Expert Opinion

Drug-eluting polymer implants in cancer therapy

Agata A Exner† & Gerald M Saidel
†*Case Western Reserve University, Department of Radiology, 11100 Euclid Avenue, Cleveland, OH 44106-5056, USA*

Background: Drug-eluting polymer implants present a compelling parenteral route of administration for cancer chemotherapy. With potential for minimally invasive, image-guided placement and highly localized drug release, these delivery systems are playing an increasingly important role in cancer management. This is particularly true as the use of labile proteins and other bioactive molecules is likely to increase in the upcoming years. *Objective*: In this review, we present the current trends in the application of Pre-formed and *in situ*-forming systems as drug-eluting implants for cancer chemotherapy. *Methods*: We outline the clinically available options as well as up-and-coming technologies and their advantages and challenges. We also describe ongoing related innovations with image-guided drug delivery, mathematical modeling of implanted delivery systems and implanted drug delivery in combination with other therapies. *Results/conclusion*: Whether used alone or combined with other minimally invasive procedures, drug-eluting polymeric implants will play a significant role in the future of cancer management.

Keywords: adjuvant therapy, biodegradable polymer implants, cancer chemotherapy, drug delivery, image-guided delivery, *in situ*-forming depots, mathematical modeling

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1. Introduction

Chemotherapy plays a vital role in effective cancer management as an adjuvant therapy before or after surgical resection and/or radiation; however, the use of therapeutic agents as a stand-alone therapy is rare for tumors that can be accessed by direct means. One of the many limiting factors is effective drug delivery to the site of action. Ideally, the drug acts as a 'magic bullet' that possesses perfect specificity to cancerous cells and has no effect on the rest of the body. Although such an ideal agent has not been found, considerable investigation has been stimulated to seek and develop means of drug targeting to achieve this goal. 'Targeting' encompasses many approaches, including the administration of a naked drug, molecular targeting of systemically administered nanoparticulate drug carriers, and local drug delivery directly in the tumor site with or without a protective carrier. The idea of local drug delivery is deceptively superficial. Although theoretically the sustained release of a therapeutic agent directly into the tumor should be sufficient for cancer treatment, experience has shown that many obstacles have yet to be overcome. This review presents a rationale behind the development of local, implantable drug-eluting implants; discusses the benefits and unresolved challenges of various approaches; and indicates potential future directions.

An effective chemotherapeutic agent can lead to extended patient survival, relieve symptoms associated with late-stage disease and enhance the quality of life. Chemotherapeutic agents are used in the management of many cancers, including those of the breast, prostate, colon and lung [1]. Anthracyclines and taxanes are

Table 1. Common routes of administration for cancer chemotherapy.

Type	Route	Associated drug delivery system(s)	Examples of clinically used technology
Systemic	Intravenous	Micelles, liposomes, nanoparticles	Doxil®, DaunoXome®, Abraxane®, iMyocet®
	Oral	Sustained-release tablets, capsules, others	Gleevec®, Tarceva®, Xeloda®, Iressa®
	Subcutaneous/intramuscular	Micro- or nanoparticles, polymer implants	Eligard®, Zoladex®, DepoCyt®, Lupron Depot®, Sandostatin LAR®
Regional	Hepatic arterial infusion/trans-arterial embolization	Microparticles	Doxorubicin-eluting beads, Lipiodol-drug combination
	Intraperitoneal	Micro- or nanoparticles	Paclimer® (clinical trial)
	Convection-enhanced delivery	Liposomes, polymer nanoparticles	Liposomal gene therapy (clinical trials)*
Local	Intratumoral – adjuvant	Pre-formed and *in situ*-forming implants	Gliadel®
	Intratumoral – primary	Pre-formed and *in situ*-forming implants	OncoGel™

the most commonly used cytotoxic agents in the treatment of metastatic disease, yielding positive responses in 20 – 80% of patients with ~ 20% being complete responders [2]. Likewise, in the treatment of some types of prostate cancer, first-line chemotherapy using docetaxel or vinorelbine has shown positive responses of ~ 40% [3]. In non-small-cell lung cancer, chemotherapy is commonly included with other treatments to increase survival time [4,5]. As a primary, stand-alone or first-line therapy, chemotherapy has limited effectiveness; more often, chemotherapy is used in combination with surgery or radiation. Neoadjuvant chemotherapy is administered prior to interventional therapy to reduce the overall size of a tumor. Adjuvant chemotherapy is administered after a treatment to eliminate residual cancer cells remaining after the intervention.

The success of systemically or non-locally administered cancer chemotherapy hinges on circumventing dose-limited toxicity. While most anticancer agents have the potential to be effective at sufficiently high doses, these doses are often associated with side effects that are severe that they cannot be tolerated. If a balance can be reached between eliminating cancerous cells and preserving normal cells, then the effects of chemotherapy can be significantly improved. To help achieve this balance, alternative drug delivery methods can be used.

2. Alternative drug delivery methods and limitations

Various routes of drug delivery and carrier technology have shown some success in cancer treatment (**Table 1**). To reduce systemic side effects and overcome dose-limiting toxicity, alternative administration protocols have been investigated. Among the many options that are available, regional chemotherapy, intratumoral infusion and nanoparticulate drug carriers have shown the most promise.

