Expert Opinion

1. Introduction
2. *In situ* forming implants
3. Implants based on natural polymeric sources
4. Synthetic, biodegradable mono-polymer and co-polymers as implant sources
5. Synthetic, biodegradable triblock polymers used for implants
6. Synthetic non-biodegradable polymers
7. Surgical pastes
8. Other implants
9. Conclusions
10. Expert opinion

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Recent advances in the design of drug-loaded polymeric implants for the treatment of solid tumors

Ameena Wadee, Viness Pillay[†], Yahya E Choonara, Lisa C du Toit, Clement Penny, Valence MK Ndesendo, Pradeep Kumar & Caragh S Murphy

[†]*University of the Witwatersrand, Department of Pharmacy and Pharmacology, Johannesburg, South Africa*

Introduction: The effective treatment of solid tumors continues to be a great challenge to clinicians, despite the development of novel drugs. In order to improve the clinical efficacy of existing chemotherapeutic agents, researchers have considered the possibility of site-specific solid tumor treatment. The greatest advantage of localized delivery is the significantly fewer side effects experienced by patients. Recently, *in situ* forming implants have attracted considerable interest. These polymeric systems are injected as solutions into tumor sites and the injected solution forms an implant as a result of local environmental stimuli and hence removes the need for surgical implantation.

Areas covered: This review summarizes the attempts that have been made to date in the development of polymeric implants for the treatment of solid tumors. Both *in situ* forming implants and preformed implants, fabricated using natural and synthetic polymers, are described. In addition, the peri- or intra-tumoral delivery of chemotherapeutic agents based on implants inserted surgically into the affected region is also discussed along with a short coverage of implants having an undesirable initial burst release effect.

Expert opinion: Although these implants have been shown to improve the treatment of various solid tumors, the ideal implant that is able to deliver high doses of chemotherapeutics to the tumor site, over prolonged periods with relatively few side effects on normal tissue, is yet to be formulated.

Keywords: chemotherapy, implant, polymeric systems, solid tumors, stimuli-responsive

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1. Introduction

Despite the advances in cancer therapy, solid tumors have remained to be difficult to treat successfully as there are a significant number of barriers to overcome during treatment [1]. One such barrier is the three-dimensional structure of the solid tumors, in which drug penetration into solid tumors is 5 – 10-fold less when compared with penetration into a single layer of cells [2]. In addition, despite the extensive angiogenesis that takes place around the tumor, blood perfusion of the region is often erratic. Tumors often consist of a well-perfused outer region and a poorly perfused necrotic center. Hence, systemically administered drugs may reach the exterior layers but rarely reach the central area [1]. This poor perfusion is mainly due to the low movement of drugs from the blood vessels into the stroma of the tumor and hence to the cancerous cells. Although the endothelium of the blood vessels in the area of the tumor does appear to 'leak' more than normal cells, drugs are not taken up well into the stroma. This is thought to be due to the high interstitial hydrostatic pressure in the stroma or a diminished vascular pressure [3]. In addition, the host (i.e., the patient) tolerability to the high doses of chemotherapy that are often used must also be considered [4,5]. Furthermore,

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Article highlights.

