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Physically facilitating drug-delivery systems

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Abstract

Facilitated/modulated drug-delivery systems have emerged as a possible solution for delivery of drugs of interest to pre-allocated sites at predetermined doses for predefined periods of time. Over the past decade, the use of different physical methods and mechanisms to mediate drug release and delivery has grown significantly. This emerging area of research has important implications for development of new therapeutic drugs for efficient treatments. This review aims to introduce and describe different modalities of physically facilitating drug-delivery systems that are currently in use for cancer and other diseases therapy. In particular, delivery methods based on ultrasound, electrical, magnetic and photo modulations are highlighted. Current uses and areas of improvement for these different physically facilitating drug-delivery systems are discussed. Furthermore, the main advantages and drawbacks of these technologies reviewed are compared. The review ends with a speculative viewpoint of how research is expected to evolve in the upcoming years.

The goal of any drug-delivery system is to provide the therapeutic amounts of drug to the proper site in the body to achieve promptly and maintain the desired drug concentration [1]. However, conventional drug formulation through systemic delivery cannot meet these requirements and has many shortcomings, such as nonspecific toxicity and side effects in nontargeted cells and tissues, and inability to precisely control the dosage. The facilitated/modulated drug-delivery systems, which first appeared around the 1960s and 1970s [2], represent advanced systems that can be tightly mediated by stimuli in order to treat diseases specifically and with controlled dosage of drugs. Among different controlled delivery systems, drug-delivery systems based on mediation of physical properties and environments offer great potential over their counterparts due to their non-invasivity, versatility in design and tunability. Thus, these delivery systems can overcome many of the hurdles of

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conventional drug-delivery systems in order to increase drug efficacies and drug targeting and to decrease drug toxicities.

Physically facilitating drug-delivery (PFDD) systems emerge as adapting a vast quantity of techniques that were initiated in other sciences and engineering fields to drug-delivery applications. The intrinsic modulation or manipulation of the PFDD requires an engineering system where a delivered drug can be manipulated by applying different physical mechanisms in an *in vivo* environment. To address the limitations and challenges introduced above, the application of diverse physical modulation techniques provides their benefits to the field of PFDD. As illustrated in Figure 1, based on their physical modulation mechanisms, the PFDD systems can be classified mainly as photo-, magnetic-, **ultrasound**- and electrical-based modulation systems. As this is a broad field, it will not be possible to cover all of the existing literature. Nevertheless, this review focuses on describing the action mechanisms and summarizes the major progresses and limitations of these PFDD systems.

PFDD methods & applications

■ Ultrasound-based PFDD

Ultrasound has been widely known to improve drug delivery into targeted tissues in the body since the 1950s [3,4]. Sonophoresis (also known as phonophoresis) is therapeutic drug delivery with the use of ultrasound to mediate drug penetration through the skin (transdermal delivery) (Figure 2). Within this technique, there are two variants that can be identifiable based upon the frequency rate being utilized:

- High-frequency sonophoresis (HFS) (>0.7 MHz);
- Low-frequency sonophoresis (LFS) (20–100 kHz).

HFS has been used since the 1950s for the specific delivery of corticosteroids [5], while LFS has been used in the delivery of high-molecular-weight compounds since the 1990s. Although there is literature indicating that LFS can enhance skin permeability more than HFS [6,7], HFS has better recorded safety usage in clinical trials [8,9], which makes it more suitable as a potential drug-delivery therapy.

Skin permeabilization induced by high-frequency and low-frequency ultrasound has different action mechanisms. With HFS, the main contributor to enhanced skin permeability is the cavitation within the skin [7,10], increasing the skin penetration of low-molecular-weight compounds, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and topical steroids [11]. It is important to understand cavitation as the process by which a liquid is pulled apart when it is acted upon by a force in excess of its tensile strength, causing the formation of voids in the system [12]. Contrary to HFS, LFS relayed on the transient acoustic cavitation occurring above skin membrane to achieve skin permeabilization [13,14], similar to microjet impinging on the skin surface [11]. Even though many studies have been carried out to understand the action mechanism of ultrasound for drug delivery, complete understanding of the factors affecting skin permeability remains unknown.

High-frequency sonophoresis—The low invasive characteristics of HFS place this technology as a promising method for drug-delivery therapies. Its well-recognized, harmless process sets HFS as a good candidate to be regularly used in many applications, such as sports and physical therapy. The US FDA certifies its potential by having approved most ultrasound devices that operate at the high-frequency ranges (0.7–3.0 MHz); as evidence of this, large numbers of *in vitro* and *in vivo* studies have been carried out in recent years [11].

