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Single compartment drug delivery

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Abstract

Drug design is built on the concept that key molecular targets of disease are isolated in the diseased tissue. Systemic drug administration would be sufficient for targeting in such a case. It is, however, common for enzymes or receptors that are integral to disease to be structurally similar or identical to those that play important biological roles in normal tissues of the body. Additionally, systemic administration may not lead to local drug concentrations high enough to yield disease modification because of rapid systemic metabolism or lack of sufficient partitioning into the diseased tissue compartment. This review focuses on drug delivery methods that physically target drugs to individual compartments of the body. Compartments such as the bladder, peritoneum, brain, eye and skin are often sites of disease and can sometimes be viewed as “privileged,” since they intrinsically hinder partitioning of systemically administered agents. These compartments have become the focus of a wide array of procedures and devices for direct administration of drugs. We discuss the rationale behind single compartment drug delivery for each of these compartments, and give an overview of examples at different development stages, from the lab bench to phase III clinical trials to clinical practice. We approach single compartment drug delivery from both a translational and a technological perspective.

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Targeted therapy; single compartment; controlled release drug delivery; local therapy; noninvasive; microfabrication

1. Introduction

The majority of pharmaceutical therapies are dosed systemically even though the pharmacologic target may reside in a specific tissue or single compartment of the body. The strategy has been to increase the specificity of the drug toward its intended target in the belief that the target is enriched at the site of disease [1].

An example of a pharmacological target directly linked to the targeted diseased tissue is human epidermal growth factor 2 (HER2). Approximately 25–30% of breast cancer patients overexpress this receptor on the surface of their cancer cells [2]. HER2 additionally activates several important signaling pathways that are involved in stimulating cell proliferation and the downregulation of apoptosis [3, 4]. HER2 has thus become the target of systemic therapies, using molecules that interfere with HER2 stimulation [5, 6]. The monoclonal antibody trastuzumab (Herceptin) is one such successful drug [6, 7].

A more typical example of targeted therapy is the development of drugs for the inhibition of cyclooxygenase (COX). This enzyme is responsible for the formation of agents such as prostaglandins and prostacyclin [8]. Prostaglandin synthesis in the inflammatory cells of the central nervous system is a factor in the development of inflammation [9–11]. Prostaglandin synthesis is at the same time necessary for the normal function of many types of cells, such as those in the gastro-intestinal tract or blood platelets [12–16]. Inhibitors of all variants of the COX enzyme may therefore help inflammation but may also have “off-target” effects. The COX enzyme, however, has several variants such as COX-1 and COX-2 [17]. COX-2 is overexpressed during inflammation [18]. It thus became the target of choice for the development of drugs such as Celecoxib, which exhibited gastric side effects that were greatly reduced in comparison to those of non-selective COX inhibitors [19–22]. It was unfortunately only after widespread use that patients using selective COX-2 inhibitors were found to be at increased risk for myocardial infarction—approximately five-fold higher than for patients using non-selective non-steroidal anti-inflammatory drugs (NSAIDs) [23–25]. The most common theory is that while both non-selective NSAIDs and COX-2 inhibitors are associated with oxidative stress, it is only the non-selective NSAIDs that reduce platelet aggregation [25, 26]. The selective targeting of disease clearly demands a very comprehensive understanding of the complexity of off-target effects.

Another typical target is the muscarinic acetylcholine receptor that pays a role at neuromuscular junctions, such as those present in the detrusor muscle surrounding the bladder [27]. Antimuscarinic agents are the predominant drugs used for the treatment of overactive bladder (OAB) [28, 29]. Most of the commonly used drugs are not selective for any of the five known subtypes of this receptor [28, 30]. This is of course problematic, as acetylcholine is an important neurotransmitter with receptor subtypes found throughout the body. The M3 subtype is thought to be overexpressed in the bladder but is also expressed in

many other tissues [31, 32]. True antagonist selectivity among the various receptor subtypes has yet to be achieved [33–36]. It is not surprising that OAB drug therapies are therefore accompanied by many side effects. An example of a common side effect is a pronounced decrease in salivary secretions, caused by off-target OAB drug effects on the M1 subtype found in the salivary glands [30, 37]. This effect is not tolerable for many patients and is the principle reason why they discontinue the therapy [38]. Attention has been drawn more recently to potential effects on cognitive function of these non-selective agents when used in older patients [28].

The latter two examples above illustrate the difficulty in achieving selective pharmacologic targeting with use of systemically administered agents. The irony is that an effective agent for treatment may be known—the difficulty lies with the management of any off-target effects in another portion of the body. This review seeks to illustrate means for more effective use of drugs that work. We specifically review examples of drug delivery to individual compartments of the body. The emphasis among these examples is on achieving pharmacologic benefit at the site of disease without systemic administration. All the methods discussed are in essence physically targeting the drug, most commonly by the use of a procedure to place the drug in the required compartment. The procedures vary from the simple to the very complex.

The review will not be exhaustive and will focus on a few select compartments. The compartments discussed are the bladder, brain, peritoneum, eye, and skin. These examples will be very illustrative of the single compartment drug delivery approach, and will introduce the reader to many existing and developing procedures for physically targeting drugs to sites of disease. Drug delivery to a single physiologic compartment or tissue, rather than systemically, has also emerged as a new opportunity for microsystems and devices made by microfabrication techniques [39]. Some examples of the latter will also be discussed.

2. Bladder drug delivery

The urinary bladder is a hollow organ that stores urine flowing from the kidneys through the ureters, until urine is excreted through the urethra. The bladder is a dynamic muscular sac that repeatedly expands and contracts as it is filled with and emptied of urine, taking charge of the majority of body fluid output by urination, which is approximately 1 to 2 L/day for normal healthy adults. Common bladder disorders include interstitial cystitis/painful bladder syndrome (IC/PBS), overactive bladder (OAB), and bladder cancer (BCa). The bladder can be non-surgically accessed using a catheter or cystoscope through the urethra by a routine procedure that can be performed by health care practitioners or even by patients themselves (self-catheterization). Such relatively easy access makes the bladder an attractive local drug delivery target.

2.1 Local delivery methods

Local delivery approaches to the bladder include direct injections into the bladder muscle, intravesical therapeutic solution instillations, or more recent intravesical indwelling physical devices, which can be either biodegradable or non-degradable. Direct injection of

onabotulinumtoxin A (Botox® by Allergan, CA) for OAB into the bladder muscle is performed using cystoscopy and has to be highly localized to prevent systemic absorption [40–42]. This review will focus on intravesical instillations and indwelling devices. They are less direct methods compared with direct intramuscular injection to the bladder, but provide more noninvasive treatment options. It is difficult to extend drug exposure from a single instillation beyond a day without an external aid such as a magnetic field, even with enhanced intravesical instillation methods described in this review [43]. A more recent approach is the use of indwelling intravesical devices that can release drug in the bladder over an extended period of time. These devices have the potential to provide improved efficacy through extended drug exposures over days and weeks that cannot be achieved with instillation alone.

2.1.1 Intravesical instillations—Intravesical instillation involves the administration of a therapeutic agent to the bladder through a catheter. The drug can be provided in liquid form or can be reconstituted, for example by mixing drug powder with sterile water or saline. A reconstituting device for intravesical chemotherapy was developed and studied to increase safety, timeliness, and user-friendliness [44, 45]. Unlike oral administration, drug can directly reach the target site while reducing the risk of systemic side effects and increasing tissue exposure to the drug. One recent study using oxybutynin showed that significantly higher bioavailability can be achieved by intravesical administration compared to oral administration [46]. Several problems exist with intravesical treatment: drug dilution occurs due to continuous urine formation as soon as drug is placed in the bladder, and the majority of the instilled drug is voided within a few hours during urination. The limitation of short drug residence time in the bladder often requires repeated instillations, which increase patient discomfort and present an infection risk due to serial catheterizations.

A main challenge of intravesical instillation is thus to prolong the residence time of drug with a high concentration in the urine, and so improve the absorption of the administered drug across the urothelial barrier into the bladder wall [47]. Once drug is administered in the bladder, its dilution is inevitable due to continuous urine production at a rate of roughly 40 to 80 mL/hour. One study using weekly intravesical instillation of mitomycin C for six weeks showed better efficacy with enhanced drug concentration in the urine. This was achieved by increased drug dose (20 to 40 mg), reduced dose volume (40 to 20 mL), minimized residual urine volume at the time of treatment, reduced urine production by voluntary dehydration, and urine alkalinization by oral sodium bicarbonate to address drug instability in acidic urine [11]. Behavior modifications such as voluntary dehydration can improve the efficacy of instillations but are susceptible to patient non-compliance. Enhanced bladder wall permeability and increased urine residence time are instead the preferred routes for improving the efficacy of instillations.