- Implants for solid tumors that can be formulated to release a drug over a number of weeks, or even months, thus decreasing the need for the patient to return to the hospital for systemic treatment. This eliminates the need to take medication daily, improves patient acceptability and compliance and reduces the chances of systemic side effects due to the localized therapy exerted by the implant.
- Systemically administered drugs usually reach only the exterior layers and rarely the central area as tumors consist of a well-perfused outer region and poorly perfused necrotic center. This, therefore, necessitates the use of implants.
- The pH and temperature of the interstitial fluid that surrounds the tumor cells differ quite considerably from the pH of the interstitial fluid that surrounds the normal body cells making them (pH and temperature) act as stimuli at the site of the tumor that can be utilized to develop stimuli-sensitive implants.
- The delivery of small chemotherapeutics through gel-forming implants may not be an effective option as the time taken for a stable gel to form is quite long and this may lead to an initial burst effect. However, the use of dual-functional microspheres and delivery of immunomodulators to the tumor site hold the potential for the effective treatment of cancer through gel-forming implants. The rate of degradation of the implant, the permeability of the hydrogel matrix, the sol–gel transition temperature as well as the burst release rate depend on the molecular weight, composition and concentration of the polymers used in fabricating the implant.
- A two-phase drug release system was formulated where a portion of the drug was entrapped in the PEG hydrogel and some within liposomes that were then loaded into the hydrogel resulting in a quick initial release followed by a longer controlled release over several days. Likewise, Gliadel®, consisting of poly(carboxyphenoxypropane/sebacic acid) anhydride and carmustine, showed that patients who received the implant had a 6-month survival rate (50% greater than those who received a placebo implant), resulting in the approval of the implant by FDA (United States).
- Cylindrical biodegradable implants intended for the delivery of tamoxifen citrate to breast cancers were synthesized for placement into the affected area employing polyanhydride polymer (poly(sebacic acid-co-rinoleic-ester anhydride)) using the standard melt manufacturing method. The *in vitro* studies that were conducted thereafter revealed that the drug release would be complete after 72 days for the 10%-loaded implant and 100 days for the 20%-loaded implant. Unlike biodegradable implants, non-biodegradable implants necessitate their removal following the drug release. This is not likely to have high patient acceptability and also multiple operations may lead to further complications.

This box summarizes key points contained in the article.

the development of resistance by the cancer cells to the drug therapy is a further challenge to overcome [6,7].

While the development of novel drugs for the treatment of cancer continues, focus has shifted to more targeted delivery systems [8,9]. It has been shown that implanted devices offer solutions at many levels [10]. The conventional treatment methods for solid tumors often involve administration of high doses of chemotherapeutic agents [4,5]. Chemotherapeutic agents such as cytotoxic drugs are limited by toxicity to healthy body cells that surround the tumor cells [11,12]. It has been shown that employing an implant at the site of the tumor instead of an intravenously delivered chemotherapeutic agent may overcome this problem [11,13]. The chances of systemic side effects are much reduced due to the localized therapy exerted by the implant. Further, the implant can be formulated to release drug over a number of weeks or even months decreasing the need for the patient to return to the hospital for systemic treatment or eliminating the need to take medication daily and hence improving patient acceptability and compliance. Examples of implants that are currently available on the market and registered with Food and Drug Administration (FDA), USA, are Gliadel®, Zoladex® and Eligard® (**Table 1**).

The use of implanted devices in the treatment of cancer can be divided into two therapeutic applications. Either the implant is intended for the delivery of chemotherapeutics as treatment or the implant is intended for 'prophylaxis' following tumor resection [14]. The reason behind 'prophylactic' applications is that there is often recurrence of the tumor within 2 cm of the resected site [14]. Implants that are intended for the treatment of tumors are often *in situ* forming implants (ISFIs) [15]. These are injected into the body and form a solid implant at the tumor site often in response to a local stimulus. While an obvious advantage of such a system is that invasive surgery is not required and the system can be easily injected into the patient using conventional methods, a possible disadvantage is the use of a local stimulus for formation of the implant since patient variability in local tumor conditions may influence the formation of the implant. Implants used for prophylaxis are often pastes or preformed implants that are applied to or placed at the site during surgery [16,17]. These implants may be formed by a number of methods, including crosslinking and photopolymerization. An advantage of such a system is that all implants are of the same size and shape while a major disadvantage is that surgical implantation is required. This review provides a critical assessment of the various attempts that have been made in the novel treatment of tumors using polymeric implants that are intended for the delivery of drugs directly to the tumor sites.

2. *In situ* forming implants

ISFIs exist as solutions (sol) at room conditions and convert into a gel-like phase when exposed to a certain stimulus.

Table 1. Currently available implant systems for the treatment of cancer.

Product	Condition	Drug incorporated	Year of approval by FDA	Company
Zoladex®	Advanced prostate cancer	Goserelin	1996	AstraZeneca PLC
Gliadel®	Malignant human glioblastoma	BCNU	1997	Guilford Pharmaceuticals, Inc.
Eligard®	Advanced prostate cancer	Leuprolide acetate	2002	Atrix Labs, Inc.

