

Review

Drug Carriers: Classification, Administration, Release Profiles, and Industrial Approach

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Abstract: This work is aimed at providing a description of the complex world of drug carriers, starting from the description of this particular market in terms of revenue. Then, a brief overview of several types of conventional and innovative drug carrier systems has been included. The types of administration routes were also analyzed, with a critical and qualitative comment on drug release kinetics and drug profile shapes. Carriers were classified according to their ability to provide a prolonged and targeted release. The concept of the therapeutic window has been presented, providing advantages of having pulsed drug release to avoid side effects to target tissues. A critical comment on the use of conventional and innovative techniques for the production of drug carriers by large industrial companies has been proposed. As a final attempt for this work, an overall unique schematization of a drug carrier production process has been added, highlighting the necessity to create a strong double link among world-requested versatility of drug carriers for human applications and the newly developed industrial processes.

Keywords: drug carriers; drug delivery; nanoparticles; nanocapsules; liposomes; niosomes; hydrogels; aerogels; quantum dots; dendrimers



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1. Introduction

Drug carriers are biocompatible tools for the transport of molecules for pharmaceutical, cosmetic, and nutraceutical applications [1], which are fields of great scientific and industrial interest. According to the scientific report “Global Markets and Technologies for Advanced Drug Delivery Systems”, drug delivery systems generated \$178 billion in 2015, while the estimation for 2020 was \$231 billion, in terms of sold products, with an annual growth rate of 4.9%. However, this estimation was underestimated, since the market generated in 2020 was about \$231 billion large, with an estimation of \$310 billion by 2025, with an increase of 6.1%. This value will further increase after the request of numerous vaccines against COroNaVirus Disease 2019 (COVID-19). Nowadays, these vaccines are being requested worldwide, and are considered life-saving drug formulations. However, it is also true that the introduction of new drug formulations in the market requires a large amount of research and investment. It is well known that approximately 100 million GBP (British pounds) is necessary to finance the research of a new drug on the market. Moreover, approximately 10,000 molecules are generally discarded before electing one as marketable [2–5].

The term drug carrier was used, for the first time, to define a system that has the capability of incorporating a precise amount of molecules to enhance their selectivity, bioavailability, and efficiency. The effectiveness of a drug carrier during its delivery stands in the necessity of having a valuable protective barrier. This barrier can add an important resistance to mass flow and diffusion from the inner core to the external bulk. Another important contribution to the character of the carrier is given by the behavior of the bulk, which can be water or gel, or even a blood-like media [6]. Depending on the viscosity of the media, the drug release will have a different kinetic shape and rate.

Microcapsules, microsphere, and lipidic vesicles have the possibility to avoid drug leakage, and its consequent administration to sane tissues [7,8].

The main advantage deriving from the use of drug carriers is their ability to protect drugs during the overall administration time, enclosing them in external protective barriers of different types and nature; thus, reducing losses of active substances and limiting any side effects in patients [9,10]. Drug delivery systems are generally designed at nanometric and micrometric levels, to combine different properties with specific aims, such as site specificity, longevity, or external stimuli sensitivity [11]. Specificity requires the capability of the drug carrier to recognize the target tissue where the drug should be addressed [12]. Longevity is, in a certain matter, linked to the capability of reaching the desired tissue without being phagocytized by the mononuclear phagocytic system before reaching the targeted site of delivery [13]. Nanosystems are drug-loaded particles characterized by different morphologies, such as nanocapsules, nanospheres, liposomes, foams, carbon nanotube, dendrimers, cubosomes, niosomes, and hydrogels [14].

The study and deepening of drug carriers led to the development of batch techniques for their explorative production at the laboratory and pilot level. To overcome problems of repeatability of the characteristics of the products, continuous chemical processing plants have been created with the aid of supercritical fluids [15,16]. Several processes for the administration of drugs and active principles have achieved therapeutic effect in human beings. However, the modification of drug release profiles and their kinetic parameter contribute to improve drug efficacy, reduce side effects, and enhance patient compliance. The artificial variation of the release profile could be aimed at a specific target tissue that needs a treatment for a defined time. One of the most significant disadvantages of the traditional drug delivery is characterized by too many adverse situations and reactions [17]. For example, one of the consequences of oral delivery is the inactivation of a drug caused by the acid action of the gastrointestinal tract, or the digestion by the mononuclear phagocytic system, before reaching the target cells [18–20]. There are many ways to overcome these problems; one possibility is to improve the rate of drug delivery with the addition of specific co-drugs or biocompatible co-polymers [21]; another solution is the incorporation of drugs into drug carriers, which help to decrease the phenomenon of biodegradation, protecting the drug until reaching the target tissue. Targeted delivery consists of the concentration of a drug in some specific parts of the body, excluding the tissues around the desired one [22]. The main advantage is the increased efficacy and the reduction in dose administration [23]. Moreover, the efficacy of a continuous release system or the delayed release would help in obtaining a steady and reproducible action of depositing the drug to the target site over a prolonged time-period. This would also decrease the cost of multiple-dose administrations, long-term therapies, and toxic side effects.

2. Types of Administration

Drug carriers can be classified according to their specific properties, such as shape, mean dimensions, application and, especially, the way the drug content is delivered [24–26].

2.1. Active or Passive Delivery

First, the delivery could be actively or passively activated. Both instances regard the case in which the drug carrier has already been administrated to the target tissue. However, in the first case, an external stimulus could be added to the system, in order to obtain the loss of drug exactly when requested, and in the place in which it is requested. In the second case, the passive delivery is not activated by artificial stimuli, but just following the natural response of the cells. However, the types of administration could be very different.