2.1.2 Enhanced intravesical instillations—Physical and chemical techniques can improve the efficacy of instillations through enhanced bladder wall permeability [47–51]. Chemical enhancers such as dimethyl sulfoxide (DMSO) or protamine sulfate (PS) that disrupt the bladder barrier can be effective, but also tend to have increased side effects due to (i) inability to target a specific bladder location or (ii) treatment duration. Physical

methods such as iontophoresis, electroporation, and hyperthermia employ instillations in combination with medical devices in an attempt to better control the location and duration of enhanced permeation.

Electromotive drug administration (EMDA) involves the introduction of an electrode into the bladder via a catheter and the external application of a second electrode on the abdominal skin. The drug solution is instilled into the bladder and a low electrical current is applied for approximately 30 minutes. EMDA has shown improved efficacy compared to passive diffusion in IC/PBS, OAB and BCa clinical trials [50]. Patients that received intravesical instillation of mitomycin with EMDA immediately before transurethral resection of bladder tumors (TURBT) had a lower rate of recurrence (38%) and a higher disease-free interval (52 mo) compared to passive diffusion of mitomycin after TURBT (59% rate of recurrence, 16 mo disease-free interval) and TURBT alone (64% rate of recurrence, 12 mo disease-free interval) [52].

Local hyperthermia can be achieved through the use of magnetic nanoparticles or gold nanoshells. These nanocarriers can induce tumor ablation or trigger release of a drug when heated [47]. Local or regional hyperthermia combined with chemotherapy instillation, termed thermo-chemotherapy, has shown improved efficacy in many BCa clinical trials [53]. The Synergo® (MEL Medical Enterprises Ltd, Petah-Tikva, Israel) and UniThermia (Elmedical Ltd, Hod-Hasharon, Israel) systems use custom flexible catheters to induce local hyperthermia. The 10-year disease-free survival rate for MMC thermo-chemotherapy with the Synergo system in patients with intermediate-/high-risk NMIBC was 53%, compared to 15% for patients treated with intravesical chemotherapy alone. Patients in the thermo-chemotherapy arm also had a higher rate of bladder preservation (86%) compared to intravesical chemotherapy alone (79%) [54]. A recent clinical trial treating superficial transitional cell carcinoma patients with MMC thermochemotherapy demonstrated stability of MMC in the UniThermia system and confirmed that plasma MMC concentrations remained well below the threshold for systemic toxicity [55].

Liposomal formulations have the potential to increase drug solubility and stability in urine while also increasing cellular uptake through endocytosis [47, 48, 50]. Empty liposomes have been shown to have a therapeutic effect on IC/PBS patients in several clinical trials, possibly by forming a protective lipid layer on the urothelial surface [56–58]. Liposomal drug formulations have also demonstrated improved stability, safety, and efficacy in animal models. An increased antitumor effect with intravesical liposomal interleukin-15 gene therapy was demonstrated in an orthotopic BCa mouse model [59]. Instillation of a liposomal formulation of tacrolimus, to treat hemorrhagic cystitis, showed lower systemic exposure, lower tissue toxicity, and increased drug concentration in the urine and bladder tissues in a rat model, compared to an alcohol-based tacrolimus instillation [60].

Physical and chemical techniques can also improve instillation efficacy through increased urine residence time. Typical urine residence times are two hours with regular instillations. These can be doubled or even extended to several days with instillations enhanced by nanocarriers, *in situ* gels serving as drug depots, or a combination of both nanocarriers and hydrogels [47, 49–51, 61, 62]. Instillation of magnetic nanoparticles in the presence of an

externally applied magnetic field has shown increased efficacy of doxorubicin against tumors in preclinical and *in vivo* studies [63, 64]. A similar approach, which combined Bacillus Calmette-Guérin (BCG) with a magnetic thermosensitive hydrogel and an external magnetic field, demonstrated continuous intravesical release of BCG over a 48 h period in a rat model. Extended BCG residence time significantly increased antitumor efficacy [43, 65].

2.2 Indwelling devices

An indwelling intravesical device differs from an instillation: it is a physical device that can safely reside in the bladder and hold a drug payload that it releases into the urine in a controlled and extended manner. An instillation, in contrast, supplies immediate dosing of drug in an aqueous environment. A successful indwelling device has to be tolerable, deliver therapeutic drug concentrations, be retained in the bladder during the treatment period, and withstand the local environment of the bladder. The device must additionally be designed for safe insertion and removal from the bladder. The device can be either biodegradable or non-degradable, each option having advantages and disadvantages. A biodegradable device eliminates the device removal step after the end of treatment. Depending on how the device degrades, however, debris may occlude the urethra instead of being voided.

A biodegradable tubular reservoir-type device made of poly(glycerol-co-sebaic acid) (PGS) for the delivery of ciprofloxacin-HCl was developed and *in vitro* release experiments were performed [66]. Another biodegradable matrix-type device made of (Poly-D,L-lactid-co-Glycolide-co-PEG)—either as drug release balls or hollow cylinders—was developed and tested *in vitro* using trospium chloride as an active agent [67]. Still another biodegradable matrix-type device for trospium chloride was developed using glyceryl tristearate and an *in vitro* release study was performed [68].

Non-degradable indwelling devices require an additional removal procedure after the treatment period. The UROS Infusor from Situs Corporation is an indwelling intravesical pump for the sustained delivery of oxybutynin solution that was developed and tested in dogs and pigs as well as humans in phase I/II trials in the US [69–72]. The device was loaded with an oxybutynin solution that it released at 10 mL/day, delivering 10 mg/day for one day [72]. The device is inserted into the bladder in a deflated state using a specially designed catheter insertion tool. The reservoir is then filled with drug solution, which changes the device conformation into a `C' shape [71]. A physician removes the device at the end of the treatment period via flexible cystoscopy. The initial clinical trial experience seemed positive and was presented at the 95th Annual American Urological Association Meeting in 2000 [71, 72], but clinical development was later halted without any further information.

Another non-degradable intravesical device was developed and tested in rabbits at the Massachusetts Institute of Technology (MIT) [73, 74]. The device, known as Lidocaine Releasing Intravesical System (LiRIS®), was further developed by TARIS Biomedical Inc. (Lexington, MA). LiRIS was well tolerated in both healthy volunteers and IC/BPS patients [75–78]. Additional clinical trials sponsored by TARIS Biomedical are ongoing in phases I and II in the US. LiRIS is a dual-lumen silicone tube that contains drug tablets in one lumen and a superelastic nitinol wire in the other. The nitinol wire provides the bladder-retentive

property of the device. LiRIS is a small, flexible osmotic pump that releases drug over a two-week time period. The device can be inserted into the bladder with a catheter-like tool (Figure 1) and removed via cystoscopy. High drug payload is achieved by using a solid drug form.

2.3 Conclusion and future directions for single compartment delivery to the bladder

The bladder can be non-surgically accessed through the urethra, which makes it an attractive local drug delivery target. Local delivery approaches to the bladder include direct injection into the bladder muscle, intravesical instillations, and intravesical indwelling physical devices. Physical and chemical techniques can improve instillation efficacy through enhanced permeability or increased urine residence time. It is difficult, however, to achieve more than a daylong drug exposure from a single instillation even with these improvements. These procedures, therefore, often require serial drug instillations and catheterizations. Indwelling intravesical devices can release drug in the bladder over an extended period of time—days, weeks, potentially months—and so prolong exposure to therapeutic drug concentrations much beyond the duration of an instillation. Such devices will see increasing use in diseases such as non-muscle invasive bladder cancer, overactive bladder, chronic urinary tract infection, and neurogenic bladder.

3. Peritoneum drug delivery

3.1 Clinical importance of the peritoneal cavity

The clinical importance of the peritoneal cavity lies in its therapeutic use for dialysis and drug administration [79]. Intraperitoneal (IP) drug administration is considered pharmacokinetically advantageous because of the peritoneal-plasma barrier. Resistance to transport through the barrier is mainly due to the wall of interstitial capillaries and the surrounding interstitial space [79]. Drug clearance through the portal circulation is slow, resulting in peritoneal drug concentrations that are much higher than those in other parts of the body and those possible via systemic administration [80]. Total drug exposure is defined as the integrated area under the concentration-time curve (AUC) [81]. IP instillation of drug results in a drug-dependent increase of the cavity-to-plasma AUC ratio compared to intravenous (IV) administration. IP chemotherapy is attractive because it can deliver the required high doses of drug while causing lower systemic toxicity.