Such a stimulus may be ionic or chemical crosslinking [18] or photopolymerization [19,20] or a local environmental stimulus such as pH, ionic strength or temperature [21]. There are also a number of ISFIs that are not based on stimuli-sensitive nature of the implant but rather form as a result of organic solvent diffusion [22]. **Figure 1** shows the main mechanisms of implant formation.

The stimuli-sensitive polymers that have been intensively investigated are those which respond to temperature change [23-26]. This is due to the slightly higher temperature of most tumors [27]. These polymers can form gels by two mechanisms. This is either through cooling after heating or on exceeding the lower critical solution temperature (LCST). Polymers that form gels by cooling after heating are said to have an upper critical solution temperature [28]. Polyethylene glycol–poly lactic acid (PEG–PLA) block co-polymers display such behavior [28]. The LCST group of polymers exists as solutions below the LCST but forms gels at temperatures exceeding the LCST [21,29-31]. An example of such a polymer is poly(*N*-isopropylacrylamide) (pNIPAAm). The biggest advantage of thermal gelation is that it occurs almost instantaneously following the polymer reaching the LCST while other methods of chemical gelation take a few minutes [32]. The lag phase between the formation of a solid from the liquid phase may give rise to an undesirable initial burst effect [33]. The pH of the interstitial fluid that surrounds the tumor cells is approximately 6.75. Thus, it differs quite considerably from the pH of the interstitial fluid that surrounds the normal body cells, which is approximately 7.23 [34]. This presents another stimulus at the site of the tumor that can be utilized to develop stimuli-sensitive implants [35].

As depicted in **Figure 1**, implants that form *in situ* may do so as a result of phase separation. In this case, the implant consists of a blend of a water-insoluble polymer and a water-miscible solvent. This is then injected into the tumor area, the solvent diffuses out of the solution causing the polymer to precipitate out and an *in situ* implant is formed [36]. The obvious downfall of such a system is the potential toxicity of the implant if the solvent used is toxic or not biocompatible. Eligard is a registered product that utilizes this technology for the delivery of leuprolide acetate. The polymer that has been employed is poly(D,L-lactide-co-glycolide) (PLG), also known as poly(D,L-lactic-co-glycolic acid) (PLGA) and the pharmaceutically acceptable solvent is *N*-methyl-2-pyrrolidone. The PLG co-polymer consists of a 75:25 ratio of D,L-lactide to glycolide. **Table 2** summarizes the attempts made by a number of researchers in the treatment of various tumors using ISFIs.

3. Implants based on natural polymeric sources

3.1 Chitosan

3.1.1 In situ *forming chitosan implants*

Of all natural stimuli-responsive polymers, chitosan has been studied extensively in terms of its use for the treatment of cancer [13,37-38]. The properties of chitosan, such as thermo- and pH-responsiveness as well as its biocompatibility, biodegradability and mucoadhesiveness, make chitosan an ideal candidate for implant formation. In addition, chitosan can be used at low concentrations for the purpose of decreasing the chances of toxic effects *in vivo* [13]. A further advantage is that the chitosan solutions can be easily sterilized [39]. Gelation of chitosan can be achieved through three mechanisms. First, in the presence of salts such as glycerophosphate [38] or dibasic sodium phosphate [40], chitosan can form a gel when exposed to body temperature. Second, the formation of a chitosan hydrogel can be triggered by UV irradiation as already documented by Ono *et al.* [41], who used azide-derived chitosan. Third, chitosan is highly soluble at low pH values and poorly soluble at high pH values, thus forming viscous gels at physiological pH [42].

Recently, Cho *et al.* [43] conjugated doxorubicin (DOX) to acrylated chitosan and Pluronic® in an attempt to obtain sustained release of the chemotherapeutic agent. The hydrogels formed as a result of both photo-crosslinking and thermoresponsiveness. As a result, the formed hydrogels were mechanically robust, and when compared with gels consisting of free DOX in a mixture of chitosan and Pluronic, the release from the DOX-conjugated–chitosan–Pluronic was significantly slower and over a longer period of time (40% DOX was released after 15 days) and the burst release that was established with the other hydrogel was not observed here. *In vivo* animal studies were conducted in athymic mice bearing human lung adenocarcinomas. The decrease in the tumor size appeared to mimic the obtained *in vitro* results as the size of the tumors decreased rapidly initially in mice receiving hydrogels containing free DOX (due to the burst release of drug) followed by an increase in tumor size indicating regrowth of the tumor due to the lack of further drug release. By contrast, mice receiving the DOX-conjugated–chitosan–Pluronic showed a slow decrease in the size of the tumor initially, but the tumor size at the end of 30 days was 22% less than the baseline tumor, indicating significant improvement. However, although the photo-initiator used was FDA approved, the use of photo-crosslinking can be

