Disadvantages	Ref.
PCL	Biodegradable, biocompatible, compatible with a range of other materials, FDA approved	Low melting point, hydrophobic, long degradation rate, inadequate mechanical properties, and soft cell adhesion	[71]
PVA	Bioadhesive, biodegradable, biocompatible, low tendency for protein adhesion, and low toxicity	Humidity reduces the polymer's tensile strength; slow biodegradation	[72]
PVP	Binder, FDA approved, excellent wetting properties, biocompatibility, low toxicity, adhesive characteristics, complexing stability, relatively inert behavior, and is resistant to thermal degradation	Certain allergic reactions, storage disease, subcutaneous granulomas, pulmonary vascularization, and reticuloendothelial system (RES) deposition, high hygroscopic nature which made it tough to store and handle, non-biodegradability in parenteral administration	[36, 73]
PNIPAM	Mechanical strength, biocompatibility, biodegradability, multi-stimuli responsibility, higher drug loading	Low mechanical strength, limited drug loading capacity, and low biodegradability	[74]
PAA	Low toxicity, super hydrophilicity properties, biocompatibility, biodegradability characteristics	Poor mechanical properties, and high solubility in water	[75]

PCL: Poly (caprolactone); PVA: Poly (vinyl alcohol); PVP: Poly (vinyl pyrrolidone); PNIPAM: Poly (N-isopropyl acrylamide); PAA: Poly (acrylic acid).

Table 1.
Most of the reported polymers are used for drug carriers' fabrication in drug delivery systems.

Depending on their polymeric functional groups, antibiotics, anticancer agents, and biomolecules such as nucleic acids and proteins can be loaded [1], where surface morphology and structure of the polymeric nanofibers are key features for regulating the delivery rate and quantity of the drug. Also, the surface of the polymers can protect the bioactive loaded molecules from corrosion or degradation of the enzyme, water, or gastric acid, prolonging the effectivity of the pharmaceutical drug [43].

8. Conclusions

Necessary human equivalent doses still need to be tuned to generate drug carriers with adequate chemical, mechanical, and biological properties that are loaded with the specific doses of the pharmaceutical drug for a certain therapy. Another opportunity for the study is the proposed different taste masking in order to avoid the bad taste of some drugs or polymers. In all these studies, still, biocompatibility, biodegradability, mechanical testing, *in vivo* efficacy, and pharmacokinetics, must be studied. Future work must be focused on the biological response of the tissue and clinical phases must be performed [33].

For all discussed, the use of drug carriers is a promising technology that can be applied in most administration routes such as oral, vaginal, transdermal, ocular, rectal, and nasal tissues. The unique qualities of these drug delivery systems include a large surface area, nanoporosity, high drug encapsulation, and fast disintegration

and dissolution properties. The advantages and limitations of various synthetic polymers and natural polymers nanofibers are discussed in the context of producing target drug delivery systems. Also, the bioavailability can be enhanced by exploiting the hydrophilic nature of polymers and their ability to form hydrogen bonds with encapsulated drugs, resulting in uniform distribution of encapsulated molecules throughout the matrices and providing the formulation with rapid dissolution abilities. Despite much literature being found, most of them still test these systems just for *in vitro* approaches. But *in vivo* and clinical trials are still poor.

Conflict of interest

"The authors declare no conflict of interest."

Nomenclature

EPR	Enhanced permeability and retention effect
PAA	Poly (acrylic acid)
PBCL	Poly (α-benzylcarboxylate-ε-caprolactone) (PBCL)
PCL	Poly (caprolactone)
PEO	Poly (ethylene oxide)
pH	Potential hydrogen
PLA	Poly (lactic acid)
PNIPAM	Poly (N-isopropyl acrylamide)
PVA	Poly (vinyl alcohol)
PVP	Poly (vinyl pyrrolidone)

Author details

Luis Jesús Villarreal-Gómez* and Graciela Lizeth Pérez-González
Facultad de Ciencias de la Ingeniería y Tecnología, Universidad Autónoma de Baja California, Unidad Valle de las Palmas, Tijuana, Baja California, México

*Address all correspondence to: luis.villarreal@uabc.edu.mx

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