3.2 Rationale for IP chemotherapy

IP chemotherapy has been used primarily to treat the peritoneal spread of metastatic gynecological and gastrointestinal cancers. Peritoneal carcinomatosis significantly lowers the patient's quality of life and is often a marker of poor prognosis [79, 82]. The rationale for IP chemotherapy of peritoneal carcinomatosis is based on the prolonged confinement of the disease within the peritoneal cavity and the steep dose-response relationship exhibited by most cytotoxic agents [82]. Extended tumor exposure to higher drug concentrations improves cytotoxic activity against the tumor cells, while systemic toxicity is reduced because of the peritoneal-plasma barrier. The depth of drug penetration into solid tumors limits cytotoxicity, so the high drug concentrations achieved by IP instillation are relevant only for patients with small-volume tumors or who have undergone cytoreductive surgery

prior to chemotherapy [83]. Avascular tumors additionally come in direct contact with the drug solution and are therefore exposed to increased drug levels compared to IV administration [82]. IP chemotherapy eventually reaches the systemic circulation via the interstitial capillaries and so enters the tumor via its own microcirculation and exposes it again to the drug, as shown schematically in Figure 2 [81]. These hypothesized benefits of using IP instead of IV chemotherapy have been investigated in phase I, II and III clinical trials that showed promising results.

3.2.1 IP therapy in ovarian cancer: biological advantage—Seventy-five percent of ovarian cancer patients are diagnosed at an advanced stage, with metastatic disease throughout the peritoneal cavity [84]. Metastasis to the peritoneal cavity is most common and, in contrast to most other cancers, metastatic spread via lymphatics is rare. Ovarian cells spread instead by direct contact with adjacent organs or by detachment from the primary tumor and regional seeding via the peritoneal fluid [84] (Figure 3). IP therapy is therefore distinctly advantageous in the treatment of ovarian cancer, because it can directly target the majority of the tumor burden with high doses of therapeutic agents.

3.2.2 Phase III clinical trials comparing IP and IV chemotherapy for ovarian cancer—The therapeutic advantage of IP therapy in ovarian cancer has been well established. Multiple randomized phase III clinical trials comparing IV and IP therapy have demonstrated a survival advantage for women receiving IP therapy [85–87]. The risk of relapse also decreases by over 20% with the use of combination IP and IV chemotherapy, as compared to IV chemotherapy alone [88].

The first phase III clinical trial documenting the advantage of IP therapy (GOG 104) was published in 1996 [85]. The delivery of cyclophosphamide IV with cisplatin IV or IP yielded a 20% increase in median overall survival (OS) in the IP arm (P=0.02). Paclitaxel proved more effective than cyclophosphamide in combination with cisplatin, however, so an additional phase III trial (GOG 114) was completed in 2001 [86, 89]. IP cisplatin again increased progression-free survival (PFS) and OS compared to the IV treatment arm. Toxicity was higher in the IP group, but the study was biased due to high-dose chemical tumor debulking with carboplatin in the IP arm alone.

The final, and most important, landmark clinical trial (GOG 172) was published in 2006 [87]. Patients were first surgically debulked to leave no residual tumor mass greater than 1 cm. Patients were then administered either (i) IV paclitaxel on day 1 (135 mg/m^2 body surface area (BSA), 24 hr infusion) and IV cisplatin (75 mg/m^2 BSA) on day 2, or (ii) IV paclitaxel (135 mg/m^2 BSA, 24 hr infusion) on day 1, IP cisplatin (100 mg/m^2 BSA) on day 2, and IP paclitaxel on day 8 (60 mg/m^2 BSA). Treatments were given every 3 weeks for 6 cycles. Median PFS increased from 18.3 months in the IV treatment group to 23.8 months in the IP group (P = 0.05), and OS increased from 49.7 to 65.6 months (P = 0.03). Patients receiving IP therapy experienced an increased incidence of side effects that included: fatigue; pain; and hematologic (leukopenia, thrombocytopenia), gastrointestinal, metabolic, and neurologic toxicities.

3.2.3 IP therapy in other tumor types—Patients with peritoneal carcinomatosis from non-gynecologic malignancies, such as gastrointestinal, colorectal, and pancreatic cancer, still face a median survival time of less than 6 months because of inadequate drug delivery to their solid tumors [91]. IP administration of antineoplastic agents has been investigated but is not as attractive as for ovarian cancer because of differences in the pattern of metastatic spread [82]. Non-gynecologic peritoneal malignancies consist of large, local tumor masses that are rarely treated with surgical debulking and tend to metastasize beyond the peritoneal cavity. Non-peritoneal spread is, however, associated with the portal circulation in some cases and so may be reached by the drug following IP administration [82]. A management approach that combines surgical cytoreduction and IP chemotherapy in non-gynecologic peritoneal carcinomatosis holds promise, as it would address many of the above issues.

3.2.4 Limitations of IP bolus chemotherapy injection—The phase III clinical trials highlighted in the previous section demonstrate a strong therapeutic advantage of IP therapy. Very few physicians follow the IP regimen to treat ovarian cancer outside of a trial setting, however [82]. Despite the significant survival benefit offered by the treatment regimen in the GOG 172 trial, only 42% of patients were able to complete all intended cycles of the IP therapy [87]. The primary reasons for early termination were catheter-related complications including infections, blockages, and leaks, in addition to the aforementioned dose-limiting toxicities [87, 92]. Lack of adoption of IP therapy can be attributed to a number of reasons: IP chemotherapy has demonstrated increased morbidity due to local drug infusion and involves higher costs, greater time and technical skill on behalf of the provider [82, 83].

3.3 Conclusion and future directions for single compartment delivery to the peritoneal cavity

Localized drug delivery in the peritoneal cavity has the potential to revolutionize the standard of care in ovarian cancer. A device that delivers low, sustained doses of therapeutic agent has the potential to minimize the side effects of high-dose, high-volume IP bolus therapy. The elimination of the catheter required for IP therapy would increase the potential for doctor and patient acceptance and minimize catheter-associated complications. A device that could be laparoscopically implanted and therefore incorporated into tumor debulking surgeries would also accelerate clinical translation.

Preclinical studies in our lab have demonstrated that sustained release of cisplatin achieves similar therapeutic efficacy to and reduced morbidity than weekly IP bolus injections in a xenograft ovarian cancer model (paper submitted). These studies also demonstrated that there is a minimum concentration above which the AUC, rather than the delivery of high peak drug concentrations, determines anti-tumor toxicity. This knowledge strongly supports the use of a device platform for IP delivery of chemotherapy. The development of this device has the potential to overcome the current limitations of clinical IP therapy and promote the widespread adoption of localized drug delivery to treat advanced ovarian cancer in the near future.

3.3.1 Sustained drug delivery for the treatment of peritoneal abnormalities—A sustained release IP drug delivery platform has numerous implications beyond the treatment of ovarian cancer. The device can replace current IP chemotherapy instillation for the treatment of non-gynecologic peritoneal carcinomatosis, and its placement may in fact encourage concurrent tumor debulking. Endometriosis is a chronic disease that commonly infiltrates peritoneal tissues. Although symptoms and treatment strategies are highly individualized, confirmation of disease via laparoscopic surgery and high incidence of debilitating pain may merit the continuous delivery of drug for sustained pain management [93]. A versatile platform to deliver therapeutic agents offers countless solutions to the management of localized disease by harnessing the clinical advantages of IP drug delivery.

4. Brain drug delivery

A significant amount of work in single compartment drug delivery to the brain has focused on brain cancer treatments. Brain cancer treatments aim to bypass the blood-brain barrier (BBB) altogether. A local delivery approach ensures that the central nervous system (CNS) is exposed to the majority of the dose. The main concerns of local delivery are developing a safe and controllable way to deliver the compounds as well as understanding the phenomena that determine the overall distribution of the drug in the brain tissue. Unfocused, non-targeted delivery is often limited by neurotoxicity caused by distribution of drugs to healthy brain tissue [94].

Neuropsychiatric disorders are a growing concern and present a unique challenge for drug delivery. It has become widely accepted in neuroscience that many neurological disorders can be classified as circuit diseases. The underlying pathology of these neurologic disorders arises due to failures in the dynamic communications between various parts of the brain that make up a neural circuit. This concept has been used to describe the pathology of many diseases including Parkinson's [95], depression [96, 97], and obsessive-compulsive disorder [98]. In the case of Parkinson's disease it has been suggested that many of the behavioral symptoms are explained by irregular neural activity in the cortico-basal ganglia-thalamocortical circuit.