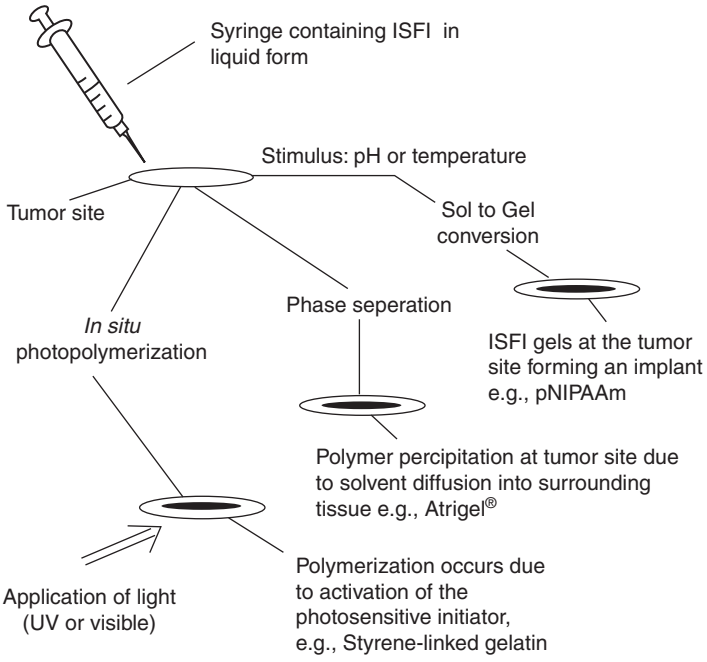

Figure 1. Schematic depicting some of the mechanisms of formation of implants *in situ*.
ISFI: *In situ* forming implant; pNIPAAm: Poly(*N*-isopropylacrylamide).

Table 2. Drug, type of tumor and the polymers employed for *in situ* forming implants.

Polymer used	Drug used	Model and tumor line	Ref.
Chitosan-GP	Paclitaxel	EMT-6 (mouse mammary tumor)	[104]
Chitosan-GP	DOX and vaccinia viral vaccine	Murine TC-1 (cervical cancer)	[33]
Chitosan-GP	Camptothecin	RIF-1 (mouse fibroblastoma)	[12]
Photo-crosslinkable Chitosan	Paclitaxel	3LL (Lewis lung tumor)	[34]
Acrylated Chitosan-Poloxamer®	Conjugated DOX	A549 (Human Lung adenocarcinoma)	[35]
Albumin-TAD	DOX	WiDr (human colon carcinoma)	[43]
Collagen–ephedrine	5-FU/DOX/cisplatin	BxPC-3 and PANC-1 (human pancreatic cancer)	[36]
pNIPAAm-co-AA	-	SKOV-3 (human ovarian tumor)	[104]
PEG	Topotecan	MAT BIII (breast cancer)	[104]
Atrigel®	Cisplatin	T4N2aMO (squamous carcinoma of supraglottic larynx)	[74]
Pluronic® F127/Poloxamer 407	Paclitaxel	B16F1 (murine melanoma)	[39]

5-FU: 5-fluorouracil; AA: Acrylic acid; DOX: Doxorubicin; GP: Glycerophosphate; PEG: Polyethylene glycol; TAD: Tartaric acid derivative.

detrimental to the drug and can lead to degradation of the drug and must be performed for the minimum amount of time [43]. This can potentially be a drawback to clinical application of the formulation as alteration of the required time for irradiation may lead to different release profiles.