To date, HFS has been mostly utilized for delivery of topical steroids (a type of anti-inflammatory drugs) [4,15–19]. However, this tendency has been modified towards NSAIDs due to the known gastrointestinal side effects of oral NSAIDs (e.g., nausea, heartburn and others [20,21]). Therefore, studies are being focused on drug delivery of diclofenac [22,23], ibuprofen [22,24], ketoprofen [24], ketorolac [25], nimesulide [26] and piroxicam [22,27,28]. Moreover, HFS has been known to lessen the systemic side effects of oral NSAID in comparative trials [29]. All this work demonstrates the potential of the HFS method as a useful localized NSAID treatment. It is expected that current progress will continue apace to enable HFS as a viable drug-delivery method of low-molecular-weight entities (<1000 Da).

Low-frequency sonophoresis—Regarding LFS, recent studies have demonstrated that skin pore size is frequency dependent [30]. In such studies, skin regions were isolated on the so-called 'localized transport regions', enabling characterization of skin permeability when treated with LFS. Results establish that LFS is a technique that permeates skin heterogeneously, gaining attention for its drug-delivery application.

Current research has focused on enhancing transportation of drugs into the body through the dermis, allowing the investigation of chemical enhancers to improve the drug-delivery rate. Surfactants (chemical enhancers) have been studied to characterize their capabilities of increasing their delivery rate, such as changing lipid organization [31], increasing the coupling medium-to-skin-partition coefficient [32,33] and many others. Recent studies using chemical enhancers in the form of sodium lauryl sulfate have shown improvement (0.5- to 1.3-fold) on skin penetration of model nanoparticles (quantum dots) [34]. Preliminary investigations on the amphiphilic nature of sulforhodamine B (a chemical commonly used as laser dye and fluorescent probe) have revealed its potential to increase skin permeability by the assessment of a positive enhancement ratio [35]. Moreover, in clinical settings, surfactants have been used along with other techniques. Such is the case of the iontophoretic technique (use of electric energy to deliver charged chemicals transdermally), which in combination with LFS treatment has resulted in shortening the voltage exposition period [36,37]. The positive results of delivering nano-size particles through dermis at low-frequency ultrasound and its similar safety of use compared to intramuscular injections [38, 39], make us expect that transdermal vaccination might represent a strong alternative for replacing conventional vaccination method; and subsequently, the issues associated with intramuscular injections [40,41].

Gene therapy—Due to the increasing attention of transportation of genetic material by ultrasound mediation, it is imperative to discuss the strategies and progress for delivery of DNA for various applications. Many studies of successful gene transfer *in vivo* can be found in applications in the fields of kidney, cardiac and skeletal muscles treatment [42], and more recent data has emerged from fields such as hematology, vascular, neurology and oncology. From these applications, cancer has gained most of the attention; this is reflected by being the subject of the majority of the gene therapy research being tracked by the NIH Recombinant Advisory Committee [43]. In the past decade, three main strategies have been followed. First, gene transfection increment has been obtained by transferring genes locally [44], offering minimal exposure of healthy tissues to ultrasound treatment. As a second strategy, DNA targeting of blood vessels upon ultrasound exposure has been used [45]. This strategy limits the transfection to a desired organ or tissue. As a third strategy, DNA transfection systemically appears, where interesting studies have increased vascularization of the myocardium in order to prevent heart failure [46]. However, more recent studies have set the trend of using an interesting strategy that uses carriers in the form of gas-filled microbubbles. This approach is discussed in the section below.

Ultrasound-mediated microbubbles—This drug-delivery strategy consists of drug-loaded microbubbles, which are triggered by cavitation caused by ultrasound manipulation. These microbubbles carriers (i.e. polymeric micelles [47] and liposomes [48]) have been mainly administrated intravenously. This procedure increases local drug/gene delivery to targeted tissues, therefore decreasing possible side effects due to excessive drug exposition. More investigation is needed to better understand the microbubble deployment mechanism, as current knowledge remains limited [43]. As proof of its valuable inclusion to the field, this strategy has proven useful for transfection rate enhancement by means of plasmid manipulation at *in vitro* and *in vivo* experiment sites [49]. Similar promising results, which involve strategies using silencing genes, have followed this, where synthetic oligonucleotides (antisense DNA) have been delivered [50]. More recent studies have shown that systemic administration of IL-12 corded plasmid DNA has resulted in an effective tumor suppressor through liposome microbubbles [51]. This sets this strategy as a promising, minimally invasive technique for gene therapy.

■ Electrical-based PFDD/electroporation

The term **electroporation** arose in the 1980s, when it was noted that high-voltage electric impulses increase cell permeability [52]. This term referred to the fact that a formation of nanopores was formed in cellular membranes to allow passage of desirable substances. For many years, research was focused on permeabilizing the cell membrane temporarily for applications such as fusion of cells, gene and drug delivery [41,53–64]. This temporary permeabilization, maintaining cell viability, was called 'reversible electroporation' (RE). A short electric pulse is applied to the targeted area and causes a disruption of cellular homeostasis through dismantling the cell membrane wall with innumerable nanopores [65,66].