The concept of circuit-based disorders presents a shift in the ideal drug delivery system design when treating such diseases. In contrast to delivering drug to a specific pathological tissue, as in cancer, the goal is to normalize activity across a malfunctioning circuit. This implication suggests that stimulating specific nodes of the brain—often regions of only a few cubic millimeters—may be sufficient to affect neurological behavior [99]. Current clinical treatments are based on systemic or brain-wide exposure of a drug and often fail due to inadequate targeting of the underlying pathological nodes of the neural circuit.

4.1 Blood-brain barrier and issues with systemic delivery

The BBB presents an additional obstacle when designing drug delivery systems to treat diseases of the brain. The BBB is composed of tight endothelial junctions formed between endothelial cells in the cerebral microvessels, which exclude the majority of molecules from the brain [100]. The BBB leads to an 8 log difference between the permeability of the liver and brain capillaries [94]. Strategies for improving systemically administered drug

treatments include receptor-mediated transport [101], chemical modification of drugs [102], liposomal formulations [103–105], and hyperosmotic BBB disruption [106]. Systemically administered drugs are diluted in the systemic circulation and other tissues; approximately 1% of an ideal drug that crosses the BBB will end up reaching the brain [94]. Off-target effects and systemic toxicity often limit the maximum tolerated dose (MTD) of systemic treatments, making it difficult to achieve therapeutic concentrations in the brain.

Advances in medicinal chemistry and BBB disruption have improved partitioning of drugs into the brain compartment. However, these approaches do not reduce systemic exposure and are thus beyond the scope of this review. Systematic studies in modifying lead active pharmaceutical ingredients have identified molecular properties that affect partitioning into the brain; the properties also affect how they are cleared from the parenchyma. A review of successful CNS drugs by Pajouhesh and Lenz identified several physicochemical properties of successful drugs (i.e. molecular weight < 500 Da, logP < 5, hydrogen bonding characteristics, and molecule flexibility) [107]. Modulating lipophilicity of drugs allows for passive diffusion of compounds across the BBB using the plasma membrane as a pathway [108–110]. Since this mechanism relies on passive diffusion, concentrations in the brain and circulation reach equilibrium, usually resulting in low brain concentrations and high systemic exposure. Bodor and colleagues developed a strategy to overcome this issue by using molecular switches to render a compound more hydrophilic in order to “lock in” the drug in the brain compartment [111, 112]. Membrane-bound proteins can shuttle drugs across cell membranes in either direction [113, 114]. Increased brain exposure can be achieved by either engaging transporters that enrich drug concentration in the brain parenchyma (i.e. glucose and amino acid transporters, transferring receptor) or evading transporters that cause a net efflux of drugs out of the brain compartment (i.e. p-glycoprotein, organic anion transporting polypeptides).

Ultimately, successful treatment of brain disorders may require rational design of drug molecules and novel ways to localize delivery to the brain tissue. Reviews on chemical modifications for neural applications [107, 114] and BBB-disruption [115, 116] may elucidate additional challenges and opportunities associated with brain drug delivery that are outside of the scope of this paper.

4.2 Current methods for single compartment delivery to the brain

Brain tumors are among the most difficult cancers to treat. Tumor recurrence is a significant issue for cases that are surgically accessible, because of conservative tissue resection. Brain tumors often recur 2–3 cm from the original tumor site, due to highly invasive cancer cells [117]. High exposures of chemotherapeutics must be achieved in the tissue surrounding the tumor resection site in order to effectively treat diseases. The BBB and dose-limiting systemic toxicity can be avoided by delivering directly to the brain. Various single compartment delivery methods will be discussed below.

4.2.1 Passive diffusion strategies: degradable polymer wafers and reservoir-based devices—Gliadel wafers are currently the only FDA-approved CNS local delivery devices for the treatment of glioblastoma multiforme (GBM). These devices are composed

of polyanhydride wafers impregnated with the chemotherapeutic carmustine. The wafers are implanted in the tumor cavity following resection surgery. The drug is released into the brain as the polymer matrix degrades, thus killing migratory tumor cells in the surrounding tissue. This approach has led to a modest improvement in patient survival [118, 119]. In the current design, however, the drug loading of the device is low (3.85% w/v) and another surgery would be required to re-administer the dose. Drug distribution is achieved primarily through diffusion from the device surface. A detailed review on diffusion mechanisms in the brain may be found in Sykova and Nicholson [120]. Drug distribution profiles have shown that high exposure of drug is only achieved 1–2 mm from the implant [121]. The drug exposure provided is not sufficient to prevent tumor recurrence and attain long-term patient survival.

Recent work has led to some improvements in the drug-loaded polymer wafer approach by creating an alternative local delivery platform that consists of a reservoir-based device. Scott et al. created a polymer reservoir based device that passively releases drug in a tunable, zero-order release rate according to Fick's first law of diffusion [39]. The design of the device is such that it achieves a similar release rate to Gliadel wafers but can contain much higher drug payloads. The device showed improvements in median survival over systemic temozolomide (TMZ) delivery in a 9L rodent GBM model, though the device utility is still limited by constant release. Devices with more active release mechanisms have also been developed and tested within the brain [122]. These microchips devices use electrical current to rupture a membrane and initiate drug release. Devices such as these could be implemented to achieve complex local dosing regimens (pulsatile release, multiple drugs, etc.) without requirements for multiple surgeries.

Gliadel wafers and the polymer microchips both rely on passive diffusion from a local point source to achieve distribution in the tissue. These approaches show that simply delivering a large amount of drug to the brain does not necessarily guarantee success in treating a disease. Achieving the proper exposure at the correct areas of the brain is required for efficacy of a given treatment. The distribution of drug depends not only on the release rate from a polymer implant, but also the diffusion and elimination rates of the molecule [123]. Drug elimination from the brain can occur via several mechanisms including metabolism, internalization, convection, and systemic elimination [121]. The result is that even large doses of chemotherapeutic achieve significant drug concentrations only millimeters from the drug source.

4.2.2 Convection enhanced delivery and direct infusion into the brain—

Convection-enhanced delivery (CED) is a method that was first demonstrated by Bobo et al. in an attempt to improve the poor passive distribution profiles of drugs in the brain interstitium [124]. CED involves inserting a catheter directly into the brain and infusing drug solutions via an external pump. The convection from the infusion greatly supplements diffusion and achieves larger distribution profiles in the brain. It was demonstrated that CED can produce concentrations of drug that are hundred-fold greater than systemic administration [124]. The use of CED to treat CNS disorders including GBM has been thoroughly investigated over the past 15 years [125–127]. Many different infusion parameters and catheter designs have been examined in these studies. These studies have

reinforced the main advantage of CED, which is to provide an increased distribution profile compared to systemic delivery or passive diffusion from implants. Several other advantages of using CED include the ability to easily deliver multiple therapeutics [128]. Catheter-based delivery provides the capability for precise temporal control. Adjusting infusion parameters (flow rate, duration, location, infusate viscosity etc.) provides adjustable control over the total drug distribution achieved by CED.

CED has not yet been readily adopted for clinical use due to several critical drawbacks of the approach. The greatest issue concerning CED is that it often leads to nonuniform distribution profiles (Figure 4). This is a result of brain tissue being heterogeneous and having anisotropic hydraulic resistance properties. The drug tends to follow paths that provide lower resistance to fluid flow, such as white matter tracts, previous infusion paths, or back along the catheter [129]. The high pressure associated with CED can disrupt tissue around the catheter, increasing the risk of backflow along the catheter. This is not desirable when treating diseases such as GBM, where a large uniform distribution profile is desired to kill migratory tumor cells. Other complications include infections resulting from chronic catheter insertion and brain edema resulting from infusion [129]. The catheter needles are also prone to clogging with tissue as indicated by high pressures observed at the start of infusion. Low infusion rates and small diameter catheters have been shown to reduce the occurrence of these complications [125].

Despite the drawbacks associated with the high pressure of CED, catheter-based drug delivery remains a potential approach to deliver therapeutics directly to the CNS. The external control associated with catheter drug delivery can result in complex release regimens that are not achievable with controlled release polymer implants. Adjusting the infusion parameters provides robust control over the region that receives therapeutic dose of chemical. Accurate implantation procedures make targeting of precise structures possible. These potential benefits make catheter-based delivery a viable strategy to treat disorders that require therapeutic drug exposures in targeted regions of the brain. Circuit disorders are one class of diseases that could benefit from a drug delivery strategy with precise temporal and spatial control. Preclinical work is ongoing to develop neural probes that combine local drug delivery and electrical stimulation for treatment of neurological disorders [130].