3.1.2 Chitosan preformed implants

Chitosan egg-Phosphatidyl (C-eP) implants were investigated by Ho *et al.* [38] as well as Soo *et al.* [44]. Both implants were intended for the local treatment of ovarian cancer and contained paclitaxel. Ho *et al.* [38] implants demonstrated *in vitro* zero-order drug release over a period of 5 days. Soo *et al.* [44] loaded the C-eP implant with PLA-b–PEG/PLA nanoparticles loaded with paclitaxel. They subsequently investigated the *in vitro* behavior of the implant in ascites fluid, of which a build-up often occurs in ovarian cancer. Furthermore, the effect of the implant in mice was investigated. The *in vitro* and *in vivo* results correlated well and the release of paclitaxel *in vivo* was over a period of 4 weeks [44]. No local signs of toxicity were observed. Ho *et al.* [45] investigated the effects of the implant on multi-drug resistance. The effect of the sustained release of paclitaxel from the implant was compared with the effect of intermittent intraperitoneal dosing with paclitaxel formulated in Cremophor EL®. The determination of multi-drug

resistance was carried out *in vitro* on cancer cell lines and *in vivo* on tumor-bearing mice. After 14 days, cells that received paclitaxel-Cremophor EL showed a twofold increase in mRNA levels, an effect that was not observed with cells receiving the implanted device [45]. In addition, there was also a significant induction of efflux activity of the drug transporter, P-glycoprotein, by the paclitaxel-Cremophor EL dosing, which was not seen with the implanted system. This indicates that the sustained delivery of drugs may be beneficial in reducing the development of multi-drug resistance.

In another study, Vassileva *et al.* [12] compared the overall toxicity as well as the antitumor effects of a paclitaxel-loaded C-eP implant with paclitaxel formulated in Cremophor EL. These studies revealed that the Cremophor EL-paclitaxel formulation was associated with significant toxicity, lethality, abnormal peritoneal organ morphology and hepatic inflammation, whereas mice receiving the implanted device encountered no such problems [12]. In addition, the maximum tolerable dose was much higher for the implant (up to 280 mg/kg/week) when compared with the Cremophor EL-paclitaxel formulation (20 mg/kg/week) [12]. A drug loading of 60 mg/kg in the implant had an enhanced cytotoxic effect compared with the same dose administered intraperitoneally as the Cremophor EL-paclitaxel formulation indicating the potential of this implant system as a drug delivery device.

3.2 Alginate

3.2.1 In situ *forming alginate implants*

Alginate is a polysaccharide derived from seaweed. It is essentially a block co-polymer consisting of β-D-mannuronic and α-L-guluronic acid, which gels in the presence of divalent cations such as calcium [46]. The polymer rapidly forms a gel by crosslinking in the presence of calcium ions and this gelation mechanism has been utilized by Hori *et al.* (2008) to develop an *in situ* forming implant. Calcium ions were entrapped within alginate microspheres and dispersed in an alginate solution. On injecting this formulation into the body, calcium ions were released from the microspheres and assisted by the calcium concentration *in vivo*; the alginate solution took 60 min to form a stable gel [47]. The implant was intended for the delivery of immunomodulators in the treatment of cancer. The soluble factor (IL2) was incorporated into the implant with ease by simple mixing with the alginate solution. Hori *et al.* [47] also investigated the feasibility of attaching immunomodulatory oligonucleotides to the microspheres for delivery purposes. The IL2 was 95% bioactive after delivery via the alginic implant indicating the feasibility of this drug delivery system. Approximately 80% of the oligonucleotides were loaded to the microspheres and the release was slow (approximately 20% over one week). This study highlights the possibility of dual-functional microspheres and the potential for the effective treatment of cancer through delivery of immunomodulators to the tumor site. However, the delivery of other smaller chemotherapeutics may not be as effective as the time taken for a stable gel to form is quite lengthy and this may lead to an initial burst effect [47]. With regard to the use of calcium-containing microspheres, the other concern is that the particles must not allow leaching of the calcium into the solution and cause premature gelation of the system as this will limit the shelf life of the formulation or require reconstitution prior to administration of the system [48].

3.2.2 *Preformed alginate implants*

Bouhadir *et al.* [49] made use of an alternate method of gelation by oxidizing the alginate to form lower molecular weight oligomers and then crosslinked them using adipic dihydrazide. The alginate-based implant was loaded separately with three drugs in different ways in order to demonstrate the different release profiles that could be obtained from this hydrogel. The three cytotoxics that were utilized were methotrexate (MTX), doxorubicin (DOX) and mitoxantrone [49]. **Figure 2** depicts the loading mechanisms that were utilized for each drug as well as the mechanisms of release of the chemotherapeutic agents.