From ions to drugs, electroporation has been proven useful *in vitro* and *in vivo*, where therapeutic drug delivery has to be performed. In addition to through the use of drugs, electroporation can also be used to deliver a wide range of potentially therapeutic agents including proteins, dyes, tracers, antibodies, oligonucleotides, RNA and DNA [67]. Nowadays, it represents one of the most widespread techniques used in molecular genetics.

Gene therapy—The RE technique has been used for delivering gene content for therapeutic purposes. Such is the case of a recent study where **VEGF** have been modulated by RE into cardiac tissue *in vivo* [68]. This therapy was compared with direct injection of plasmid showing significant increase on the expression of VEGF. As VEGF has been proven to stimulate angiogenesis, its usage along with electroporation represents a promising therapy for treating vascular diseases in future clinical trials.

Moreover, in a comparison investigation in the administration of human papillomavirus DNA vaccine, electroporation has been reported to elicit a higher effective rate compared with gene gun and traditional intramuscular vaccination [69], placing RE as an ongoing popular technique for gene therapy.

Clinical studies—Both preclinical and clinical trials of human and various species utilizing the electroporation technique have been successfully recorded in recent years [201]. One of the more relevant applications has been in the study of melanoma treatment, where administration of IL-2 and IL-12 by electroporation has demonstrated its anticancer capabilities. Since the initial human trials, gene therapy (IL-12) by electroporation has been proven as safe, effective, reproducible and titratable [70]. Moreover, major advances have been encountered in the field of prostate cancer, where electroporation has been utilized for gene delivering of prostate-specific antigen DNA vaccines. Intradermal treatment results

have demonstrated an increase up to 1000-fold in gene expression compared with DNA by itself [71,72]. There is a currently recruiting clinical trial studying a DNA vaccine by means of intradermal electroporation in patients with prostate cancer [202]. Along with these clinical studies further trials are ongoing for possible treatments of HIV, hepatitis C and human papillomavirus infection [73].

■ Magnetic-based PFDD systems

In biomedical engineering, **magnetic nanoparticles** (MNP) have gained interest in various applications, including:

- Magnetic separation for cell and other biological entities labelling;
- Therapeutic drug delivery;
- Heating treatment of tumors through radio frequency methods;
- As a contrast enhancement agent for imaging (i.e., MRI).

Moreover, recent studies have demonstrated novel applications for MNPs in the form of nanomagnetic actuation for tissue engineering and regenerative medicine. One application of this is the magnetic targeting of stem cells to sites of injury in the body, an approach that was first reported *in vitro* by Sura *et al.* in 2008 [74] and *in vivo* by Kyrtatos *et al.* in 2009 [75]. As a promising tool, MNPs represent an appealing solution for PFDD. Here we will briefly describe its mechanism of action and discuss the current research progress and limitations with regards to drug carriers and targeting studies.

Drug carriers modulated by an external magnetic field—The manipulation of this technology is based on the influence of external magnetic fields on polymer-coated ferro-MNPs used as drug carriers. Such physical manipulation enables the particles to be agglomerated and/or transported to reach a highly localized therapeutic effect. Furthermore, the nanoscale property of such particles allows them to be introduced into targeted cell nuclei, making them capable of interacting with the cells' genetic information. Therapeutic strategies are generally classified based on their relation with biochemical objects, such as chemotherapeutic, biotherapeutic, or genetic drugs:

- Chemotherapeutic agents – many chemicals have been studied within this category, where the main approaches have been via cytotoxic, cytostatic and antineoplastic effect. To date, body internalization of drug-loaded MNPs have been achieved under prolonged circulation times [76]. In cancer therapy, MNPs have been loaded with common therapeutic drugs such as paclitaxel, doxorubicin (DOX), curcumin, chlorotoxin and methotrexate [77–80].
- Biotherapeutic via peptides and antibodies – the inherent cell specificity of peptides and antibodies makes them valuable for investigation as potential therapeutic agents. The strategies followed in this therapeutic include the initiation of apoptotic/necrotic pathways, function blocking and stimulation of immune response [81]. Cell-penetrating peptides have been reported, showing improvement in nuclear and cellular uptake; for example, tat [82] and chlorotoxin peptide [83]. Regarding antibodies, Herceptin® has been used in recent investigations, where studies have shown its inhibitory characteristics of cancerous tissues [84,85].
- Gene therapy – the use of genetic material for therapeutic purposes has also gained attention in magnetic-based drug-/gene-delivery systems. Development of specific coatings that can successfully carry such materials has been required, where cationic polymers have been more frequently used [76]. However, their

achievements are limited to *in vitro* studies, whereas *in vivo* studies are restricted due to their toxicity and stability preoccupations. However, the first successful targeted/siRNA treatment *in vivo* study was reported by Medarova *et al.*, where antisense RNA bonded to MNPs were used, resulting in enhanced therapeutic application for human colorectal carcinoma tumors [86].