The simplest approach to circumvent the BBB involves direct infusion of a drug into the CSF or brain parenchyma via an Ommaya reservoir. The Ommaya reservoir is a device consisting of a catheter positioned in the brain, with a fluid reservoir implanted under the scalp that delivers intermittent bolus injections of drug and allows subsequent percutaneous access. It has been used to deliver doxorubicin, mitoxantrone, bleomycin, interleukin-2 and radioactive reagents [131–134]. The Ommaya reservoir has also been modified to achieve continuous drug release, by covering the catheter with a semipermeable polyvinyl alcohol membrane [135]. Continuous controlled drug release over an extended period of time can also be accomplished with implantable pumps, such as the Infusaid pump and Medtronic SynchroMed system.

Direct infusion appears to be a promising strategy in treating neurological diseases, but its limited efficacy in clinical trials has hindered its implementation in the clinic. Two phase I

trials demonstrated the benefits of glial cell-derived neurotrophic factor (GDNF) infusion into the putamen of patients with Parkinson's disease, while two other clinical trials reported no significant improvement and development of major adverse events [136]. Salvatore et al. suggested that the lack of efficacy of GDNF in the studies was possibly because GDNF did not reach the target tissues in sufficient concentrations [137]. This is a common problem with diffusion-based drug delivery technique. Additionally, drug infused intrathecally penetrates the ependyma rapidly, but penetration into brain parenchyma is limited owing to diffusion, tortuosity, and clearance by the CSF into blood.

4.2.3 Convective transport in the CNS—The CSF plays a variety of roles to protect and assist brain function. In the context of single compartment drug delivery, CSF convection provides a clearance mechanism for metabolic wastes, drugs and other compounds [138, 139]. Composition of the CSF is highly regulated by tight junctions between brain endothelial cells. The BBB prevents many compounds and proteins in the systemic circulation from crossing into interstitial brain space. The CSF exchanges with several fluid compartments, including the brain interstitial fluid, and on the whole represents a sink for compounds in the brain (Figure 5). CSF production primarily occurs in the choroid plexus at an average rate of 0.4 mL/min/g in mammals [140]. CSF then flows through the ventricles into the subarachnoid space where a large portion is drained into the venous blood via arachnoid granulations. Remaining CSF circulates to the spinal column and other parts of the central nervous system where it is cleared via lymphatic systems.

4.3 Conclusion and future directions for single compartment delivery to the brain

The success of any local delivery approach centers on the ability to achieve effective exposures within the target tissue region. While CED is limited by nonuniform distribution, passive polymer implants are limited by the mm-scale diffusion distances in the brain. Future efforts should focus on techniques to achieve more uniform large-scale distributions. This is critical to the success of treating diseases such as GBM in which cm-scale regions of tissue need to be exposed to drugs. Another approach to overcoming limited diffusion profiles from local implants is to implant multiple implants distributed throughout the target tissue (Figure 6). Overlapping diffusion profiles of multiple devices properly placed via a biopsy needle would combine to produce the desired exposure profile.

The drug delivery methods mentioned in this section are highly invasive, requiring a craniotomy. In the case of diseases such as brain tumors, this may be acceptable as the standard of care involves a resection surgery anyway. More noninvasive drug delivery techniques would be beneficial for other CNS diseases that don't necessarily require surgery. Delivering drugs trans-cranially through the skull could be an option for noninvasive local drug delivery, particularly when the target is tissue on the exterior of the brain, as in traumatic brain injuries [142, 143].

Much of the existing body of research for single compartment drug delivery to the brain has focused on treatment of brain tumors. Current and future advances in neuroscience will likely provide new exciting drug targets for local delivery to the central nervous system to treat neurological disorders, as well as the need to develop new technologies. The ability to

bypass the BBB and avoid systemic toxicity also enables new drugs to be investigated for treatment of brain cancer or other neural diseases that would otherwise be restricted due to their toxicity profiles or bioavailability.

5. Ophthalmic drug delivery

The eye is an ideal organ for localized drug delivery due to both its anatomy and physiology. The eye has two main compartments: the anterior chamber, made up of the cornea, iris, lens, and a fluid called the aqueous humor, and the posterior chamber, comprised primarily of the retina and a jelly-like substance called the vitreous humor. There is some fluidic communication between the two chambers, but the eye as a whole is separated from general circulation by a blood-retina barrier, which is similar in structure and function to the better known blood-brain barrier [145]. The blood-retina barrier allows oxygen and nutrients to pass freely, but it protects the retina and neighboring ocular tissues from pathogens and larger molecules in systemic circulation, thus eliminating systemic drug administration as a viable method to treat ophthalmic disease. The dual compartment structure of the eye is particularly favorable for targeting drug therapies to a particular location or tissue within the eye; many drug delivery approaches are therefore tailored to address disorders of either the front of the eye or back of the eye.

The eye is also considered an immune privileged tissue. The term immune privilege as used herein does not imply that the eye is devoid of effective immune responses to deal with pathogens, inflammation, or trauma. The microenvironment of the eye is designed instead to modulate the cellular and molecular immune response to effectively address various insults, but at the same time suppress the portion of the immune response most responsible for tissue damaging inflammation using built-in mechanisms [146]. Such targeted immune suppression is particularly important in the eye, where inflammation can be destructive to its delicate tissue structures, potentially leading to vision loss and blindness. An unintended benefit of immune privilege is that the eye is more tolerant of sight restoring and drug delivery implants and other non-biological materials than other body tissues.

5.1 Methods of administration

Numerous drug delivery approaches have been applied to the treatment of serious eye diseases (Figure 7) [147–150], including glaucoma, wet age-related macular degeneration (wet-AMD), diabetic macular edema (DME), diabetic retinopathy, and uveitis. Thus far, small molecule drugs such as steroids have proven easier to deliver than large molecules due to their superior stability and ability to permeate eye tissue. Here we review several ophthalmic delivery approaches at various stages of development, including: injection by syringe, microneedles, or micropumps; topical methods such as iontophoresis and sonophoresis; and extended duration therapy by depots and implants.

5.1.1 Injection—Injection into the aqueous or vitreous humor is the quickest and most direct way to get drug into the eye. This method bypasses the barrier properties of the eye wall, so it is compatible with both small and large molecule therapeutics and is less influenced by the chemical properties of the drug or the formulation.

There were over 2.3 million intravitreal injections administered in the US in 2012 [151], which makes it one of the most frequently used medical procedures. In fact, the three most popular drugs for treating wet-AMD—LUCENTIS® (ranibizumab injection), Eylea® (aflibercept injection), and Avastin® (bevacizumab)—are administered every 1–2 months exclusively by intravitreal injection. These three drugs alone accounted for over $4.4 billion in annual sales in 2012. A disadvantage of this route of administration is that complications such as infection, hemorrhage, or retinal detachment may result from repeatedly breaching the eye wall. A more important issue with chronic injection therapy is that a high overall burden of care, which comprises numerous trips to the doctor, procedure pain, and high drug costs, is placed on patients, caregivers, and doctors. This increased burden of care can be significant and may ultimately result in non-compliance or complete discontinuation of treatment. The reason why this method is tolerated for such widely used drugs is that there is no other commercially available delivery system for the eye that can stably store and deliver macromolecules such as antibodies, antibody fragments, and fusion proteins.

Another approach to ophthalmic injection involves the use of microneedles to accurately control the depth of needle penetration, so as to deliver drug to a specific location within the eye wall. Using this approach, researchers at Georgia Institute of Technology and Emory University showed that a 1 mm-long stainless steel microneedle can deliver fluorescent molecules, steroids, and microparticles to the suprachoroidal space, allowing these materials to distribute around the eye and diffuse into the vitreous for treatment of diseases of the posterior chamber [152, 153].

Micropumps are also under development as a way to inject drugs into the eye. The goal of pump systems is to deliver drug solutions over long periods of time, while at the same time limiting the number of times the eye wall is breached. In this approach, a needle or catheter is inserted into the anterior or posterior chamber and is connected to a fluid reservoir that can be refilled on a periodic basis. It may be possible to deliver both small and large molecules using this method, as long as the drug formulation is stable at body temperature over extended periods. A simple version of a micropump is made of polymethylsiloxane (PDMS) using soft lithography technology. The pump is designed to inject drug when the drug reservoir is manually compressed with a finger or other instrument [154]. Another micropump can deliver drugs at variable rates using pressure created in a drug reservoir by the generation of gas created by the electrolysis of water. The drug infusion rate is controlled by adjusting the applied electric current that generates the gas and pressure [155]. The use of an applied magnetic field to deform a membrane and generate pressure on a drug reservoir is yet another way to potentially control the rate of drug infusion into the eye from a micropump [156].