MTX was released over 2 days, but this was extended to 7 days with a higher concentration of the covalent crosslinker, adipic dihydrazide [49]. The reason for the prolonged release was the reduced swelling of the hydrogel that occurred with the higher concentration of the crosslinking agent, resulting in a slower diffusion-based drug release. The release of doxorubicin was over a period of days to weeks depending on the concentration of adipic dihydrazide. Likewise, the release of mitoxantrone was substantially controlled on increasing the concentration of adipic dihydrazide. At high concentrations of adipic dihydrazide, the release of mitoxantrone was only 10% over a period of 22 days [50]. Thus, this system exemplifies that a number of drugs may be loaded into the hydrogel depending on the chemical nature of the drug. This allows specific loading for specific drugs and allows the implant to have many uses. Bouhadir *et al.* [49] also investigated the release of the three drugs when loaded simultaneously to determine whether the implant had potential to be used to deliver multiple drugs. MTX was released completely over 9 days, whereas DOX and mitoxantrone were released over 17 days. More than 20% of DOX was released over the first 13 days while majority of the mitoxantrone was released in the last 4 days. This sequential release of drug shows that the implant may be used to deliver multiple drugs that may prove useful in the treatment of drug-resistant tumors [49].

3.3 Gelatin

3.3.1 In situ *forming gelatin implants*

Gelatin is derived from naturally occurring collagen and exhibits thermoreversible behavior. At temperatures below 25°C, the polymer forms a gel while above 30°C it reverts back to solution form [22]. This is not a favorable behavior for pharmaceutical preparations and, therefore, various attempts have been made to modify the temperatures of gelation-containing preparations to a more physiologically acceptable temperature range [22,51]. Gelatin is also a

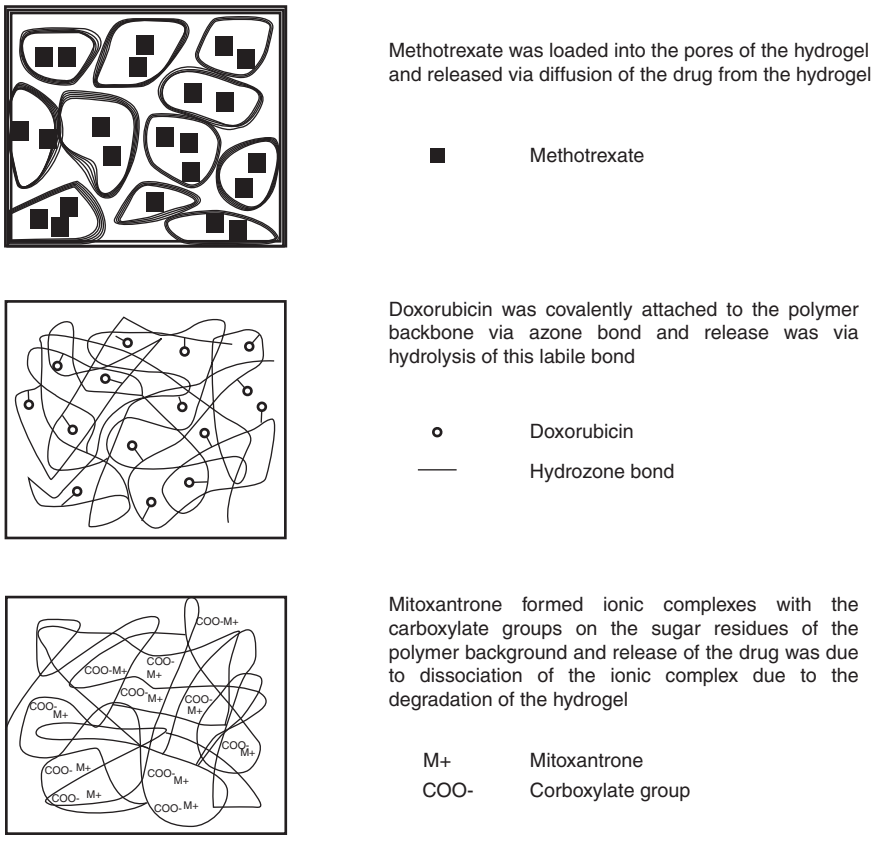

Figure 2. Schematic showing drug loading and release of the drugs from the modified alginate hydrogel.
Adapted from data in Bouhadir *et al.* [49].