Drug carriers design—Effective design of MNPs as drug carriers is a complex task. The generally accepted main design requirements for them as drug-delivery vehicles are:

- Capability to carry and maintain an appropriate drug load;
- Capability to carry multiple drugs to improve therapeutic efficacy;
- The drug/gene release mechanism and rate.

Extensive studies have been carried out on the fabrication of target-specific MNPs to engineer its magnetic core and its typical polymer coatings [76], characteristics that are tightly related, to meet those requirements. However, along with these needs, MNPs are required to overcome the biological barriers established by the human body. For instance, gene carriers have to be engineered in such a manner that they can withstand cell-internalization processes (endocytosis) and effectively meet their transfection purposes by reaching the cell nucleus, avoiding any degradation that might compromise their therapeutic application [87]. Moreover, the role of key properties such as morphology, hydrodynamic size, charge and other surface properties [88,89] have to be kept in designer's mind to advance the establishment of better design conditions to create stealth MNPs. As progress continues in this field, studies that individually evaluate the design parameters discussed above and enhance characterization tools are required.

Coatings of drug carriers—The development of novel MNP carrier formulations continues apace. Functions such as endosomal release and drug loading/release of the MNPs are mainly controlled by the engineered coating of the drug carriers. Several polymers have been investigated, including polyethylene glycol (PEG), dextran, chitosan, polyethyleneimine (PEI) and phospholipids [76]. From these polymers, PEG is closer to clinical implementation than the rest, as variations of it have been approved by the FDA for a long period of time [90]. In contrast, polymers such as dextran are further away from clinical trials, mainly due to its failure to degrade and clear from the body [87]. Moreover, it is worth mentioning that copolymers have gained interest in their development due to the varied benefits derived from their distinct elements. For instance, a recent study have reported a mixture of PEI and PEG polymers, which in conjunction formed a structure capable of carrying DNA (PEI functionality) and maintaining a phantom profile (PEG functionality) for improved gene therapy [91].

Multifunctional carriers dual imaging & drug-delivery applications—A key element to deliver drugs effectively *in situ* is the ability of controlling the position where the MNPs are placed in real-time. For instance, one element highlights the importance of visualizing the injected drug-loaded MNPs by MRI. Recent investigations for application of both functionalities (drug delivery and traceability) have been made. Simultaneous functions have been demonstrated by Sun *et al.* [92], in a study using PEG-coated superparamagnetic iron oxide nanoparticles for chemotherapeutic purposes. A similar demonstration in treatment of breast cancer tumors was made using a magneto-polymeric nanohybrids composed of magnetic nanocrystals and a chemo therapeutic agent encapsulated by an amphiphilic block copolymer shell [93]. These investigations illustrate the advantages of developing multifunctional MNPs. In more recent research, β -cyclodextrin coated nanoparticles (CD2000) have been evaluated for its improved capacity of hyperthermia

effect under alternative magnetic stimulation at distance [94]. In this study, ferro-MNPs were coated by a copolymer compound (β -cyclodextrin and pluronic), where its high water solubility enabled this treatment to continuously release the drug embedded on its coating surface.

Clinical trials—The magnetic PFDD systems have also been used in clinical trials. Contemporary studies have reported the first achievable brain tumor therapy utilizing MNPs in clinical trials [95]; this therapy was based on hyperthermia. The trials that followed were focused on prostate cancer therapy based on the same technique [96,97]. However, a remaining concern persists on the debilitation of a magnetic field as targeting deeper tissues, restricting the demonstrated therapy to superficial targets.

Although current MNPs decorated with PEG and dextran have been approved by the FDA for clinical trials, concerns regarding decomposition and long-term toxicity of MNPs still need to be addressed prior to further advancement into clinical settings. As this concern gets resolved, MNPs based technologies can step over other techniques to improve current diagnosis, treatment and monitoring of aggressive ailments that require high dosage and localization of drug delivery.

■ Photo-based PFDD

Therapeutic properties of light have been known and applied to medicine for thousands of years by ancient civilizations [98,99]; however, it was not until in the last century that light-based therapies such as **photodynamic therapy** (PDT) were developed. The attractive properties possessed by light represent a great therapeutic advantage. Light properties such as intensity and wavelength can be manipulated by means of filters, photomask and/or lasers for set it up to a desired light spectral range. However, for *in vivo* applications, the most suitable light spectral range is in the **near-infrared region** (nIR), due to its better capability for penetrating tissue [100].

In the following section, PDT, photo-reactive **nanocages** and **photovoltaic (PV) drug delivery** are discussed. The three techniques are activated by light to cause drug therapeutic release, and in the case of PDT, ablation of malignant tissues by heat generation.

Photodynamic therapy

Phototherapy was introduced as science in the early 19th century when Nobel Prize winner, Niels Finsen, studied the effects of light in living organisms [98]. From then on many studies have evolved the field into a mature research field known as PDT. PDT involves three main elements. The first of these elements are drugs called **photosensitizers**, which are made of composite material and are reactive to photon energy, enabling the selectivity and specificity of tissue to be treated. The second element is light. Red light (wavelength ≥ 600 nm [101]) usually serves as a trigger to activate the photo sensitizers to produce the third element at the site of interest. The third element is oxygen. Activated photosensitizers interact with nearby molecules, resulting in reactive oxygen species that ultimately cause cell death by oxidative stress.