5.1.2 Topical delivery—Eye drops are the simplest and most common form of ophthalmic topical delivery. Only a small fraction (typically < 5%) of the applied drug reaches the target ocular tissues, however, due to drug solution run-off, tears, the barrier properties of the cornea, and loss of drug to the systemic circulation through conjunctival capillaries [150, 157]. Typical drugs delivered by eye drops are therefore relatively inexpensive, small molecules, such as steroids, antibiotics, and glaucoma drugs like prostaglandin analogs and beta blockers.

Another approach to topical delivery involves the use of chemistry or applied energy to change the barrier properties of the outer eye tissues, including the cornea, conjunctiva, and sclera. The Visulex™ technology is designed to maintain drug contact with the surface of the eye for several minutes, increasing the amount of drug that passively diffuses into the eye, and possibly even creating a depot effect in the tissue that will allow slow diffusion of the drug into the eye over an extended period. Chemical permeation enhancers and iontophoresis can be used with the system to enhance delivery further [158]. Another topical system based on the use of iontophoresis to drive charged drug molecules into the eye is called the EyeGate® II. A phase III clinical study for the administration of dexamethasone in anterior uveitis using this delivery system was recently completed, as was a clinical trial in dry eye [159]. Drug delivery using sonophoresis (or ultrasound) to increase ocular tissue permeability is earlier in development and has not yet been demonstrated in clinical studies. Delivery of steroids, antibiotics, and, most recently, a large molecular weight dextran has been demonstrated in preclinical models, however [157, 160, 161].

5.1.3 Depots and implants—Depots and implants are best suited for situations where extended or repeated exposure to a therapeutic is desired, but frequent administration is not practical or possible. Several implants, both degradable and non-degradable, have been commercialized or are under development for use in the eye.

The anterior chamber is relatively accessible for placement of a device or depot, while the posterior chamber is difficult to access due to its location deep in the orbit. One device located in the anterior chamber is the Capsule Drug Ring (CDR) by iVeena. This refillable implant is made of polymethyl methacrylate (PMMA) and is placed in the lens capsule during cataract surgery. It works by releasing drug through a semipermeable membrane, and small release rates of bevacizumab have been demonstrated [162]. The Verisome® technology consists of a degradable liquid polymer that forms a solid or semi-solid depot after injection into the eye. It is under development for both anterior and posterior chamber delivery for indications such as cataract surgery inflammation, glaucoma, and uveitis. A pivotal phase II/III trial for anterior chamber delivery of dexamethasone for post-cataract surgery inflammation was recently conducted, as was a phase I study of triamcinolone delivery to the posterior chamber for cystoid macular edema [163]. Another degradable implant, Durasert™, is implanted in the subconjunctival space and is designed to provide controlled release of latanoprost for glaucoma. This product is currently in a phase I/II clinical trial [164].

Due to limited accessibility of the posterior chamber, other implantable therapies directed at the retina are placed by surgery or by a needle inserted through the eye wall near the pars plana (located just behind the anterior chamber). The Medidur™ implantable, non-degradable delivery platform has been used as the basis for three approved products for the treatment of posterior chamber disease. The Vitrasert® intravitreal implant for the delivery of ganciclovir was approved by the FDA in 1996 for the treatment of CMV retinitis in people with AIDS. This surgically implanted device consists of a 3.5 mm tablet containing 4.5 mg of ganciclovir coated with polyvinyl alcohol (PVA) and ethyl vinyl acetate (EVA) and attached to a suture tab. The drug is released slowly by diffusion over 5–8 months [165]. A similar but slightly smaller (2 mm × 3 mm × 5 mm) implant called Retisert® was

approved in 2005 for the treatment of non-infectious uveitis of the posterior segment of the eye. This surgically placed implant contains 0.59 mg of the steroid fluocinolone acetonide, and releases the drug over approximately 2.5 years [166]. Iluvien® is the third implant from the Medidur platform. This implant does not require a surgical procedure, but is instead placed in the vitreous through a 25G needle. Iluvien is 3.5 mm long and 0.37 mm in diameter; contains 0.19 mg of fluocinolone acetonide; and releases drug for 2–3 years. It was approved in 2012 in several European countries for the treatment of DME based on phase III studies in this indication [167]. Approval for use in the United States is still pending. Another non-degradable, steroid delivery implant is called i-Vation™. This metal device is shaped like a screw and is inserted into the vitreous of the posterior chamber through a 0.5 mm hole in the eye wall. The implant has a drug coating containing 0.925 mg of the steroid triamcinolone and is designed to deliver drug over a two-year period. Results from a phase I clinical study of the implant for DME have been reported [168]. Ozurdex® is a fully degradable PLGA polymer implant for the delivery of dexamethasone to the posterior chamber. It is shaped like a rod having a diameter of 0.46 mm, is 6 mm in length, and is inserted into the vitreous through a 22G needle. Ozurdex contains 0.7 mg of dexamethasone, and is designed to release drug over 3–6 months. It was approved by the FDA for treating macular edema following retinal vein occlusion in 2009 [169], and for treating non-infectious uveitis of the posterior segment of the eye in 2010 [170].

The current standard of care for wet-AMD involves the chronic administration of a vascular endothelial growth factor (VEGF) inhibitor by intravitreal injection every 1–2 months. A VEGF inhibitor is typically an antibody, antibody fragment, or fusion protein. These types of macromolecules unfortunately have limited stability when hydrated at body temperature. It is no surprise therefore that the polymeric and solution-based delivery approaches described above have not been successfully applied to these drugs. New delivery approaches are needed to address the challenge of limited macromolecular stability at body conditions. Encapsulated cell technology (ECT) is a biology-based approach for the long-term delivery of macromolecules to the eye. The ECT device is a hollow polymer tube filled with recombinant cell lines derived from retinal pigmented epithelial (RPE) cells that is surgically implanted and sutured to the inner surface of the posterior chamber. The semipermeable polymer tube allows (i) nutrients from the vitreous to diffuse into the implant and so nourish the cells and (ii) recombinant protein produced by the cells to diffuse out of the device and into the vitreous. Products designed to release a VEGF antagonist for wet-AMD and the cytokine CNTF for orphan diseases like retinitis pigmentosa are currently in clinical trials [171]. An engineering-based approach for ophthalmic macromolecule delivery involves the delivery of current anti-VEGF drugs hermetically sealed in dry, solid form in discreet reservoirs of an implant. The implant is placed in the vitreous through a needle, and the stability of the dry drug is maintained in the sealed reservoirs until release is desired. The ophthalmologist can then use a standard ophthalmic laser to open each reservoir and release the drug into the vitreous as needed [172].

5.2 Conclusion and future directions for single compartment delivery to the eye

The anatomy and physiology of the eye make it well suited for localized, compartmental drug therapy. Numerous drug delivery technologies have been applied to the eye, including:

injection by syringe, microneedles, micropumps; topical methods such as iontophoresis and sonophoresis; and implants and depots. A variety of methods are available for the controlled delivery of small molecules such as steroids, but fewer options are available for macromolecules, largely due to drug stability challenges. These challenges, however, point to future opportunities to improve ophthalmic drug therapy. A near-term approach includes the development of devices that store and deliver macromolecule drugs in a dry or other non-aqueous formulation to minimize hydrolytic degradation. A longer-term opportunity exists for engineering specialized drug molecules that incorporate active groups on scaffolds that have greater stability or that are activated by enzymes or other factors at the desired site of delivery, similar to a traditional pro-drug.

6. Dermal drug delivery

Dermal drug delivery is an important method of drug administration, particularly for localized delivery. This method enables administration of a therapeutic directly to the necessary site in the skin. This can potentially reduce the first-pass metabolic effects associated with the oral route, including a decrease in the required drug dose. Creation of a drug depot directly at the intended skin site can additionally help achieve a more constant drug concentration, minimizing drug concentration spikes associated with bolus administration [173–176]. Drugs commonly administered topically for local delivery include anesthetics, corticosteroids, and retinoids [177–179].

The skin architecture, however, acts as a transport barrier, limiting passive diffusion to small, lipophilic molecules. Specifically, only molecules smaller than 500 Da in size can diffuse through the skin passively [180, 181]. The barrier results from the outer layer of the skin, the *stratum corneum*, a 15–20 μm thick layer composed of flat, tile-like keratinized corneocytes locked in a lipid matrix [181–183]. Below the *stratum corneum* is the viable epidermis, a layer composed of keratinocytes that serve a predominantly protective function [184]. The entire epidermis is approximately 100 μm thick [185].