2.2. Oral Administration

The most used and conventional method for the administration and the delivery of drugs is the oral delivery system. This is performed to delivery drugs in solid form, generally powder, but, in some cases, it could also be in liquid solutions. This way of

delivery is based on dissolution in mouth, diffusion, and combination of both phenomena for the proper control of drug release. This kind of delivery could be provided either for lipophilic or hydrophilic drugs [27–29].

2.3. Ocular Delivery

Another way could be the well-known ocular delivery. Ophthalmic drug delivery systems consist of the administration of drugs for treating eye illnesses locally, using drops of liquid drugs, generally made of high molecular weight compounds and hydrophilic polymers. In this kind of application, long residence times are necessary and multiple administrations, once or twice a day, for many days [30–32].

2.4. Transdermal Delivery

The transdermal drug delivery system is also known as drug delivery through skin penetration. This kind of drug delivery can occur in a passive or active manner. The passive manner is characterized by gradient diffusion, while the active way is performed after artificially induced penetration with the help of an electric field, electroporation, microporation, laser ablation, heat, or ultrasound [33–35].

2.5. Nasal vs. Pulmonary Drug Delivery

It could be interesting to indicate the nasal drug delivery [36]. It characterizes only the nasal tract and has some advantages, such as the large surface area, the use of a porous topical membrane, fast delivery, and rapid systemic adsorption. Moreover, these systems can control the drug rate clearance from the nasal cavity, protecting it from degradation operated by enzymes in nasal mucosa.

Pulmonary drug delivery systems are another kind of delivery, which consist of treating lung diseases. This is raising much attention during this COVID-19 pandemic for the most difficult cases. These applications include nebulized drugs and aerosols, but also the site treatment through the bloodstream, after syringe administration. In this specificity, dry powders of drugs are inhaled using nebulizers, providing inhalation into the lungs. Famous examples of these drugs are salbutamol [37] and desmopressin [38].

2.6. Vaginal Delivery

Intravaginal drug delivery systems [39] are normally considered a route for the administration of contraceptives, anti-fungal drugs and antibiotics. The external cellular barrier of the vagina is very adaptive for the absorption of drugs for local or systemic adsorption. This is, sometimes, a good way to use oral delivery, avoiding disadvantages, such as hepatic side effects. Other advantages of vaginal delivery are increased bioavailability, the possibility of performing self-medication, avoidance of digestive fluids, and a quick onset of action [40].

2.7. Urinary Drug Delivery

Intravesical delivery systems are aimed at the administration of specific drugs directly into the bladder, using a catheter [41]. An example is the treatment of bladder cancer, and the most used and famous drugs are doxorubicin [42], gemcitabine [43], and mitomycin [44]. A system similar to the previous described one is recorded as the urethral administration, used for the treatment of erectile dysfunction [45].

2.8. Sub-Cutaneous Delivery

Sub-cutaneous delivery consists of the administration of drug formulations using a needle [46]. However, there are some cases in which the needle is not used, but a high velocity jet administration is employed, using a kind of gun that deposits drugs inside the subcutaneous tissue [47,48]. The most famous example is characterized by insulin, used for the treatment of type 1 and type 2 diabetes, even if there are some risks for pediatric treatments [49,50]. Another possibility is the pellet implantation, which consists of the

introduction of drugs in pellet form with the use of a cannula. This provides sustainable release of the drug over weeks and a reduced number of administrations. An example of a drug delivered using this method is testosterone [51].

2.9. Microelectromechanical Systems

Systems that are more modern are characterized by microelectromechanical systems (MEMS) [52]. These systems are generally the size of a fingernail [53]. They are typically first loaded with a lyophilized or freeze-dried drug, stored in a plastic or silicone reservoir. The drug is then delivered by pressing the device to the skin; this happens as a fast one-time administration. This device contains a chip that is characterized by microneedles that have the ability to anchor to the skin, where the human fluids can help to rapidly absorb the drug directly into the bloodstream.

2.10. Micropumps and Patches

Micropumps are used essentially for type 1 diabetes treatment. Moreover, this device could be used for the delivery of insulin in type-1 diabetes (insulin pumps) [54,55]. Therefore, this method of administration is associated with computerized miniature pumps, which are programmed to release drugs at defined rates, in a continuous or pulsed manner. These chips need to “communicate” with the glucose level sensors applied on the skin; after reading the glucose concentration, the pump tunes the amount of insulin to administer to the body. In case the glucose level is higher than the limit of 180 mg/dL, it can be regulated to increase the amount of insulin administered. Instead, if the glucose level measured is lower than 60 mg/dL, the insulin feeding is stopped until reaching an optimal glucose level again.

Implantable release systems deliver a drug following a predetermined pattern for a desired time; in some cases, they can be introduced in the body after surgery operations, but in these cases, the necessity to cover the system using a biocompatible polymeric film is important. Some applications of this kind concern the post-surgery implant to treat brain tumors.

3. Classification of Drug Carriers

Drug carriers can be classified according to their shape, geometry, and production methods. In Figure 1, a schematic representation of the artificial drug carriers divided into subsets is proposed and then described.