This technique has been applied mainly for cancer therapy. Research has enabled many PDT drugs to be approved for clinical usage in different countries [102]. PDT has been demonstrated for the treatment of early lung cancer [103], bladder cancer [104], head and neck cancers [105] and skin cancer [106]. In addition to directly killing cancer cells, PDT appears to shrink or destroy tumors in two other ways. First, the photosensitizer can damage vasculature within the tumor. Second, PDT may activate the immune system to attack the tumor cells [101,107,108].

However, researchers have focused on other applications as well. Antimicrobial applications utilize the same mechanism to treat diseases such as malaria [109], blood, water, and surface disinfections [110], cardiovascular treatments [111,112], ophthalmology diseases [113,114], dermatology [115,116] and rheumatology [117].

Photosensitizers—With this technique, the photosensitizers act as a specific drug to be delivered. Even though this technique does not carry a drug as itself, its research is highly related to minimally invasive and highly located requirements of current drug treatments. Research is ongoing to design the most suitable photosensitizers for oncology and antimicrobial applications. It is well-recognized that the ideal PDT agent is required to:

- Be chemically pure, with known composition and good stability;
- Be preferentially accumulated and retained by the target tissue;
- Have minimal toxicity in the absence of light and be cytotoxic only upon photoactivation;
- Have high quantum yield of singlet oxygen;
- Have high molar extinction coefficient and high absorbance, particularly in the red and far-red spectral regions (600–800 nm) [101,102].

Many materials have been tried for fabrication of the photosensitizer. However, it is not within the scope of this article to review in detail the limitation of each material that has been investigated. Further progress and limitations can be found in comprehensive reviews [102,107,118].

The action mechanism of this technique is initiated by the insertion of a ground singlet stated photosensitizer in the desired site (usually by injection). When this photosensitizer is activated by light it starts the race towards an excited triplet state, which lasts long enough to interact with the desired target [119]. The triplet-stated photosensitizer will react with the ground triplet-stated oxygen embedded in tissues. As a result of this reaction, energy will be released, relaxing the photosensitizer to its singlet state and exciting the nearby oxygen molecules to their singlet state [120]. At this stage, **singlet oxygen** achieves oncologic therapeutic effects by rapidly interacting with its surrounding tissues and compromising these structures towards apoptotic and necrotic fate [107,121].

Light wavelength—The light can directly affect the PDT effect in clinical practices. That is why it is important to investigate the sources of light that can be used to interact in PDT. Therapy for surface tissues, such as skin cancer [115], can accommodate the usage of LED technology. Meanwhile, therapies for deeper tissues need different strategies; for instance, endoscopy has been used to direct light into profound areas in the body for cancer treatment in the lungs and esophagus [122].

PDT future development—One of the most relevant remaining limitations of PDT is the limited light penetration of tissues. Two-photon absorption-induced excitation of photosensitizers is a promising approach for increasing light penetration, because it makes it possible to use two photons of lesser energy (higher wavelength) to produce an excitation that would 'normally' be produced by the absorption of a single photon of higher energy (lower wavelength) [123]. Indeed, appropriate photosensitizers can simultaneously absorb two photons of lower energy, which makes excitation possible in the nIR, thereby avoiding wasteful tissue absorption or scattering and allowing a deeper penetration of light into the tissue. To this end, various molecules with increased two-photon absorption cross-sections have been designed [124].

Further areas of improvements have been identified. For instance, it is the case of the ability of PDT to stimulate the immune system, which is a relevant and promising area under active research [101]. Another significant area of research is the combination of PDT with other treatment modalities, such as chemotherapy and radiation therapy. Moreover, avoiding tumor recurrence is also an area of improvement [102]. Beyond the laboratory, this technology still requires further advancement on manipulation appropriate dosage, delivery system and exposure times to maximize clinical effectiveness while minimizing side effects [118]. In some other uses, photosensitizers may also be examined as potential agents for intra-operative settings, such as photodynamic diagnosis, where tumor tissue boundaries can be visualized to assist in surgical resections [125].