Various methods are available to achieve localized delivery to the skin, as shown in Figure 8. Some of these methods physically disrupt the barrier function of the *stratum corneum*, while others rely on passive diffusion or special formulation methods. Physical and chemical methods to disrupt the skin barrier, as well as formulation-based methods to achieve localized delivery to the skin will be discussed in this section.

6.1 Barrier-disrupting methods

Examples of methods that actively permeabilize the *stratum corneum* include low-frequency ultrasound (<100 kHz), microneedles, and chemical penetration enhancers [182]. Low-frequency ultrasound works by generating cavitation bubbles in a coupling solution in contact with the skin. Ultrasound creates large local pressure gradients, causing the bubbles to collapse and form microjets [187]. When these microjets impinge against the skin, they painlessly erode away the dead corneocytes of the *stratum corneum*, making it more permeable [187]. This technology has previously been approved by the FDA for the local delivery of lidocaine, and has been shown to dramatically reduce the onset time of action compared to the application of lidocaine cream on unperturbed skin [188–190].

Microneedle devices utilize needles on the micron scale to pierce the *stratum corneum* [191]. Their size, combined with the ability to accurately control the length of the needles, permits targeted and localized delivery with great control over the depth of penetration [192, 193]. Microneedles have been shown to be more efficient than topical placement of drug for various substances, including methyl nicotinate, plasmid DNA, and lidocaine [174–176]. The long-lasting formation of pores in the skin through pretreatment with microneedles in addition allows for drug delivery over extended periods of time [179].

One of the most important methods involves use of chemical penetration enhancers. These are chemicals that are able to disrupt the regular structure of the *stratum corneum*, fluidizing lipid bilayers to increase permeability [181]. Common chemical penetration enhancers include fatty acids such as oleic acid and ethanol, and surfactants such as sodium lauryl sulfate [181, 183]. The use of chemical enhancers, however, needs to be balanced with the potential risk of skin irritation at the site of use. Therefore, there are limitations on the quantity of chemical enhancers that a typical formulation can contain [183].

6.2 Passive delivery methods

Many delivery methods have little or no impact on the barrier function of the *stratum corneum*. Delivery is achieved instead through special formulation of the drug. The general goal is to enhance drug permeability into the skin, while limiting its uptake by blood capillaries in the lower dermis [177]. While the formulation itself may not have a direct effect on the permeability of the skin, some enhancement is achieved through occlusion of the site by the application of the drug. Occlusion leads to increased skin hydration. The additional water content in the skin can swell and open the *stratum corneum*, thereby increasing its permeability [194, 195]. This effect can allow for the delivery of a broad class of substances, including topical creams and ointments. However, the drug being delivered must also be small enough to diffuse into the skin. There is nothing preventing the drug from diffusing to the dermal capillaries as a result, which limits its localization in the skin [177, 194].

More advanced formulations have been studied in order to decrease systemic uptake, thereby localizing the drug in the skin. One of the simplest methods is the use of chemicals that reduce subsequent permeability of the *stratum corneum*. The exact mechanism of action, however, is still an active area of research [194, 196]. More advanced methods include the use of vesicular carriers, which is an important area of research due to the utility of these carriers. Depending on their composition, vesicles may be used to control drug delivery, to enable depot delivery in the skin, or to enhance transdermal delivery to achieve systemic release [177, 197]. Recent *in vitro* studies have shown the ability to deliver and localize a wide variety of molecules in the skin, including tretinoin, minoxidil, and diclofenac [198–200].

Other formulation methods include drug encapsulation in microparticles and nanoparticles. Nanoparticles have been shown to traverse hair follicles, in addition to penetrating the *stratum corneum* [197, 201]. The depth of the hair shaft (over 2,000 μm below the skin surface) can also allow for greater penetration of the particles, where they can slowly release their payload for an extended time [202]. For example, sodium fluorescein, a model

fluorescent dye, was shown to be detectable in the skin for up to ten days when encapsulated in nanoparticles [201]. This should be contrasted with the dye's four-day detection limit in the skin when administered free in solution [201]. As in the case of vesicular carriers, the size, composition, and other physical attributes control the depth of penetration and the clearance time of the particles [203, 204].

6.3 Conclusion and future directions for single compartment delivery to the skin

Localized dermal delivery is an important route of drug administration. It can potentially reduce drug side effects associated with systemic administration and decrease onset time of action. Most drugs are delivered through some enhancement in the permeability of the *stratum corneum* to facilitate drug uptake. The extent of permeability enhancement must nevertheless be balanced with safety and tolerability of the treatment. Appropriate applications for dermal delivery must consider both the kinetics of delivery, the amount of material that can be delivered, as well as the convenience of the regimen to promote patient compliance. Another application on the horizon is gene delivery to the skin. This could be useful for skin-specific ailments such as melanoma, dermatitis, and psoriasis, to name a few. This is a burgeoning field with significant room for growth and experimentation.

7. Conclusion

The benefits of drug administration directly to the compartment of the disease include controlled, sustained drug delivery; higher payloads; and reduced toxicity and side effects. This review takes note of several technologies developed for single compartment drug delivery, and discusses challenges and future directions associated with the approach.

This review discusses several interesting examples of compartmentalized drug delivery. An indwelling intravesical device within the bladder is noninvasive, and avoids multiple catheterizations for serial drug injections. IP delivery of chemotherapy proves to be more efficacious at treating peritoneal carcinomatosis than systemic administration, while its toxicity can be minimized with an implantable reservoir for sustained, low-dose drug release. This drug delivery platform can significantly improve the management of malignant and benign peritoneal disease. Local drug delivery to the brain must treat pathologic lesions while avoiding toxicity in adjacent healthy brain tissue. Existing technologies are limited by the uniformity and penetration of the drug diffusion profile currently attainable, and require highly invasive procedures that can be clinically disadvantageous. Ophthalmic drug delivery has been pursued extensively and successfully, but is limited by the stability of macromolecules at body conditions. Drug delivery to the skin can circumvent first-pass metabolism to lower the necessary dose. Breaching the skin carries several risks, however, from local irritation to systemic drug intake through the vasculature.

The success and limitations of compartmentalized drug administration, as illustrated collectively by the different sections in this review, emphasize the importance of single compartment drug delivery for the safe and efficacious treatment of localized disease. The future of drug delivery stands to benefit from applying the principles of single compartment drug delivery to more conditions that call for local treatment, and from addressing the obstacles currently faced by this approach.

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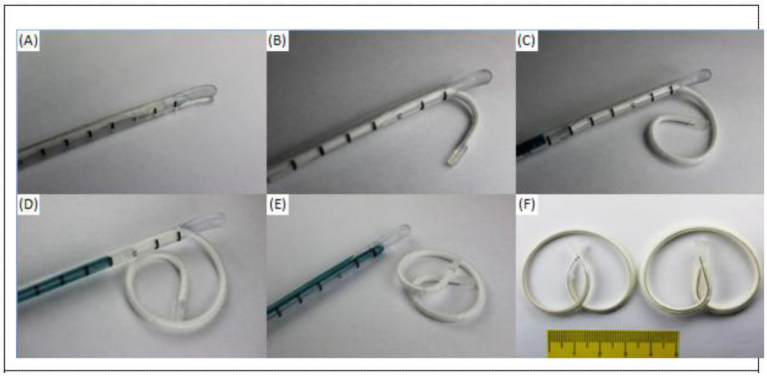

Figure 1.

Deployment of LiRIS® through a specially designed catheter-like inserter with 1 cm markings. The sequences are from (A) to (E). Two devices are shown in (F) with a 5 cm strip; the devices on the left and the right contain approximately 300 mg and 900 mg of mini-tablets, respectively.

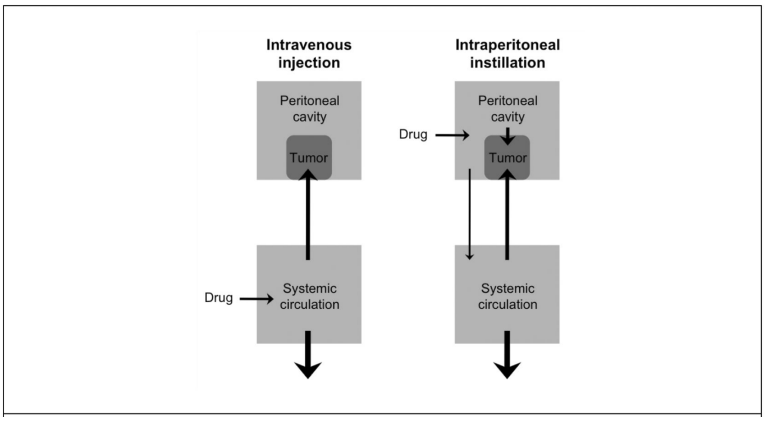

Figure 2.