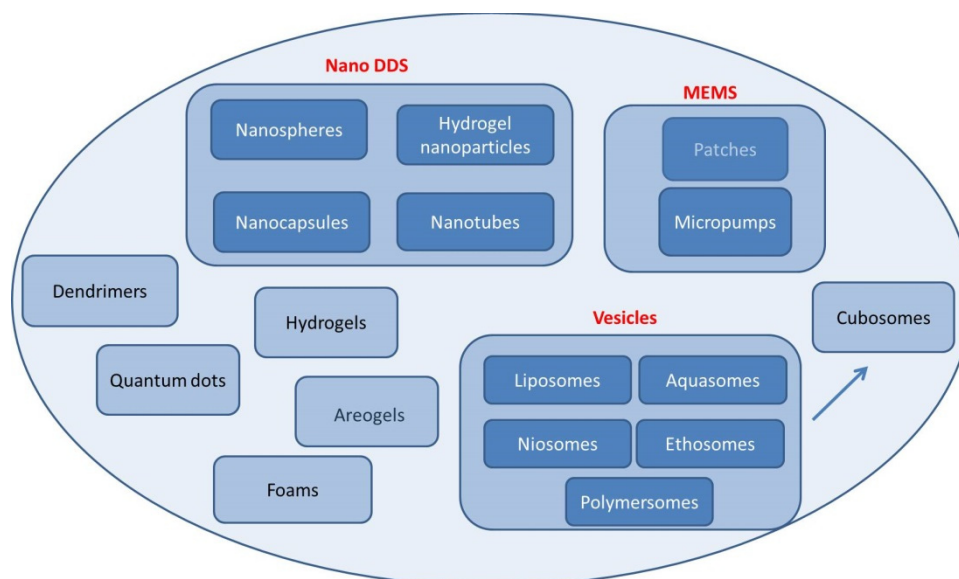


Figure 1. A representation of the set and sub-sets of artificial Drug Delivery Systems (DDS), among nano systems, microelectromechanical systems (MEMS), other specific systems and their derivatives.

3.1. Nanoparticles

Nanoparticles are characterized by several applications, such as cancer therapy, gene therapy, virus treatment, and radiotherapy, and they are largely employed in the delivery of proteins, antibiotics, vitamins, and vaccines [56–58]. According to the great improvement of nanotechnology, these drug carriers nowadays have the ability to find all of the solutions necessary to improve the delivery of drugs, overcoming the disadvantages such as poor bioavailability, low tissue absorption, and loss of drugs during transport to the target cells. In recent times, medicine has improved its capability to enhance drug delivery, arriving to the avant-garde goal of producing nano-robots for the treatment of cancer. These units are specifically able to attack carcinogenic cells, and, in a certain manner, they can drill them mechanically, if properly programmed to do this. Since there are so many different applications, nanoparticles can be divided into groups: nanocapsules and nanospheres [59–61]. The first ones are classified as vesicular systems in which the drug is confined in an inner-core cavity that is surrounded by a polymer membrane. On the other side, nanospheres are simple matrices, in which the drug can be dispersed in a uniform manner.

3.2. Nanotubes

Another kind of artificial drug carrier is characterized by nanotubes [62,63]. These systems are hollow cylinders of carbon, also called carbon tubes; these carbons are filled with drugs and are used to attack carcinogenic cells. The diameter is generally one of the three dimensions at nanometric level. The length could be visible at micrometric level using a SEM microscope. They are just rolled-up sheets of a single layer of carbon atoms. They can be made of one layer or several concentric layers, in the case of more complex structures. Carbon nanotube layers are linked with sp^2 bonds. With respect to steel, they can have up to 400 times higher mechanical strengths, they can have a weight down to 6 times less than steel, and they have high chemical stability. That is why they are employed in electronic devices, in biosensors. In particular, nitrogen doped carbon nanotubes are generally used for drug delivery. However, cytotoxicity information about carbon nanotubes still needs to be studied deeply.

3.3. Dendrimers

Fascinating subsets of drug carriers are characterized by dendrimers [64–66]. These can be defined as branched and globular macromolecules, generally employed to encapsulate individual and small drug molecules. Their shapes can be hexagonal or cubic, and are self-assembled spontaneously, by creating the proper environmental conditions. These macromolecules can be used as hubs for the transport and protection of loaded drugs; they are linked to the branches by the creation of covalent bonds. A classic example is 5-fluorouracil, used as a basis to form dendrimers and applied as biological sensors. In these systems, the drug can be encapsulated in the inner branches of the dendrimer or attached at the external extremity of the branches. Moreover, more than one single drug can be transported, hindered by different empty sections created among branches. What is also important for dendrimers is that they provide a modification of the environment for guest molecules, changing properties, such as solubility.

3.4. Liposomes

Liposomes [67–70] are the most famous and used drug carriers for pharmaceutical, cosmetic, and nutraceutical applications. These spherical vesicles consist of one or more double layers of phospholipids. These systems can be used to load hydrophilic drugs in the inner core and/or lipophilic drugs in the double layer of phospholipids. Examples of drugs that are generally loaded into liposomes and transported to target cells are amphotericin and daunorubicin, especially for their anti-carcinogenic properties. The main advantages deriving from the use of liposomes is their increased stability and decreased toxicity of the encapsulated drug. They are also characterized by the possibility to be

fused directly with the target cell membranes, since the liposome layers are very similar and biocompatible to them. A better pharmacokinetic than other drug carriers and a good therapeutic index have also been observed. These vesicles are biologically inert, biodegradable, non-antigenic, and non-pyrogenic. The main problem of liposomes is 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 expensive.

3.5. *Ethosomes and Aquasomes*

Very little difference exists among liposomes and ethosomes; the last ones are a particular kind of liposomes [71], which have the ability to enable drugs to reach deeper skin layers; they are made of phospholipids and a water/ethanol solution in the inner core. Similarly, the aquasomes are characterized by an inner core constituted by non-crystalline calcium phosphate, or ceramic diamond, covered by a polyhydroxy oligomeric film.