Nanostructured devices for controlled drug delivery

In the past decade, an attractive emerging technology is the one in charge of entrapping drugs by means of nanoscale structures. In a recent report, which increased the relevancy of this technology, it has been suggested that cancer cell drug uptake is particle-size dependent, and the maximum uptake by cells occurs at a nano particle size ($< 100\text{nm}$), indicating that particles less than 100 nm may be the most suitable candidates to serve as a drug carrier for further studies in biological applications [126]. Taking advantage of unique light interaction property of noble-metal nano-structures, gold nanocages have been developed as one option for entrapping drugs at nanocages [127,128]. Gold nanocages are small-size structures (e.g., $\sim 45\text{ nm}$ in edge length) that have been tailored to achieve strong absorption in the nIR for photothermal effect. The basics of its mechanism start when light is absorbed by the nanocage and converted into heat, triggering the smart polymer to collapse and thus release the preloaded effector. When the laser is turned off, the polymer chains will relax back to the extended conformation and terminate the release. Yavuz *et al.* demonstrated experiments on an Au nanocage covered with polymers for controlled release with near-infrared light. Advantages such as high spatial/temporal resolutions and the convenient variation of their scattering and absorption cross-sections were identified [128]. Figure 3 shows the working mechanism for the nanocages for drug release. Further discussion on this method can be found elsewhere [127]. In the following, it will be review a few important aspects associated with the new nanostructured drug-delivery system, which is modulated by photo effect.

Nanocage fabrication—The nanocages are fabricated by using a special nanofabrication method in which the solid form of a silver (Ag) nanostructure can be transformed into the Au nanostructure with a hollow interior via the galvanic replacement reaction with HAuCl_4 solution being controllably added to a boiling suspension of Ag nanocubes. As the reaction proceeds, this pinhole serves as the anode, where Ag is oxidized and electrons are stripped. The released electrons migrate to the nanocube faces and are captured by AuCl_4 , generating Au atoms that epitaxially grow on the nano-cube. As the Au layer forms, the initial pinhole serves as the site for Ag dissolution facilitating the conversion of the nanocube into a nanobox. Thus, cubic nanocages with pores at all corners (Figure 3) are produced (for further detail refers to the protocol [129]).

It is important to understand how drugs are loaded into the nanocages. Nanocages are shaken in a temperature-controlled drug solution to expand the coating polymer and allow drug introduction. Subsequently, sealing of the nanocages is achieved by returning the temperature of the polymer to its solid state. However, polymer chains relax into a peculiar form similar to stand up brushes (as illustrated in Figure 3). Once these steps have been followed, drug-loaded nanocages are obtained. Therapeutic drug release will be achieved by exposing the nanocages to laser light at their resonant frequency, resulting in a polymer collapse and, therefore, drug liberation [128]. Once light stimulation is removed, the polymer will reseal the nanocages.

In vitro and in vivo studies—Initial research using dyes and model drugs have found the degree of control of nanostructure devices. Results indicate that the release rate has a direct relation to the intensity of the light stimulation (usually nIR laser) [128]. These studies also indicate a drug release/delivery rate within 16 min. To further test if the new nanocages work for cancer drug delivery, nanocages capturing DOX have been evaluated for their efficacy in treating breast cancer in an *in vitro* model [128]. In these experiments, the breast cancer cells were cultured in the presence of nanocages loaded with DOX, and the cultures were irradiated with nIR light. As anticipated, they observed a fast release of DOX when the sample was subjected to light activation, resulting in breast cancer cell apoptosis. Moreover, DOX release was shown to be dependent on laser irradiation time. Moving further into an *in vivo* study, Su *et al.* demonstrate the therapeutic efficacy of DOX-loaded nanocages [130]. Hollow DOX-loaded mesoporous silica nanocages were compared against free DOX on a liver cancer mice model, resulting in superior inhibition conditions. Setting nanostructured devices as an attractive potential candidate for cancer therapy and drug delivery.

In spite of these advances, parameters including cage concentration, drug loading, laser irradiation time and power density all need to be optimized to further improve the efficacy of therapeutic practices [128]. Although nanocages have progressed recently as *in vivo* contrast enhancement agents for imaging, more studies with respect to their feasibility for *in vivo* drug delivery are needed at this time. It is undeniable that they possess great potential for the development of advanced drug-delivery systems. In general terms, this technique needs further attention to find its way to clinical settings and this is expected to happen in the coming decade.

PV devices for targeted drug delivery

A remaining major drawback of current drug-delivery mechanisms is the cytotoxicity over healthy tissues surrounding targeted malignant tissues. In order to effectively select treatment-desired tissue, our research group has recently developed a novel methodology for drug delivery, termed **PV device**-based drug delivery. This method utilizes micro-sized PV devices to load drugs and release them upon external light stimulation [131,132]. A PV device material features two regions, one exhibiting an excess of electrons, the other an electron deficit, referred to as *n*-type doped and *p*-type doped, respectively. When the former is brought into contact with the latter, excess electrons from the *n* material diffuse into the *p* material. An electric field is thus set up between them, tending to force electrons back into the *p* region and increasing its voltage: the electric current passes through the circuit (Figure 4A) [133].

In this new strategy, drug loading onto PV devices based on electrical charge is proposed, sustaining drug load by means of electrical attraction (negative/positive) and releasing the drug by changing the polarity of the PV device elicited by repulsion effect (Figure 4B). Micro- or even nano-scale PV devices will be injected into patient, enabling physicians to physically stimulate the site of interest by appropriate light causing the release of a desired drug dosage [132].