pH-responsive polymer [52]. *In situ* forming gelatin hydrogels for postoperative chemotherapy have been formulated by Okino and co-workers [53]. Styrene-derived gelatin together with the initiator camphorquinone was utilized and polymerization in the presence of visible light irradiation occurred. This *in situ* forming hydrogel was intended for the delivery of drug to newly resected tumor sites. The formation of the hydrogel was investigated on the surface of rat liver, and despite the potential toxicity of the free radicals produced by the initiator, the *in vivo* application of the hydrogel showed no necrotic damage to the hepatocytes [53]. The mechanism of formation of these hydrogels is due to photopolymerization and is not dependent on the temperature sensitivity of the gelatin. However, due to the application of UV light that is required, this formulation can be used only during surgical resection of the tumor or for tumors occurring on the skin.

3.3.2 *Preformed gelatin implants*

Liu *et al.* [54] attempted to develop gelatin hydrogels for the treatment of cancer using a method previously developed by Tabata and Ikada [54], Kang *et al.* [55] and Hong *et al.* [56] for producing gelatin hydrogels meant for purposes other than cancer treatment. The hydrogels contained interleukin 12 (IL12) and were tested on colon carcinoma cells implanted subcutaneously into the backs of rats. The effect of these hydrogels on the tumors was evaluated and the cytotoxicity of the IL12 was found to be higher in the subcutaneously administered gelatin hydrogel formulation than in the subcutaneously administered free IL12 [54]. Kinoshi *et al.* [57] have also studied the release of chemotherapeutic agents namely cisplatin and Adriamycin from preformed gelatin hydrogels intended for implantation following tumor resection. They established that the release of the incorporated cisplatin was not via diffusion but rather via a function of degradation of the hydrogel [57]. In 2005, the same group investigated the release of cisplatin and Adriamycin from the hydrogel. Adriamycin was released at a quicker rate than the cisplatin and the combination showed a synergistic inhibition of tumor growth *in vivo* [57]. In addition, when Adriamycin was injected percutaneously into the mice as a control, scar formation was noted at the injection site. Contrary to this, the Adriamycin-loaded hydrogel did not induce such an effect in the mice [57]. The authors postulated that the lack of scar formation was due to the slow release of the drug from the hydrogel.

3.4 Albumin

3.4.1 In situ *forming albumin implants*

Human serum albumin has been used to produce an *in situ* forming hydrogel, which was combined with a tartaric acid

derivative (TAD) [58]. TAD is a tissue adhesive that has the advantage of maintaining the position of the implant in the desired site [58]. The release of doxorubicin from this hydrogel was investigated and *in vitro* studies showed an initial burst effect due to surface drug followed by release from within the gel for up to 100 h (4 days). A follow-up *in vivo* study by Kakinoki and Taguchi [59] tested the formulation in rats bearing the human colon carcinoma. They found that the size of tumors in rats had decreased to a greater extent in comparison with the tumors treated with free drug or the control. However, the drug was detectable only for 3 days, as expected from the *in vitro* results [59].

3.5 Collagen

3.5.1 In situ *forming collagen implants*

Collagen is a naturally occurring polysaccharide from which gelatin is derived. An injectable formulation containing collagen and ephedrine together with cisplatin as a drug registered as Intradose® (Matrix Pharmaceuticals) has provided some promising results in treating hepatocellular carcinoma [60,61]. Ephedrine serves to constrict blood vessels in the affected area thereby reducing the diffusion and hence loss of drug from the area. The delivery of these chemotherapeutic agents to tumors of the head and neck, trunk and liver for the treatment of hepatocellular carcinoma has been shown to be successful in humans [58,60]. In addition, the collagen/ephedrine combined with cisplatin has also demonstrated efficacy in obstructive esophogeal cancer in humans [62] while the gel in combination with 5-fluorouracil has proven good efficacy in pancreatic cancer of rats [63]. Collagen-poly(HEMA) (hydroxyethylmethacrylate) hydrogels were synthesized by Jeyanthi and Rao [50]. The drug release from the gels was found to be independent of time and followed zero-order kinetics. The maximum amount of drug release from the gels that followed zero-order kinetics was 98% over 10 days for 5-fluorouracil [50]. The gels containing mitomycin C and bleomycin had zero-order release of 52% over 12 days and 74% over 11 days, respectively. This is longer than the release profiles obtained for collagen and ephedrine indicating that this formulation is superior to Intradose. However, the drug release is still for a short period of time only.