3.6. *Polymersomes and Niosomes*

Polymersomes are, instead, liposomes whose external surfaces are further covered by polymer coating, for example polyethylene glycol (PEG). This has the property to compact vesicle structure, providing delayed drug delivery for specific tissue applications. Another kind of spherical vesicle is made up of niosomes [72–75], which are much younger than liposomes, in terms of their discovery and proposition to the academic and industrial world. Niosomes are novel drug delivery systems characterized by layers of non-ionic surfactant active agents. Their main difference with liposomes is that they use non-ionic surfactants in the place of phospholipids. For this reason, they are substantially similar to liposomes in terms of shape and geometry, but provide several advantages, due to their reduced tendency to aggregation and enhanced stability. These vesicles can be produced using tween or span compounds, possibly with the addition of cholesterol. As demonstrated for liposomes, niosomes can be used to transport both hydrophilic and lipophilic compounds. However, they are osmotically active and stable, particularly flexible in composition and fluidity. The drug transported by niosomes is better protected from external biological environment. In terms of therapeutic efficacy, they are improved by the delayed clearance after administration, reduced side effects and, especially, the possibility of emulsifying them in a non-aqueous phase. Instead, liposomes, in some cases, tend to be disrupted and degraded by emulsification processes, applying specific process parameters. From one side, the handling of these vesicles does not require particular conditions. Improving the bioavailability of poorly soluble drugs, niosomes can be divided into multilamellar vesicles (1–5 micron), large unilamellar vesicles (0.1–1 micron), and small unilamellar vesicles (20–500 nm), similar to liposomes. The formation of niosomes depend on some process parameters, such as hydration temperature, non-ionic surfactant nature, and properties, membrane additives, and specific properties of the drug that needs to be encapsulated. Indeed, the type of surfactant influences the encapsulation efficiency, the toxicity, and the stability of niosomes. Moreover, the drug loaded into niosomes influences the charge and the rigidity of the niosomes bilayer. This means that the drug can interact with the surfactant head groups, causing mutual repulsion among the surfactant bilayers; hence, avoiding the aggregation phenomenon. The high absolute value of the surface zeta charge on niosomes prevents coalescence, and hence makes these vesicles singularly stable. As for the liposomes, the addition of cholesterol makes the niosomal membrane more rigid, reducing leakage of drugs, and increasing the entrapment efficiency. There are many methods and processes for the production of niosomes, such as the thin layer hydration, ether injection, sonication, reverse phase evaporation, heating, microfluidization, extrusion, and high-pressure systems. As for liposomes, the film method consists of dissolving surfactants in an organic solvent, evaporating the solvent under vacuum at room temperature. The resultant dry surfactant is then hydrated under agitation at the temperature of 50–60 °C, obtaining vesicles.

3.7. Foams

Foams [76–80] are generally defined as two-phase systems in which a gas is dispersed into a liquid continuous phase. In detail, polymeric foams are thermoplastic or thermoset polymer matrices with bubbles literally incorporated in them. They find many applications in the nutraceutical field, for the production of beer, cakes, ice cream, and many other food products. Bubbly foam is formed when the amount of gas is low enough for creating spherical-shaped bubbles. The production process involves the injection of air into the liquid using a mixer, breaking large air bubbles into smaller ones, and then hardening the overall structure, which prevents fusing of the smaller bubbles among them. The addition of an active foaming agent is necessary for the formation of stable foam, having the main role of reducing surface tension of the liquid phase, and forming a closed packed film around the dispersed bubbles. For the treatment of proteins, there are several processes developed to improve stability, such as the adsorption of protein at the gas–liquid interface, surface denaturation, and coagulation of the protein. There are two more factors affecting the stability of foams: drainage and disproportionation. Drainage means draining the liquid from the foam, while disproportionation is the variation of the bubble size distribution operated by gas diffusion from small to large bubbles. The liquid phase can drain from the foam under gravity, while the foam drains along the junction of the lamellae. In absence of a stabilizing agent, disproportionation occurs very quickly, but this is the largest cause of instability.

3.8. Hydrogels

Hydrogels [81–83] are systems made of distilled water and smart polymers, acting as gelification agents. They are largely used to develop smart drug systems. Hydrogels are characterized by a network of hydrophilic polymers that can hold large amounts of water, saving the backbone of the structure. The key consists of using a polymer able to form a three-dimensional network by cross-linking its chains, exploiting weak forces, such as covalent bonds, hydrogen bonds, or van der Waals forces. Hydrogels have the ability to protect loaded drugs from the external environment, such as the acidic pH of the stomach during oral administration. Hydrogels can modulate drug release, changing the kinetics by changing the gel structure sensible to environmental external stimuli. Similar to hydrogels, lipogels are similar preparations based on vegetables or animal oils used as gelification agents. Aerogels [84,85] are low-density solids with high porosity, with the ability to keep their structure intact after exchanging their liquid pores with gas. They are employed in several biomedical applications, such as diagnostic agents, and for the artificial reconstruction of human tissues, especially with the use of supercritical carbon dioxide for biocompatibility for drug delivery applications.

3.9. Cubosomes

Cubosomes [86] are described by crystalline and bicontinuous cubic liquid phases, which can be formed by the self-assembly of lipids in water, by using specific surfactants and working at a defined and optimized surfactant/water ratio. Indeed, cubosomes exist in an excess of water, and they are produced by high-energy dispersion of bulk phase, followed by colloidal stabilization using polymeric surfactants. Cubosomes can promote therapeutic benefits, minimizing side effects. They have many similarities with liposomes, but they also present some advantages. They represent a novel approach for the treatment of cancer. Cubosomes are characterized by an interconnected structure, such as a sort of honeycomb structure. The increased stability of lipids is due to the fact that the structure is more compact, and being constituted by several hubs for the deposition and transport of drugs. A surface area of 400 m²/g and a mean slot dimension of 50–100 nm results in higher adjuvant incorporation of molecules. Cubosomes are generally employed in the creation of bioelectrodes and biosensors.