Regional chemotherapy has many modes, but the most common is the infusion of drugs via the hepatic artery (i.e., hepatic arterial infusion [HAI]) for the treatment of hepatic metastasis [6]. Infusion of a therapeutic agent directly into the feeding artery of the tumor can increase the local concentration of the agent. A related approach based on the same principle is trans-arterial chemoembolization (TACE), which involves the infusion of embolizing agents (with or without chemotherapeutics) into the hepatic artery [7,8]. Both methods are typically used as neoadjuvants to surgical resection or image-guided ablation of colorectal metastasis to the liver, and both have shown significant improvement over systemic chemotherapy [8,9].

Intratumoral infusion of drugs (or convection-enhanced delivery) has been applied in the treatment of malignant brain tumors [10]. In this setting, the drug is infused directly to the site of action through a catheter. The primary advantage of this administration is the increase in penetration of the drug in the brain tissue compared to a single, direct intratumoral injection [11]. While the technique is somewhat limited by drug solubility, drug encapsulation in micelles, liposomes or other nanoparticles can be used to increase the scope of suitable agents [12-14].

Success has also been obtained with new drug delivery techniques. Drug carriers that are administered intravenously have met with keen interest and relative success. Vehicles (such as liposomes and micelles) have been used in a number of clinically available formulations [15,16]. Other particulate carriers (such as polymer micro and nanoparticles) have been used in extended-release oral formulations, but only to a limited extent in intravenous chemotherapy [17-19]. Particulate delivery systems can protect labile therapeutic molecules, extend their circulation time and offer potential for targeting and/or multimodal functionality. Current investigation

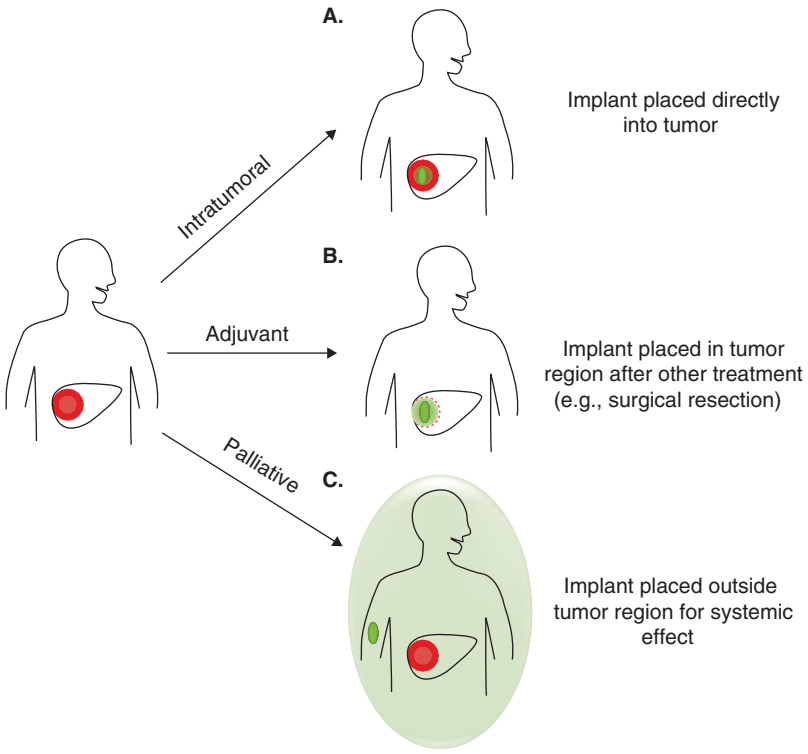

Figure 1. Categories of drug-eluting polymer implants in cancer chemotherapy. A. Intratumoral implants are placed directly into a tumor with the goal of achieving local control without systemic involvement. Implants can potentially serve as first-line treatment. **B.** Adjuvant implants have the same goal as intratumoral ones, but are placed into the site following other treatment, such as surgery or ablation. **C.** Palliative implants are used to eliminate repeated injections and improve patient compliance in late-stage palliative care.

focuses on improved carrier stability, extravasation and effective release of the cargo [19,20].

Regardless of the carrier technology or administration route, most chemotherapeutic drugs share common barriers that need to be overcome to improve their efficacy. Most of these barriers are associated with systemic and intratumoral pharmacokinetics. When a drug or drug particle is introduced into the body, its fate is dependent on surviving in different environments [21]. Drugs introduced orally must be transported with minimal loss across the gastrointestinal system into the bloodstream, through the liver and into desired tissues [1]. Even if intravenously and regionally administered drugs can overcome the gastrointestinal barrier and first-pass effects to enter the circulation with full availability (intravenous) or minimal loss (regional), they can be taken up by non-specific systemic interactions [1]. This is true for 'naked' drugs as well as those packaged into a carrier system, which must avoid scavenge by the reticulo–endothelial system and uptake by non-targeted cells [21-23]. Furthermore, high interstitial pressure within solid tumors has been cited as a significant hurdle to drug diffusion into the tumor center. Transport across capillary walls as well as cell and nuclear membranes poses many additional barriers [21]; such factors limit the amount of the therapeutic agent available to the intended target site and decrease drug efficacy.

3. Types of drug-eluting polymer implants

An alternative approach to increasing drug dosage at the tumor site can be achieved with drug-eluting polymer implants. These implants can have specified structure before implantation (i.e., pre-formed implants) or form a structure after implantation (i.e., injectable *in situ* implants). The underlying idea is to entrap a therapeutic agent (small-molecule drug or, more recently, proteins and other large molecules) within a matrix. The composition and structure of the implant can vary from a monolithic mixture of polymer and drug to a sophisticated layered or composite system. Regardless of their form, these implants can deliver chemotherapeutic drugs directly to cancerous lesions. The primary benefit comes from locally elevated drug levels without systemic involvement. Implants not only localize the drug, but can provide drug release over extended time periods. This avoids repeated external drug administration and problems with patient compliance. These attributes make local delivery especially beneficial for drugs with a narrow therapeutic index or a short *in vivo* half-life.