Utilizing the PV effect, a study of the capability of drug loading and releasing *in vitro* has been carried out. It was demonstrated that positively or negatively charged drugs can be loaded to opposite sides of a miniature solar cell. Upon exposure of a light beam, one side of the device became positively charged, repelling the positive-charged drugs placed there, having the same result with the negatively charged side and negative-charged drugs. Moreover, a direct relation was found between the density of the exposed light and the amount of drugs being released [131]. More work is planned to explore animal models to better demonstrate the capabilities of this proposed drug-delivery modality.

To date, PV devices have not been used as drug-delivery systems. That is why it is noteworthy to present it in this review, as further attention is required by researchers to better develop this emerging therapy as it provides a potential approach for cancer and other diseases with promising specificity characteristics. This drug-delivery modality requires further attention from researchers in different fields. For instance, in electronic engineering and physics, PV devices need development to move towards micro- and nano-scale size devices. A brief explanation of the working mechanism and *in vitro* studies made from our group were reviewed in this section.

Future perspective

There is an increasing interest in applying a variety of physical facilitators/modulators, including photo-, magnetic-, ultrasound-, thermal- and electrical-based techniques, to the applications of drug delivery and cancer therapy. This review describes key fundamentals, progress and limitations of different modalities of PFDD systems, in order to provide the reader an overview of this field (Table 1).

In spite of progress in the field, there are still opportunities to investigate the various limitations. For example, PFDD techniques generally have limited penetration depth because of their intrinsic 'outside the body manipulation'. Parameters and strategies have to be modified to increase drug penetration depth, i.e. maintain investigations on co-materials to improve drug-carriers responsive characteristics, or developed alternative strategies to reached core tissues. Other area of continuous improvement, among all techniques discussed, consists in maximizing the amount of drug loaded on the carriers.

In particular, ultrasound- and electrical-mediated drug delivery are expected to continue apace in their clinical studies and enlist further therapeutic drugs into their arcs, and ultimately deal with FDA approvals to set their place within the market as well-recognized therapies. Regarding magnetic manipulation, further composite materials need to be studied and developed for fabricating the nanocarriers. On the photo-based methods, it is expected that nanostructured devices improve their control over the fabrication and design characteristics to extend their capabilities and the understanding of them. The PV-based drug-delivery method is still in early development at the proof-of-concept stage and, as a very promising technique, requires more attention by scientific community to further improve its relevancy in the field.

In summary, the PFDD methodologies presented herein offered a broad area of investigation within therapeutic drug delivery. Even though more research is needed to move forward to clinical applications (in some instances) as well as to overcome many current limitations, these methodologies prove to be promising for future cancer therapy and drug delivery.

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Papers of special note have been highlighted as:

■ of interest

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Key Terms

Physically facilitating drug-delivery systems

The usage of physically responsive materials such as drug carriers for versatile, tunable and on-site drug delivery for cancer and other treatment diseases. Physical manipulation can be achieved based on ultrasound, electricity, magnetism and photonic emission technologies.

Ultrasound

Cyclic sound pressure with a frequency greater than the upper limit of human hearing (above 20 kHz). This sound pressure is widely used for obtaining real-time images of the body.

Key Terms

Electroporation

Methodology that facilitates drug delivery by skin permeabilization through electrical stimulation. Such stimulation causes nanopores at cell membranes to allow passage of therapeutic drugs. Depending on the amount of energy utilized and its temporary effects, it can be divided in reversible and irreversible electroporation.

VEGF

Signal protein produced by cells that stimulates growth of new blood vessels.

Magnetic nanoparticles

Particles of small size (range of micron, 1×10^{-9} m) made of materials that are sensitive to magnetic fields (e.g., iron) causing either attraction or repulsion forces, allowing manipulation by extracorporeal magnetic fields.

Key Terms

Photodynamic therapy

Minimally invasive therapy that utilizes a photosensitizing agent and an appropriate wavelength light stimulation for cancer treatment or drug delivery. In the case of cancer therapy, upon light stimulation, the photosensitizing agents produce free radicals, which ultimately cause its death.

Near-infrared region

Range of the electromagnetic spectrum within 750-2500 nm wavelength, which is longer than visible light. A well-recognized application is found on the night vision systems used by military.

Nanocages

Porous and hollow nanoscale boxes used as carriers for therapeutic drugs. Mainly made of noble metals, which have photoresponsive properties.

Photovoltaic drug delivery

Drug-delivery system that uses as a carrier a photovoltaic device (e.g., solar cell), enabling modulation and dosage control based on light exposure.

Photosensitizer

Chemical compound excitable by light at appropriate wavelength. This interacts with nearby biomolecules, generating singlet oxygen.

Singlet oxygen

Form of oxygen that is a very aggressive chemical that reacts with nearby molecules, causing damage to surrounding cells and tissues.