3.10. Quantum Dots

Quantum [87] dots (Qdots) are used for biological semi-conductive applications; they are considered a bridge among bulk and molecules, at an atomic level. They can be produced using several methods, and are colloidal bio-conjugated suspensions. Surface modification of Qdots is a demanding technique, generally performed by depositing organic or inorganic layers.

3.11. Natural Drug Carriers

In addition to artificial drug carriers, natural drug carrier systems also exist, and can be directly produced by the human body. One example is characterized by neutrophils, which transport agents to areas specific to the treatment of acute inflammation [88]. Moreover, lymphocytes are produced for the transport and transfer of macromolecules, such as DNA; nanoerythrocytes, also called “golden eggs”, are characterized by drugs loaded in the erythrocytes, which have large space for drug incorporation and accumulation; monoclonal antibodies, which are produced by a single clone and are directed against a single antigenic determinant, called epitope [89–91].

3.12. Exosomes

Among natural systems, exosomes [92] are similar kinds of liquid based lyotropic liquid crystals, which are characterized by highly ordered nanostructures, but do not have a unique backbone of surfactants. They are membrane bound extracellular vesicles that are produced in the endosomal compartment of most eukaryotic cells. They can function as cargos of lipids, proteins and genetic materials. They are extremely important since they offer prognostic information about the diffusion of tumors. In a certain manner, the human body uses exosomes to “communicate” among cells. A carcinogenic cell produces an increasing (and not controlled) number of exosomes that often cause the diffusion of the tumor.

3.13. Macrophages

To conclude this section, it is also worthy to indicate another way that is a (sort of) hybrid among natural and artificial manners to deliver drugs, working as a Trojan horse. It is the drug delivery to macrophages [93]. The hybridity of this system is due to the fact that external artificial drug carriers could be programmed using proper peptides of antigens, in order to be directed to naturally self-produced macrophages and be digested by them. In this manner, the drug could be uptaken and delivered, for example, for the treatment of inflammatory diseases.

4. Drug Delivery Profiles Classification

The efficient and safe delivery of drugs has always raised discussions on the importance of “being into the therapeutic window”, i.e., providing a drug concentration included among the upper and lower limits, during the administration period [94].

4.1. Definition of the Therapeutic Window

Qualitative diagrams of this concept are reported in Figure 2. The therapeutic window represents a diagram in which, on the y-axis, the drug concentration is reported, while on the x-axis, the time variable is indicated. During administration, the concentration of drugs starts to increase with time. However, this concentration profile must be included between an upper concentration limit and a lower concentration limit (Figure 2a). The first one represents the condition above which a toxic effect is registered, causing damages to target tissues, but also to the other cells, while the second is the concentration limit under which there is no significant effect on the target cells.