Drug-eluting polymer implants that are either already clinically available or undergoing development can be grouped into three main categories: intratumoral, adjuvant and palliative (**Figure 1**). These are based on the end goal

of the implant. An intratumoral implant achieves a locally elevated drug concentration with minimal systemic involvement and its purpose is to replace or supplement systemic chemotherapy. An adjuvant implant is placed into a previously treated tumor (e.g., following tumor resection or ablation) to prevent local recurrence. The palliative subcutaneous or intramuscular implant provides a sustained-release depot for a systemic effect, but obviates the need for repeat injections or oral doses.

3.1 Pre-formed polymer implants

Pre-formed polymer implants have been used for various applications ranging from adjuvant chemotherapy following brain tumor resection to palliative care for end-stage prostate cancer [14,24,25]. There are several advantages to such systems. First, the shape of the implant can be designed to meet any number of specifications of the end application. The shape and surface area of the implant play a significant role in the rate of drug diffusion out of the implant as well as the rate of polymer degradation. Because the shape is pre-formed, the implant properties are consistent and reproducible. The formulation of such systems involves either extrusion or compression of the implants into their desired shape. As such, the implant fabrication scale up can be easily accomplished. A recent review has discussed various aspects of pre-formed polymer implants [26]. The present review emphasizes other aspects.

Polymers used in drug-eluting implants can be grouped into two main categories non-degradable and biodegradable. Non-degradable polymers, such as silicone elastomers, poly(ethylene–co-vinyl acetate) or EVAc, and polyacrylates, have been used in pre-formed implants with a semipermeable outer membrane [27]. The release rate of the drug loaded in the center of the implant is controlled by transport across the membrane. The primary disadvantage of all non-degradable devices is the complication of surgical removal of the device(s) at the end of treatment. The removal is often invasive and painful due, in part, to the fibrous encapsulation of the foreign body over time [28-30].

To avoid complications with the use of non-degradable polymers, biodegradable polymers, such as polyesters, poly(ortho esters) and polyanhydrides, have become the preferred material for the formulation of drug delivery systems. Poly(lactic acid), poly(glycolic acid) and their copolymer poly(lactic–co-glycolic acid) (or PLGA) have been widely used in clinical applications, most frequently in the formulation of degradable sutures [31]. PLGA undergoes degradation via hydrolysis of the ester linkages mediated by water. Hydrolysis of the polymer backbone is accompanied by bulk erosion of the device [32]. The degradation process can be suited to the application type and vary from weeks to > 1 year depending on numerous factors, including device geometry, porosity, lactide:glycolide ratio and molecular weight [32]. PLGA is amenable to various formulations from nano- and microspheres to films to monolithic implants and injectable solutions, and is generally accepted as being safe. The host response, drug-release mechanisms, erosion and degradation of PLGA have been repeatedly documented [31,33,34].

Experimental studies exploring the development, characterization and efficacy of various intratumoral drug delivery strategies for a wide range of therapeutic agents have been reported. Several anticancer agents have been examined more frequently (e.g., cisplatin, carboplatin, doxorubicin [adriamycin], carmustine [BCNU] and paclitaxel [PTX]) due to their narrow therapeutic windows [1]. Cisplatin is a platinum-based agent used in the treatment of sarcomas, small cell lung cancer, lymphomas and germ cell tumors [35-39]. To minimize its nephrotoxicity, cisplatin has been entrapped in matrices of polyanhydride, poly(methylmethacrylate) and EVAc [40]. Carboplatin, a less toxic analog of cisplatin with other deleterious side effects, has been entrapped in pre-formed [41] as well as *in situ*-forming implants [42] for intratumoral therapy of liver and colorectal tumors in animal models. These intratumoral implants lead to improved local effectiveness with minimal systemic effects.

One comprehensively examined pre-formed implant system is called the 'millirod'. This implant involves a compression heat-molding procedure [43] that consists of entrapping the active agent into PLGA microspheres followed by compression under temperatures exceeding the glass transition temperature (T_g) of PLGA. Another design is the encasement of the monolithic implant body with a membrane coating [44]. The implant is comprised of two phases: an inner drug-loaded millirod and an outer membrane impregnated with NaCl. On immersion into an aqueous environment, NaCl leaches out, leaving behind a semipermeable membrane. Membrane thickness and porosity (controlled by the amount of NaCl) alter the release rate. The difference in the profiles of the drug released from sustained- and dual-release PLGA millirods has also been studied [45]. Monolithic implants and implants with a quick-dissolving drug coating have been formulated to provide either sustained or dual-phase release. For the latter, the burst dose was achieved by loading the drug into the quick-dissolving coating, which was followed by sustained release from the inner domain. The dual-release implants lead to a more rapid increase in local doxorubicin concentration and penetration distance in liver tissue [45].