Key Term**Photovoltaic device**

Product used to generate electrical power by transforming solar radiation into direct current electricity using semiconductors that exhibit the photovoltaic effect, such as solar panels.

Executive summary

- Physically controlled drug-delivery systems enable biomedical engineering to manipulate and facilitate drug dosage, localization of therapeutic treatment and so on, through nano- and micro-carriers for promising applications including cancer therapy.
- Ultrasound represents a facilitating technology to increase skin permeability for passage of drugs transdermally.
- Electroporation has been demonstrated as being useful for drug delivery *in vitro*, *in vivo* and in clinical trials. Molecules delivered include drugs, proteins, dyes, traces, antibodies, oligonucleotide, RNA and DNA.
- Physical manipulation at a distance by means of magnetic fields denotes a promising approach to increase aggregation of nanoparticles to improve therapeutic actions of drugs.
- Research in photoresponsive materials at the macro- and nano-scale have enabled engineering to develop drug-release systems based on light irradiation at appropriate wavelength.

Figure 1. Physically facilitating drug-delivery systems, which mainly include photo-, magnetic-, thermal-, ultrasound- and electrical-based modulation systems.

Figure 2. Ultrasound mechanism

(A) Layered skin tissue; (B) ultrasound waves applied causes cavitation within skin layers; (C) drug passes through skin cells towards target and; (D) drug delivers into target.

Figure 3. Nanocages

(A & B) Silver nanostructure transform into silver nanocage by galvanic reaction with HAuCl_4 . **(C)** The light is absorbed by the nanocage and converted into heat, triggering the smart polymer to collapse and, thus, release the preloaded effector. **(D)** When the laser is turned off, the polymer chains will relax back to the extended conformation and terminate the release. Printed by permission from Macmillan Publishers [Nature Materials] [128] (2009).

Figure 4. Photovoltaic mechanism

(A) In the typical PV device cell, photon energy frees electrical charge carriers, which become part of the current in an electric circuit. A built-in electric field provides the voltage needed to drive the current through an external load. (B) Drug release from a PV device upon external photostimulation.

PV: Photovoltaic.

Table 1

Advantages and disadvantages of different physically facilitating/modulating drug delivery systems.

Physically facilitating drug-delivery technique	Advantages	Disadvantages	Ref.
Ultrasound-based			
	Good recorded safety usage on clinical trials (HFS) Minimally invasive and highly localized HFS (0.7–3.0 MHz) has been proven useful for current treatments in sports and physical therapy rehabilitations. Can decrease side-effects of NSAIDs in comparison with oral intake Can permeate skin heterogeneously (LFS) Can deliver small molecules and transfer genes of interest locally (LFS)	Action mechanism still not fully understood Efficiency is relatively low	[8,9,11,29,30,44]
Electroporation-based			
	Safe, effective, reproducible and titratable Demonstrated useful for both <i>in vitro</i> and <i>in vivo</i> studies	Possibility of irreversible nanoporation of healthy tissues when excessive energy is used Action mechanism is still not fully understood Evidence of nanopores need to be elicited	[52–73]
Magnetic-based			
	Physical manipulation at a distance by means of magnetic field Long circulation times of drug-loaded MNPs in the body MNPs have been loaded with common therapeutic drugs such as paclitaxel, doxorubicin, curcumin, chlorotoxin and methotrexate Drug delivery and traceability (i.e. MRI) MNPs decorated with PEG and dextran have been approved by US FDA for clinical trials	Achievements are only limited to <i>in vitro</i> studies, whereas <i>in vivo</i> studies are restricted due to their long term toxicity and stability concerns Need better design conditions to create stealth MNPs	[77–80]
Photo-based			
Photodynamic therapy	Ability to manipulate high intensity and wavelength Minimally invasive and highly localized Endoscopies might be used to reach deeper tissues Possibility of using as photodynamic diagnosis	Action mechanism still not fully understood Limited light penetration of tissues Stimulation of immune system by PDT still to be fully elicited Tumor recurrence has occurred	[102]
Nanostructured devices			
	Gold nanocages have strong light absorption High spatial/temporal resolutions and convenient variation of scattering and absorption cross-sections Useful as <i>in vivo</i> contrast enhancement agent for imaging	Preliminary research stage Cage concentration, drug loading, laser irradiation time and power density all need to be optimized to further improve the efficacy of therapeutic practices Studies to prove its feasibility for <i>in vivo</i> drug delivery are still required	[128]
Photovoltaic			
	Minimally invasive, highly localized and target specific The amount of drugs released can be modulated by light intensity and wavelength	Proof-of-concept stage Further attention is required by researchers in different fields for development	[131,132]

HFS: High-frequency sonophoresis; LFS: Low-frequency sonophoresis; MNP: Magnetic nanoparticle; NSAID: Nonsteroidal anti-inflammatory drug; PDT: Photodynamic therapy; PEG: Polyethylene glycol.