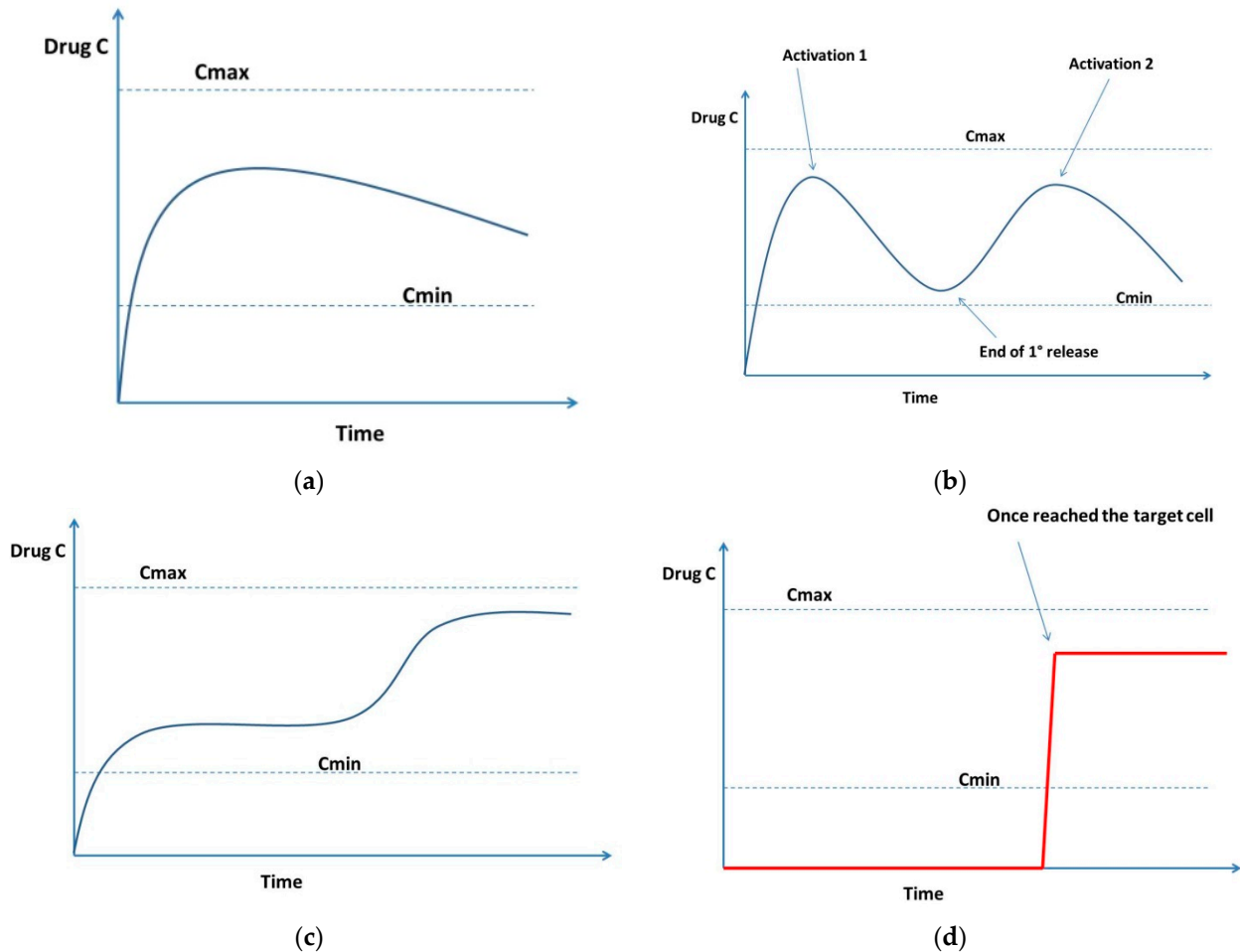


Figure 2. (a) A qualitative therapeutic window diagram, describing drug concentration vs. time during drug release. Drug C means drug concentration, C_{max} represents the maximum drug concentration above which there is a toxic effect on target tissues, C_{min} is the minimum drug concentration to have an effect. (b) A qualitative therapeutic window diagram, describing two pulsed release steps after one unique drug administration. “End of first release” means the time in which the effect of drug released by the first artificial activation is ended, and a new external stimuli is necessary (c) A qualitative therapeutic window diagram, describing drug release mediated by diffusion (first) and erosion (second) phenomena. (d) A qualitative therapeutic window diagram, showing the typical drug release behavior from long-circulating liposomes to targeted cells.

4.2. Pulsed Drug Delivery

If a drug needs to be addressed to a human or animal body, it is important to control its concentration profile [95]. The ideal situation is to provide a pulsed delivery [96], which activates the drug loss from drug carrier only when requested by an external stimulus [97,98], such as temperature increase [99,100], pH variation [101], or the presence of a magnetic field [102]. In this case, the concentration could be increased or decreased by activating or deactivating the stimulus (see Figure 2b).

Thanks to this kind of release, drug concentration will never exceed the therapeutic window, and no side effects will ever be registered, obtaining the best administration efficacy [103]. This will also reduce the number of administrations and the suffering of the patient [104,105], with the aim of direct pharmaceutical application to medical doctors and hospitals. This could also prevent a huge cost increase in the health system, with the possibility of loading more drug amounts and releasing it in a delayed and controlled manner [106,107]. Generally, the addition of cholesterol can also delay release by providing more compact barrier protecting drugs [108]. As indicated above for polymersomes, polyethylene glycol is also often added on the surface of external particles [109–111], in

order to provide long circulating behavior to the drug carrier. This finds great and powerful applications against the carcinogenic cells, which are treated using Polyethylene Glycol (PEG)-loaded anti-cancer drugs, such as daunorubicin [112].

4.3. Multi-Effect Release Phenomena

Regarding polymeric microparticles, generally there are two main phenomena controlling drug release: the drug release by diffusion and the drug release by erosion (see Figure 2c). In the first case, drug diffuses through the barrier among the inner core of the carrier and the external bulk, cell, or tissues. Then, the external environment could cause a progressive degradation of the carrier barrier, causing further leakage of the remaining drug and, therefore, its release. This particular behavior of drug during release has been fully described by Dr. Owen I. Corrigan in the last two decades [113–117]. As a final comment, the thermodynamics of the system is set once that pressure and temperature of the system has been set. However, it is possible to improve the kinetic of the system, which is the rate at which the drug will be solubilized or digested by the receiving medium.

4.4. The Importance of Particle Size for Drug Delivery

Mean size of drug carriers is another important issue to be addressed during production [118]. Lipidic drug delivery systems are largely employed to enhance bioavailability of poorly soluble drugs, protecting them from degradation [119]. Among the physical properties of lipid-based nanocarriers, which determine their safety of use, the average mean size and the PolyDispersity Index (PDI) are included. In particular, the PDI is an indicator of how particle size distribution is narrow and homogeneously distributed. Nanometric dimensions also give the possibility of being uploaded by cells [120].

New technologies have been developed to control compound size, especially to produce nano and micro devices to obtain the controlled release of a substance [121]. This approach was recognized as successful, not only in the pharmaceutical field, but also for other kinds of applications, such as cosmetic and nutraceutical. The micronization of a drug is necessary for a double importance: it improves drug bioavailability and address drugs to a specific organ. A drug delivered in all of the body can be encapsulated. For a specific drug, it is important to compare its dissolution rate and its degradation rate [122,123].

Nanosystems loaded with two or more active principles can circulate in the blood without being removed by the mononuclear phagocytic system [124], and accumulate in the target tissues in a controlled manner, avoiding side effects. In the last decades, liposomes have been recognized as one of the most promising formulations to enhance drug bioavailability for biomedical applications, providing chemical and physical stability, facilitating cellular uptake, and their delivery into the cytoplasmic environment.