Intratumoral delivery of polyanhydride wafers (i.e., polymer disks) with BCNU is currently in use for the treatment of malignant glioblastoma. BCNU administered orally in high doses causes considerable systemic toxicity [14,40,46]. However, drug delivery with an implanted biodegradable polyanhydride wafer not only exposes the tumor to a high drug dose, but also avoids limitation by the blood–brain barrier. The drug is delivered from the wafer as its polymer matrix undergoes surface erosion and releases the drug. The Gliadel® wafer (MGI Pharma, Inc., Bloomington, USA) is

the sole biodegradable, solid drug-eluting implant approved by the FDA for clinical use. The wafers, comprised of a copolymer of poly(bis[p-carboxyphenoxy]) propane:sebacic acid (PCPP:SA), can degrade over a range of days to years [47]. This implant device has been extensively studied and characterized [46]. The same implantable polymeric wafer has been used for the delivery of other agents, including doxorubicin, carboplatin and PTX [14,40,46].

With a few exceptions, a drawback of the typical pre-formed implants is the relatively invasive procedure needed for the implantation of the devices. In fact, the majority of these implants cannot be placed inside a solid tumor without surgical procedures and, most likely, removal of the tumor, as with the Gliadel wafer.

3.2 Injectable *in situ*-forming polymer implants

Among the less invasive strategies is the use of injectable *in situ*-forming polymer implants [48]. These systems consist of a solution or suspension of the matrix and active agents that can be injected into the target site with a needle, eliminating the need for more invasive surgical procedures. The liquid mixture solidifies into an 'implant' in response to a stimulus (e.g., water, temperature, pH or light) via a process of precipitation, cross-linking or polymerization. Depending on their formulation, injectable implants will release the agent through a process of diffusion and degradation from a period of hours to months. The relative simplicity of *in situ*-forming implants has encouraged their development and clinical application for palliative care. The main formulations are based on biodegradable polyesters, hydrogels and low glass-transition temperature thermoplastics. The polyesters (such as PLGA) are used primarily in phase-inversion systems, while hydrogels are important in cross-linking and thermally responsive systems. As details of the injectable *in situ*-forming implants have been reviewed elsewhere recently [48,49], we will focus on aspects pertinent to cancer chemotherapy.

3.2.1 *Implants formed by phase inversion*

Phase inversion occurs with the precipitation of a hydrophobic polymer dissolved in a water-miscible solvent on injection into an aqueous environment [50]; for example, the addition of PLGA to an organic, water-miscible solvent such as 1,2-*N*-methyl pyrrolidone (NMP) creates a low-viscosity, low-toxicity liquid polymer that can then be mixed with any agent (even fragile DNA or RNA molecules and proteins because the fabrication requires no heat) and injected into the desired site with a hypodermic needle. The polymer, which is insoluble in water, precipitates immediately in the site on contact with any bodily fluid to form an implant. The active agents are normally entrapped in the polymer solution either as a homogeneous suspension with agitation or through dissolution in the organic solvent. Drug release occurs through a combination of passive diffusion (early stage) and polymer degradation, which depends primarily on drug solubility, polymer:solvent ratio (affecting the matrix pore size) and polymer properties.

This formulation has been applied clinically in the treatment of advanced prostate cancer (Eligard®, sanofi-aventis, USA). Treatments with repeated injections of hormone agonists (e.g., luteinizing hormone-releasing hormone [LH-RH]) lower plasma testosterone levels and lead to an inhibition of prostatic tumor growth. When the therapeutic agent is fragile, daily injections may be required to sustain drug levels within the therapeutic range. Injectable delivery systems provide extended release of the active agent, at the same time protecting the unreleased labile payload. Eligard formulations, which deliver the active agent from 1 to 6 months, can effectively reduce testosterone levels in ≤ 98% of patients [51-55].

Although most applications of injectable systems have been used simply to eliminate repeated injections of labile proteins, other local applications with various active agents have been examined. One example is an intratumoral gel consisting of a PLGA matrix incorporating the anticancer agent cisplatin and adrenaline [39]. The goal of this system is to improve local drug retention in the tumor by first reducing blood flow by vasoconstriction using adrenaline. In patients who received the cisplatin/epinephrine gel, the tumor burden and cancer-related symptoms were reduced in the treatment of head and neck carcinoma. Other innovative *in situ*-forming implants have recently been proposed by Packhauser and colleagues [56]. The implants are formulated using dialkylaminoalkyl-amine-poly(vinyl alcohol)-g-PLGA nanoparticles, which form semisolid depots on injection into an aqueous environment by a process of ion-mediated aggregation and fusion [56]. The depots offer several advantages, including improved homogeneity of drug distribution, ease of injection and potential for long-term storage.

In contrast to pre-formed implants – which can be made of highly reproducible size, shape and homogeneity – formation of phase-inversion implants is highly dependent on the surrounding tissue. The dynamics of the phase-inversion process are directly related to the drug-release dynamics; for example, when the polymer solution is injected into fatty versus highly vascularized tissues of clearly different water content, the rate of phase inversion can be altered and lead to significant variation in drug release [50,57]. The phase inversion is also responsible for the potentially dangerous large initial drug burst that occurs as the polymer–drug solution comes in contact with water [58,59]. To reduce these effects, solvents with different polarity (propylene glycol [PPG], acetone, dimethyl sulfoxide [DMSO] and glycofurol) as well as excipients have been investigated [50,57-59]. These affect the rate of phase inversion in the implant-formation process. Polar solvents result in a relatively fast phase-inversion process with haphazard implant structures and fast drug release. Solvents with less polarity lead to a slower phase inversion, better organized implant structures and more consistent drug release [58,60,61].