Schematic diagram of IV and IP drug delivery routes. Weight of arrows illustrates relative rates. Adapted from [81].

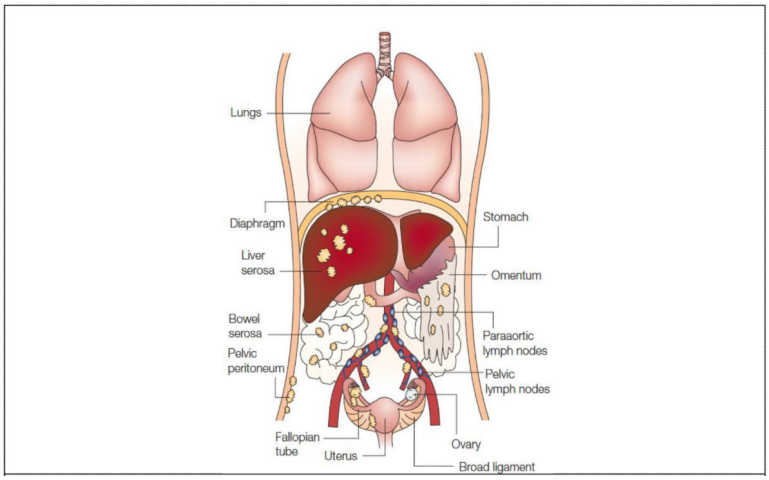

Figure 3.

Ovarian tumors preferentially metastasize to adjacent tissues throughout the peritoneal cavity. Reproduced with permission from [90].

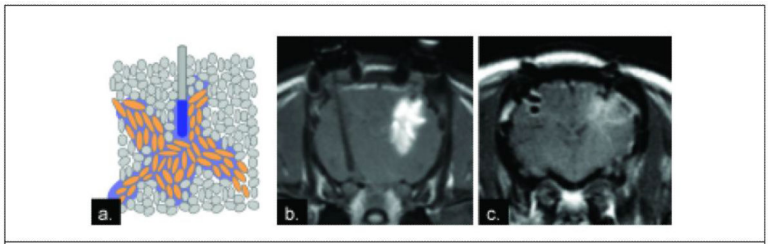

Figure 4.

Sketch Illustrating the irregular distribution resulting from CED infusion. The drug preferentially follows white matter tracts (illustrated in orange). B, C) T1 weighted MRI image after infusion of Gd-DTPA into pig brain. The infusion pattern has an irregular shape due to motion along lower resistance white matter tracts. Reproduced with permission from [129].

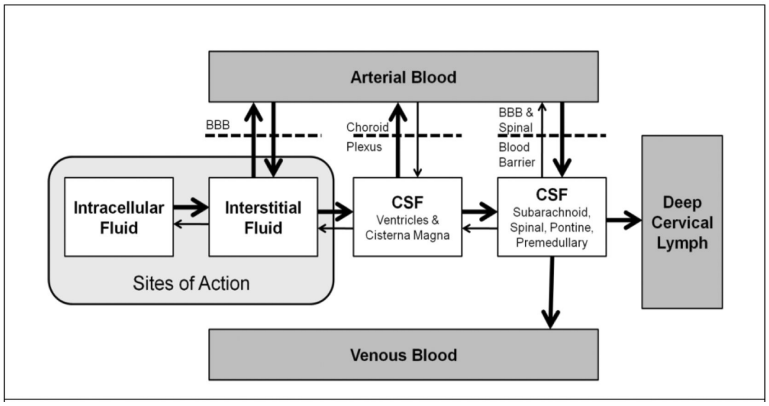

Figure 5.

Drug delivery compartments in the brain. Drugs and compounds can partition in a variety of different compartments in the brain. Drugs need to reside in the intracellular or interstitial fluids in order to exert intended pharmacologic effects. Major drug clearance mechanisms from the sites of action include crossing the BBB into the systemic circulation or into the CSF where it makes its way into the venous blood pool. Line weight represents relative magnitude of traffic between each compartment. Adapted from [141].

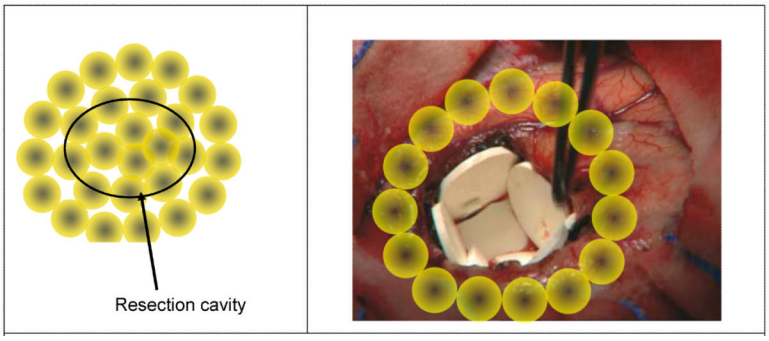

Figure 6.

Schematic of potential treatment approach utilizing multiple passive diffusion devices implanted using a large biopsy needle. Overlapping diffusion profiles (depicted in yellow) around the tumor dissection site could be used to achieve a larger drug distribution. Right image reproduced with permission from [144].

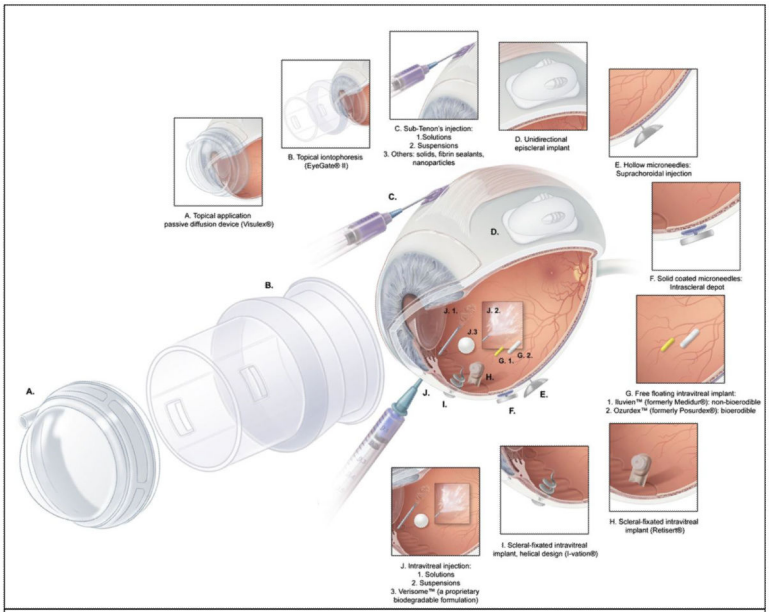

Figure 7.

Diagram of the eye showing various ocular drug delivery approaches. Reproduced with permission from [148].

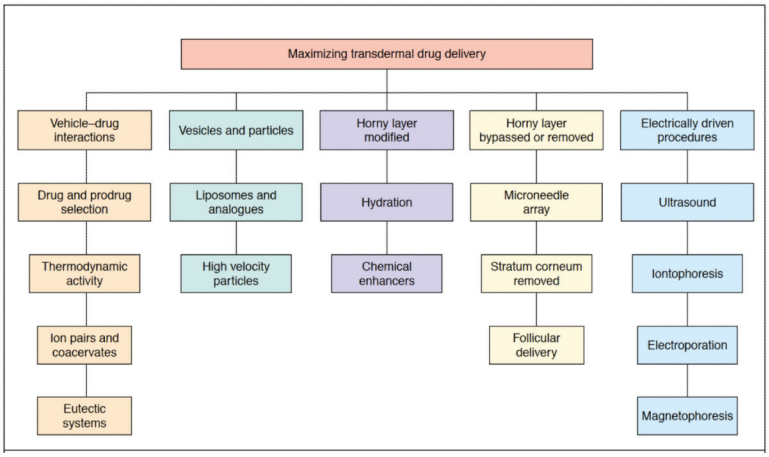

Figure 8.

Various techniques to achieve dermal drug delivery. Reproduced with permission from [186].