4.5. Drug Release from Liposomes

As indicated above, liposomes are versatile lipidic drug delivery systems, characterized by an inner aqueous core surrounded by one or more double layers of phospholipids [125]. These molecules are generally characterized by a polar hydrophilic head and a non-polar lipophilic tail, as indicated in the sketch of Figure 2d. The most known property of phospholipids is their capability to put themselves at the interphase of two immiscible phases; for this reason, they are considered surfactants. In an aqueous environment, phospholipids naturally rearrange to capture molecules of water, thus creating spherical vesicles used as drug carriers. After administration, these nanovectors retain the drug encapsulated in their core and deliver, gradually or directly, to the target tissue [126]. Moreover, liposomes are biocompatible, since they have a basic composition similar to human cell membranes.

The most simple drug release from liposomes is characterized by its uptake by target cells, imaging a long-term release without hypothetical drug loss during administration. If not activated by external stimuli, the drug release from liposomes should be described by the qualitative diagram of Figure 2d. In this case, it is evident that liposome can retain a

drug in the inner core, releasing it only when it reaches the target tissue, in particular when it becomes part of the target cell membrane, releasing all of the content in the cytoplasm. Many examples of drug release from liposomes and cellular uptake are reported in the literature [127,128].

5. Conventional and Industrial Processes for the Production of Drug Carriers

Several conventional methods have been employed to produce drug carriers. A well-known and employed example could be the production of polymeric particles from emulsions. A water phase containing a drug is emulsified into an organic phase that is immiscible in the first one, obtaining droplets of water inside an oil phase. Then, the organic solvent containing a polymer can be evaporated, hardening the polymeric structure and resulting in the creation of particles. Moreover, double emulsions can be obtained by an Oil-in-Water emulsion into another external water phase, resulting in the production of a Water-in-Oil-in-Water emulsion. The creation of smaller droplets can be aided using sonication probes working at proper amplitudes and for a fixed time.

Another conventional method is the thin layer hydration, which is generally considered the most famous and traditional way for the production of liposomes. Together with the thin layer hydration, other techniques, such as ethanol injection, reverse phase evaporation, and microfluidic channel [129–131] were developed. However, these processes are characterized by several drawbacks, mainly concerning the high polydispersity, low reproducibility, high solvent residue [132], and low encapsulation efficiencies of the entrapped molecules [133]. To overcome these issues, high-pressure systems have been developed in a semi-continuous configuration, such as supercritical reverse phase evaporation, supercritical anti-solvent, Delos suspension, and depressurization of an expanded solution into an aqueous medium [134–137]. However, these methods enhance the production of vesicles, increase their stability, and minimize solvent residue, but there are still problems concerning low encapsulation efficiencies more than 60%) of hydrophilic compounds [138]. Supercritical assisted liposome formation has also been designed in the last few years [139,140]. This atomization system has already been studied and optimized for this high-pressure system and tested for the incorporation of dyes, proteins, antibiotics, essential oils, and dietary supplements, showing encapsulation efficiencies up to 99%, and a good control of particle size distribution [141].

The largest industries working in the pharmaceutical field generally have quite a small percentage of their resources employed in the research and development of new methods for the production of drug carriers. Drug discovery is a very difficult, time-consuming, and expensive process, which often focuses on the drug itself, its testing *in vitro* and *in vivo*, and its patenting for the protection of the discovery and the selling of royalties. Modern pharmaceutical industries are continuously identifying drugs with potential good properties, such as limited side effects, long-term circulation, and availability to self-administration. Industries are not often interested in developing novel production plants and processes. For example, one of the most innovative methods concerns the use of supercritical fluids, but not all societies have the funds, courage, time, or space to develop these novel techniques. Moreover, not all scientists working in the pharmaceutical industries have the proper expertise and knowledge to work at high pressure, for example, using supercritical carbon dioxide. Industrial large multinational corporations have a vertical conception of drug development. They take part in the studying, discovery, and manufacturing of new drugs, but they often require the help of academies for basic research. Then, they provide product approval (Food and Drug Administration), large-scale production, quality control, distribution, and sales. The actual main problem is that industries concentrate most of their money and human resources in all of these product development steps, leaving process development and testing to academies, which often do not receive the proper finances to develop seriously innovative and Good Manufacturing Practice (GMP) processes. For all of these reasons, the industries generally employ conventional consolidated techniques for

the production of drug carriers, considering them much more secure in terms of payback time and large-scale production.

6. Potential Discussion about an Overall Process

The main processes used for the production of artificial drug carriers generally involve the following simple steps: acquisition of raw materials, i.e., all of the drugs, components, surfactants that need to be used in the formation of the drug carrier, as well as the gases, water, and organic solvents needed for the formation. Then, the first step is the preformation of the carrier, which means the first preparation step, or maybe the first action that could be the preparation of the inner core, or the external layer, or the first branch formation, in the case of dendrimers. Then, the incorporation of a drug or active molecule occurs, followed by the formation of a protective barrier, and then, by the closure or hardening of the structure, after which no further changes can be performed.

This step is generally also characterized by post-processing processes. These could be characterized by the addition of elements on the surface of the carrier, such as antibodies, antigens, peptides, or providing coverage of polymer fragments or layers, performed with chemical strong bonds or weak forces, such as van der Waals'.

Post-processing steps could be sonication, extrusion, and filtration. In particular, the filtration could be useful to create sterile conditions. If the drug carrier is produced in liquid form, it can be filtered using proper nanometric filters, in order to avoid any viruses or bacteria to pass through. In a more professional manner, it is possible to use a laminar flow biological safety cabinet, under which the whole drug carrier process can be included. However, this would increase significantly the overall cost.