3.2.2 Hydrogel-based systems

In situ-forming hydrogels can be of either natural or synthetic origin. An example of a synthetic hydrogel is one formed by the amphiphilic surfactant Pluronic (or poloxamer), a triblock copolymer comprised of poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) repeat units. At sufficiently high concentrations, this polymer shows temperature-dependent gel formation, which has been studied for a number of applications [62,63]. When not stabilized by cross-linking, the gel is highly water soluble and only lasts for several hours; however, because it is relatively non-toxic and biologically active in chemo- and thermosensitization, the polymer has gained considerable momentum as a hydrogel, excipient and functional component of implantable systems [16,63,64]. Another thermosensitive but biodegradable, synthetic polymer hydrogel is a triblock copolymer of either poly(lactic acid) (PLA) or PLGA and PEG. The system, marketed as OncoGel™ (Protherics, Brentwood, TN, USA) is an injectable formulation consisting of PLGA–PEG–PLGA and PTX. It is currently under examination for local tumor treatment [65,66].

In situ-forming systems can also be manipulated by other stimuli [49]; for example, an insoluble but biodegradable hydrogel of photocrosslinkable chitosan (a natural product) can be formed by a brief 30-s exposure to ultraviolet light [67]. A new class of biodegradable hydrogels derived from oxidized sodium alginate and gelatin, which cross-link in the presence of sodium tetraborate, has also been reported [68]. Because these systems often require either a prolonged gelation time or direct access to the polymer solution to stimulate cross-linking, they may not be optimal candidates for minimally invasive cancer treatment; however, polymers that undergo ion-mediated gelation (such as alginate or chitosan) possess potential implications for injectable chemotherapeutics [49].

3.2.3 Glass-transition temperature-dependent polymer systems

Polyanhydrides, having low glass-transition temperature or melting temperature (typically < 65°C), can be used as thermoplastic 'gels' that are heated prior to injection [48]. The primary advantage of these materials is that, unlike the phase-inversion systems, no organic solvent is required for injection. Typically these thermosetting implants have very low porosity that yield low drug-release rates, which are not suitable for drug delivery with a high therapeutic window; however, low molecular weight hydroxy fatty acid-based polyanhydrides have been developed to degrade by both surface and bulk erosion, and expedite drug release [69]. Another new material is a biodegradable multi-block amphiphilic and thermosensitive poly(ether ester urethane) consisting of poly(*[R]*-3-hydroxybutyrate) (PHB), PEG and PPG blocks [70]. The poly(PEG/PPG/PHB) urethanes, which are water soluble and can be formulated at low temperatures, have the potential to form drug depots *in situ* following injection.

4. Limitations and new research directions

In the laboratory, drug-eluting polymeric implants have met with reasonable success; in practice, this approach has not shown significant improvement over systemic chemotherapy or other treatments. In general, the inability to treat the tumor from the inside with drugs alone, even if delivered for a sustained period of time, is largely a result of the irregular and unpredictable tumor structure and function [21-23]. The type of cancer, location, size, homogeneity and extent of vascularization all impact the final outcome [22,23]. It is also difficult to generalize the relative importance of these factors to a specific drug or specific type of cancer; for example, properties of the active agent (such as molecular weight, solubility and stability) will dictate the type of implantable system that is suitable for the application. The balance of drug and implant properties that satisfies the requirements and leads to a desired release and tissue drug distribution is essential for the success of a delivery system. Other persistent challenges are invasive implantation of devices, lack of techniques for *in vivo* characterization and limited drug penetration in tissue [14,27,46,71]. Often, passive drug release may also be a limitation. Finally, the implants have not been able to manage metastatic disease. For these reasons (which are summarized in **Table 2**), implantable systems are currently favored for adjuvant applications following surgical resection, radiation or other related interventions. In Sections 4.1 – 4.3, we present relevant technologies that are important for improvements in the development of implanted drug-eluting devices.

4.1 Image guidance and monitoring for drug delivery

Implantation of drug-eluting polymer implants in tumors can be accomplished with minimal invasiveness under image guidance by computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound. In most procedures, a cannula with a small diameter is introduced into the target site via a minor incision in the skin, which allows the introduction of the necessary tools [72-75]; the procedure is carried out on an out-patient basis or with minimal hospitalization. This field offers unprecedented opportunities for implantable chemotherapy systems by granting straightforward access to sites that used to be accessible only through open surgical procedures. The same cannula can be used for minimally invasive implantation of devices or injection of *in situ*-forming polymer solutions; for example, the pre-formed drug-eluting polymer millirod is suitable for image-guided implantation. Such biodegradable PLGA implants have been studied in several models [26,41]. A similar implantable system delivers 5-fluorouracil [76]. Both systems were designed as adjuvant chemotherapy following tumor radiofrequency ablation. Exner *et al.* have examined the use of *in situ*-forming polymers for direct intratumoral injection for use alone and or in combination with tumor ablation [42]. Other exciting research in this field includes the development of near real-time

Table 2. Considerations for drug eluting polymer implants in cancer chemotherapy.

Challenge	Potential resolutions
Invasive placement	Minimally invasive image-guided placement via ultrasound, computed tomography or magnetic resonance imaging
Difficult *in vivo* characterization	Non-invasive longitudinal characterization with small animal or clinical imaging modalities. Can be functional and anatomical Mathematical modeling for characterization and prediction
Passive drug release	Control of release using external stimuli such as ultrasound energy or magnetic field
Limited drug tissue penetration	Combination therapies including elimination of vasculature with thermal- or cryo-ablation, combination with antiangiogenic agents, co-administration with targeted nanoparticles or other systemic agents
Limited drug retention	
No effect on metastases	
Wound healing response interference	Inclusion of enzymes to decrease scar tissue formation

imaging techniques and robotic systems that facilitate the precise placement of the necessary equipment [77,78].

For local therapy to attain maximum efficacy, the implanted device must deliver the therapeutic dose of a drug to a nearby target area without substantially affecting the normal tissues. Typically, the local drug-release and -transport properties in tissues are not known, but must be quantified to plan for successful local therapy. The crucial factor is the concentration of drug in the tissue reaching a desired level for a sufficient period of time. Other parameters that need to be studied are the tissue-penetration distance of a predetermined therapeutic drug concentration and drug concentration distribution in tissue over time relative to the implant [47,79]. For local drug-eluting implants, this information is not available from standard pharmacokinetic (PK) analysis. The relationships between plasma drug concentration and its effect associated with local drug-eluting implants are considerably more complex [1]. To circumvent limitations associated with standard PK analysis, non-invasive imaging techniques have been developed to characterize the movement of the drug in the target tissue *in vivo* [80-87]. Techniques include single-photon γ-emission imaging (SPECT), dual-photon positron emission tomography (PET), MRI and CT [82,83,86-88]. These techniques offer high sensitivity (SPECT and PET), high contrast with spatial and temporal resolution (MRI and CT) and real-time opportunities (MRI and ultrasound). These modalities are available for human and animal studies, and have been investigated for implantable systems as well as many systemic delivery schemes [89,90]. Furthermore, molecular imaging techniques (such as bioluminescence, fluorescence, MR spectroscopy and CT perfusion) provide functional information that can be combined with higher-resolution anatomic imaging techniques for structural information [80,84,85].

4.2 Techniques for modulating drug release

Diffusion is a primary mechanism for drug release from drug-eluting polymer implants. In biodegradable systems, drug release involves not only diffusion but also polymer degradation and implant erosion. Release of the drug by these mechanisms can be controlled to various degrees depending on the matrix material, structure and formulation. Release rates depend on parameters that are relatively simple to modify (such as surface area and drug loading) and others that require more sophisticated methods (such as multi-lamellar formulations) [91,92]. The diffusion rate depends on interaction of the drug and matrix. To expedite drug release and polymer degradation, highly soluble excipients (such as NaCl) can be incorporated to create large pores in the matrix. Other excipients (such as Pluronic, which is useful in phase-inverting systems) to modify drug release and improve biological activity have also been examined [50,60-64,93-96]. Polymer degradation and polymer matrix erosion can be altered; for example, by varying the ratio of co-polymers of PLGA. Likewise, the diffusion and degradation processes can be controlled by polymer molecular weights and end-group modifications.

Post-processing techniques to control drug release from polymer implants are typically carried out by an external stimulus after implant placement. Two prominent examples of this approach are the use of ultrasound and of an external magnetic field. The highly refined ultrasound technology available today can be used in a number of different applications from local hyperthermia and tumor ablation to the modulation of drug release from drug delivery systems. It can facilitate the release of a drug from systemically administered nanoparticles, micelles or liposomes [97-99] by inducing their localized destruction or contribute to the degradation of certain polymers [100]. Although ultrasound enhancement of drug release from lipid particles is more prevalent than that in implantable systems, future composite systems may be developed to take advantage of this technique; for example, drug-loaded, ultrasound-responsive nano- or microparticles that are entrapped in a polymer or hydrogel matrix can be used for on-demand drug release.

External modulation has also been demonstrated with oscillating magnetic fields. Despite *in vitro* and *in vivo* feasibility studies, no application to cancer chemotherapy has been established. More commonly, magnetic particles are used either as drug delivery vehicles localized at the tumor site or as means of heating the tissue by an external magnetic field [101-103] for the treatment of prostate cancer. A recent study reported on the use of a magnetic implant inserted directly into the site of interest that creates an internal local magnetic field gradient, in lieu of the external magnet. This technique permits local treatment of tumors in which external magnetic fields would be too weak to achieve targeting [104]. Other stimuli (e.g., temperature, electric field and light) can also modulate drug release from implantable delivery systems [105].

4.3 Computational models to predict drug delivery

Mathematical models of drug release are ideally intended to predict how the dynamic output of a device under various conditions based on a small set of experimental studies. A thorough review of computational models of drug release from hydroxypropyl methylcellulose (HPMC)-based matrix tablets was reported in 2001 by Siepmann and Peppas [106]. Although this review was limited to a particular device, it emphasized the major advantages of drug-release models more generally: i) elucidating the underlying mass transport mechanisms; and ii) predicting effects of device design (e.g., shape, size and composition). As a consequence, such models can facilitate the development of new and improved drug delivery devices. Since 2001, many advances in such computational models have been presented. These models are much more complex than the early semi-empirical model of Higuchi [107] in which the rate of drug release is inversely proportional to the square root of time. Although the Higuchi model is valid under some conditions, it fails to represent the dynamic responses of many devices and does not have predictive capability. More recent models incorporate complex mechanistic theories to account for diffusion, swelling and dissolution processes. The choice of the appropriate mathematical model depends on the desired predictive ability and accuracy. This section focuses on models of drug release from implantable devices developed since 2001 and on those for which dynamic responses of model simulations have been compared to experimental data, with the primary emphasis on drug delivery from macroscopic polymeric matrices. Although not directly related to the thrust of this review, a shortened review is also given of drug delivery from micro- or nanoparticles.