Sterility of the drug carriers is one of the most important characteristics of the drug formulation; however, post-processing steps can also be performed in order to decrease mean size, homogenize drug carrier population, and obtain a narrow distribution. Pharmaceutical industries accept a polydispersity index of 0.05 to 0.10 to consider a sample as monodispersed.

After all the indicated operations and steps, finally, the produced samples must be stocked in proper conditions, which could be freezing, refrigerating, or just leaving them in room temperature tanks (see Figure 3).

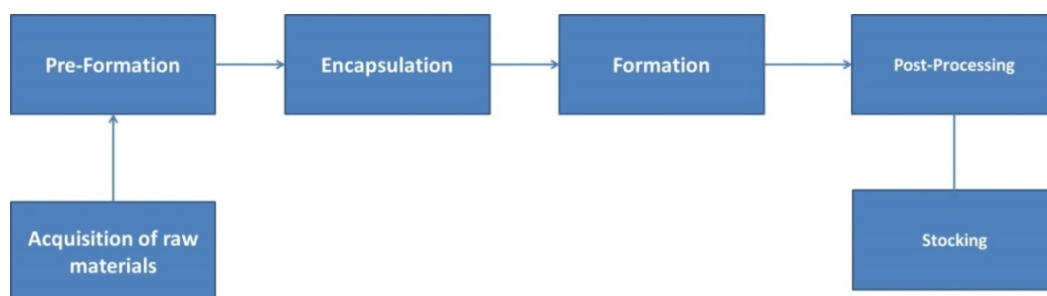


Figure 3. Description of the main steps for drug carriers' production.

The production of drug carriers is generally characterized by the use of reagents, such as liquid or gas, which are involved in a process that will be preliminary described as a black box (Figure 4). A native drug could be solid, but it will be preliminary dissolved into an organic liquid solvent or liquid water. According to the conventional methods, the gas is generally not involved in the earlier dissolution step. Instead, in high-pressure methods, the gas is used as a co-solvent, which is mixed to the organic liquid [142,143].

A loaded drug could, of course, be a lyophilized solid powder. From the description of the main known processes, the drug carriers will be provided in liquid or solid form (for example, as colloidal solid/liquid suspension). Moreover, the stocking conditions could be different according to the kind of produced drug carrier and the type of application.

An overall process could be the key to solve the problems linked to the production of drug carriers at all levels and for each kind of application. A versatile process may provide industries and academies with the solution toward having a unique undiscussed aim. The preliminary qualitative idea of a technique would be the basis to develop, at a large scale, any kind of the main drug carriers, shapes, and functions, as depicted in Figure 4.

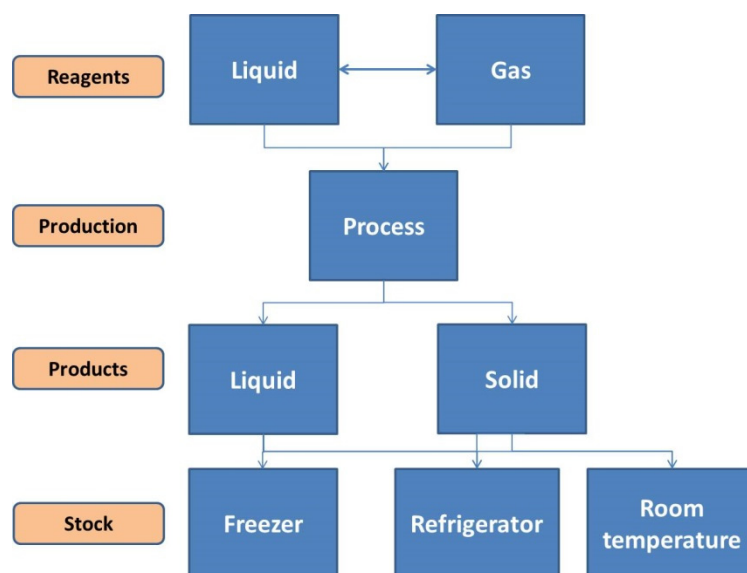


Figure 4. A sketch of the main steps for drug carrier production.

7. Conclusions and Future Perspectives

Drug carriers are the most effective vehicles for the preservation of molecules during their release pattern. Researchers have significantly contributed to the improvement of these carriers in the previous decades, synthesizing more complex materials, capable of becoming smart nanovectors of active principles. Second generation carriers have also been developed in order to achieve a targeted and selective release without causing side effects, while adding peptides, polymer fragments, and antibodies on the surface of the carrier particles. Drugs can be delivered into the body through several methods: among these, topical, intranasal, oral, and sublingual are the main ones. New methods of release have been identified to activate the administration only when required and only in the specific sites. All of these improvements reduced treatment cost and effectiveness.

In this review, the description of the market segment of drug carriers was analyzed in terms of revenue, variety of carriers, and administration of the drugs. The shapes of the release profiles have been qualitatively analyzed and classified according to the type of drug. Disadvantages and advantages of drug carriers were indicated in terms of conventional and innovative methods of production.

Most of the processes for the production of drug carriers have been specifically designed for the production of a single type of “transporter” (plant for liposomes, plant for polymer particles, plant for polymer fibers, etc.). However, it could be possible to create a versatile process for the formation of versatile carriers. This will guarantee the production of many types of drug carriers working on demand. The realization of this project would make it possible to diversify research activities according to the scientific objectives.

New targets need to be reached in the future. A better comprehension of biology will furthermore improve these carriers; this, coupled with an improved and increased collaboration among engineers, scientists, medical doctors, and private companies, will lead to the resolution of major illnesses causing suffering nowadays.

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