With respect to drug delivery from a high-viscosity HPMC matrix, a one-dimensional (1-D) model of drug concentration dynamics within the delivery device has been presented that accounts for swelling, diffusion and erosion front movements [108]. This is a three-phase, concentric ring model with the solid drug in the inner and intermediate rings, dissolved drug in the outer ring, and water in the outer and intermediate rings. The concentration changes in the radial position and time are described by diffusion equations with moving boundaries that depend on the rates of swelling, dissolution and erosion. Model simulations are compared with transient experimental data for drugs of different water solubility. The simulations correspond well with the experimental swelling and erosion fronts, but not with the diffusion front. Another limitation of the model is that it could not simulate the continued swelling of the matrix subsequent to the disappearance of the swelling front.

Grassi *et al.* [109] developed a model to describe drug release from an extruded cylindrical matrix with theophylline, stearic acid, monohydrate lactose and PEG. They used a cylindrically symmetric (2-D) diffusion model of the soluble drug within the device incorporates a dissolution rate proportional to the difference between the drug saturation level and local drug concentration, which is common for many models. The release kinetics were mainly affected by stearic acid and theophylline content. Comparison of simulations with experimental data showed that the early release rate was determined primarily by dissolution and the later release rate by diffusion.

Diffusion of a water-soluble small-molecular drug from dissolving polyethylene oxide (PEO) cylindrical tablets has been modeled to include swelling of the hydrophilic matrix and water penetration [110]. Model simulations of drug release are compared with data from *in vitro* studies of swelling and dissolution of PEOs with different molecular weights. Simulations of water uptake, dimensional change and polymer dissolution rate dynamics are in agreement with results from pure PEO tablets with two different molecular weights. In addition, the simulated drug release-rate dynamics correspond to experimental data for different initial loadings. The overall drug-release process is highly dependent on the matrix swelling, drug and water diffusion, polymer dissolution and initial dimensions of the tablets.

A model developed by Raman and McHugh [60] simulates protein-release kinetics from injectable, polymer solution depots, which undergo rapid phase inversion on injection. The model includes 1-D diffusion-reaction equations in cylindrical and rectangular coordinates in polymer- and solvent-rich phases, respectively. In the polymer-rich phase that incorporates solvent, water and the dissolved drug, the radius of dispersed drug particles depends on the rate of dissolution. In the water-rich phase incorporating solvent and the drug, variations of the volume fraction and the protein mass-transfer coefficient lead to predictions of diverse release dynamics. Some conditions produce a release rate with a rapid burst followed by drug trapping; others produce various release rates. Simulations were compared with lysozyme-release data for experimental PLGA and PLA systems. The simulated transition from rapid release to zero-order kinetics on addition of Pluronic agrees with experimental data.

Drug release from PLGA cylindrical millirods that incorporate free excipient, drug-excipient complex, free drug and crystalline drug in a PLGA matrix was modeled by Wang *et al.* [111]. The model characterizes dynamic transport and reaction processes that include radial diffusion, excipient complex formation and crystalline drug dissolution. In the liquid phase, the diffusion-reaction equations describe the dynamic spatial distributions of free drug, bound drug and excipient. In the solid phase, the drug–excipient complex diffuses and is lost with a solubility-dependent dissolution rate. Free drug in the solid phase can undergo diffusion, dissolution and recrystallization. Optimal estimates of the model parameters were obtained by minimizing the difference between model simulation and experimentally measured drug-release kinetics. The effects of different experimental conditions (such as drug loadings) on the drug-release rate were simulated and compared with data. The complex binding capacity affects drug initial conditions, drug–polymer interactions and bound drug behavior in aqueous solution. This binding capacity is crucial in controlling the drug-release rate.

Computational models have also been presented for drug delivery from micro- or nano-particles. Drug release from tablets such as agglomerated micronized cellulose (AMC) that disintegrate into many particles was modeled by Frenning and Strømme [112]. This model, which assumes spherical symmetry, combines drug dissolution, diffusion and immobilization caused by adsorption of the drug to the tablet constituents. A simplified analysis assumes that liquid absorption, matrix swelling and tablet disintegration are much faster than drug dissolution and subsequent drug release. Model-simulated release rates correspond well with experimental release rates of NaCl from disintegrating AMC tablets.

Simulations with the spherically symmetric diffusion model were compared with drug-release data from non-degradable microparticles based on ammonio-methacrylate copolymers containing the hydrophilic drug propranolol HCl and/or the lipophilic drug nifedipine [113]. The resistance for drug release within the unstirred liquid boundary layers on the surfaces of the microparticles was found to be negligible compared with the diffusional resistance within the polymeric devices.

The release of small molecules from degradable microspheres (e.g., poly[D,L-lactide-co-glycolide] or PLG particles) has been modeled by drug diffusion and polymer degradation [60]. As the model can describe corresponding experiment data, drug release occurs apparently by diffusion through the dense polymer matrix rather than through pores that could be formed by degradation and erosion.

In comparison with previous single-phase models, Zhang *et al.* developed a model of drug diffusion in porous, biodegradable, polymeric microspheres to account for the kinetics of drug release with bulk erosion and surface erosion of the polymer matrix [114]. For bulk erosion, the drug diffusion model in the liquid phase incorporates erosion and dissolution. For surface erosion, drug concentration changes with diffusion and dissolution in both liquid and solid phases in which the boundary decreases with time. Predictions by model simulation are compared with a variety of experimental data.

5. Summary

Drug-eluting polymer implants for cancer chemotherapy have been a prolific area of research for several decades. Whether used to improve patient compliance, prevent or delay tumor recurrence, or as a first line of treatment, implantable systems offer considerable advantages over systemic administration. Among the most notable advantages are the localization of therapeutic drug concentrations at the site of action with minimal systemic involvement and improvement in patient compliance by eliminating the need for repeated dosing. The immense range of materials, formulation methodologies and controlled-release mechanisms offer unprecedented opportunities for the delivery of most chemotherapeutic drugs, from small molecules to large proteins. Appropriately designed drug-eluting polymeric implants should bring compelling benefits and minimal patient risk for the treatment of solid tumors.

6. Expert opinion

Each type of drug delivery system has advantages and unresolved challenges that make some much more directly applicable to cancer chemotherapy. The most challenging problems with this approach are insufficient tissue penetration, retention of released drugs and the inability to treat metastatic disease concurrently with the primary tumor site. Combination therapies that use the synergy of drug-eluting implants with other minimally invasive treatment or targeted systemic particulate drug carriers are most likely to continue improvement in their clinical effectiveness.

6.1 Combination therapeutics

Just as a single chemotherapeutic agent is an unlikely candidate for a cancer cure, it is also unlikely that successful tumor treatment will be obtained with a single drug delivery strategy. Combination therapy consisting of at least two drugs is used frequently in oncology [115]. Targets for combination therapeutics can affect molecular pathways, improve drug retention in a region of interest, enhance drug uptake into a cell and alter the metabolism of the active agent. One compelling new treatment is the combination of *in situ*-forming implants with tumor thermal ablation [42]. This approach is of interest because it provides an easily customizable formulation that can be combined in the operating suite and modified to any number of needs,

including drug dose, release profile and injection site. The therapy also offers some benefits over examined pre-formed systems, namely the possibility of being injected into the site using already-existing multi-tined needle technology [116-118]. The efficacy of combination therapy consisting of tumor thermal ablation followed by an injection of a chemotherapy depot was examined by Krupka *et al.* Tumors treated with ablation followed by drug delivery showed a significant reduction in the tumor growth rate compared with ablation control, suggesting that local adjuvant chemotherapy plays an essential role in preventing the progression of tumor unaffected by the ablation treatment.

Molecular targeting of systemic agents and direct intratumoral delivery are especially promising for effective chemotherapy. Ideally, agents and their carrier vehicles are targeted to a receptor site apparent only on the tumor [21,22,80,119-121]. While retaining the ease of intravenous administration, targeting of systemic agents can make drug delivery highly specific to the tumor with significantly fewer side effects. Cancer-specific targets include enzymes, receptors, anti- and pro-apoptotic proteins, angiogenesis-related molecules and related pathways that present many new opportunities for further advancement in drug development and delivery [122-130]. Molecular or chemical targeting methods may also complement the 'inside-out' approach of implantable chemotherapeutics by addressing the issue of metastasis.

Improving the delivery of chemotherapeutic agents to solid tumors may also be achieved by 'normalization' of the tumor microenvironment [131]. The concept assumes that irregular tumor vasculature can be returned to a 'normal' state by manipulation with antiangiogenic agents. The 'normalized' vessels would have reduced tortuousity and leakiness, decreased interstitial pressure, decreased hypoxia and a more neutral pH. Under these conditions, improved drug penetration has been demonstrated [132]; however, such an approach may also prevent the effective use of nanoparticulate carriers due to reduced 'leakiness' of the vasculature and thus hampered extravasation of larger particles. Another approach of reducing the complex tumor properties into a more homogeneous condition is the localized destruction of the tumor microvasculature prior to administration of chemotherapy [76,133-137]. The destruction of local vasculature creates significantly improved retention of drugs delivered by implantable chemotherapy devices as well as those delivered systemically. This can be achieved by thermal ablation with local radiofrequency, microwave or laser energy sources as well as cryoablation. The combination of tumor ablation followed by a drug-eluting polymer implant offers a significant advantage over drug delivery implants alone because the irregular tumor structure and vasculature are destroyed by the ablation. This is advantageous from two standpoints. First, the implants assure that no residual tumor cells remain following the ablation procedure. Second, the destruction of vasculature allows for longer retention of the drug in the tumor volume [133-137]. This combination offers a new, minimally invasive tumor management approach.

6.2 Conclusion

In synergy with combination therapeutics, several advanced technologies will play a crucial role in the advancement of implantable cancer chemotherapeutics. Techniques for modulating drug release and mechanistically based computational modeling are essential elements in optimizing implantable systems. Mathematical models of implant formation, drug release and local pharmacokinetics can aid in predicting the best-suited formulations for an application. Innovative technologies (such as non-invasive molecular imaging) can be used for the characterization and efficacy assessment, and will be instrumental in future developments. Whether combined with targeted systemic delivery or minimally invasive interventional oncology procedures, or used as a preventive measure, drug-eluting polymeric implants will play a significant role in the future of cancer management.

Declaration of interest

The authors have no conflict of interest to declare and have not received financial support in the preparation of this manuscript.

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Affiliation

Agata A Exner[†1,2] PhD & Gerald M Saidel[2]
[†]Author for correspondence
[1]Case Western Reserve University,
Department of Radiology,
11100 Euclid Avenue,
Cleveland, OH 44106-5056, USA
Tel: +1 216 844 3544; Fax: +1 216 844 5922;
E-mail: Agata.Exner@Case.edu
[2]Case Western Reserve University,
Biomedical Engineering,
11100 Euclid Avenue,
Cleveland, OH 44106-7207, USA