4. Synthetic, biodegradable mono-polymer and co-polymers as implant sources

4.1 Poly(*N*-isopropylacrylamide)

With the increasing interest in the polymers that are stimuli-sensitive, otherwise referred to as 'smart polymers', a number of studies have focused on pNIPAAm due to its thermosensitivity [10,64]. The polymer exists as a solution below its LCST and gels at temperatures above LCST. The LCST of pNIPAAm is 32°C [65]. This temperature can easily be increased to body temperature or the temperature of a tumor by co-polymerization of pNIPAAm with hydrophilic polymers [66]. However, the problem with pNIPAAm is its lack of biodegradability [67]. In an effort to overcome this problem as well as to improve the LCST of the hydrogel, researchers have polymerized pNIPAAm with various other polymers (often hydrophilic in nature) such as HEMA [65], acrylic acid [67,68], dextran–allylisocyanate and dextran–maleic anhydride [69], as well as gelatin and hyaluronic acid [27]. Co-polymerization with polymers such as propylacrylic acid and poly(2-dimethylamino) ethyl methacrylate leads to the formation of polymers that are pH- and thermoresponsive [70-72]. Although most of these polymeric hydrogels were not synthesized specifically for the treatment of cancer, they have shown promising potential for use in such applications.

4.2 *In situ* forming Atrigel® implants

Atrigel® (Atrix Laboratories, Inc) consists of biodegradable polymers such as PLA or poly(lactic-co-glycolic acid) (PLGA) together with a biocompatible hydrophilic solvent such as *N*-methyl-2-pyrrollidone. The solvent renders the polymer soluble, and when the system is injected into the body, the solvent dissipates into the surrounding tissue leaving behind a formed implant. This technology was initially designed for the treatment of periodontal disease [10]. In 2000, Ravivarapu *et al.* [36] developed a formulation of Atrigel loaded with leuprolide acetate and showed the ability of the implant to suppress serum testosterone for a 3-month period. A 6-month formulation has since been developed and Atrigel is now used to deliver leuprolide acetate for the treatment of advanced prostate cancer in the product known as Eligard. One of the problems facing the ISFIs is the quick initial release of drug [36]. In order to overcome this problem, Astaneh *et al.* [73] created a zinc–leuprolide complex, which was loaded into a PLGA *in situ* forming implant. This implant was compared with Eligard showing that the use of the zinc complex reduced the burst period slightly and also resulted in a continuous zero-order release profile following the burst phase. Comparably, Eligard showed a very rapid initial release of the drug (almost 40% over 24 h) [73]. Atrigel has also been loaded with cisplatin for the potential treatment of head and neck cancers [74]. The efficacy of this system was investigated in a chimeric mouse model carrying the human head and neck squamous cell carcinoma [74]. Drug release was 80% at the seventh day. The ALZA Corporation, Inc., has also designed ISFIs that are very similar to the Atrigel technology (except for the solvents used), but they have not yet been investigated for use as anticancer formulations.

4.3 *In situ* forming poly(organophosphazene) implants

Recently Al-Abd *et al.* [75] investigated the release of DOX from a poly(organophosphazene) hydrogel *in vitro* and in rats with human gastric tumor xenografts. Release of the drug was over 5 weeks and the hydrogel was retained for 7 weeks. The concentration of polymer used was also relatively low (10% w/v). This group of polymers has shown a great potential for the development of an ideal implant system for cancer chemotherapy due to the ease with which they can

be modified to serve the purpose of the respective drug delivery system [75].

4.4 *In situ* forming poly(ε-caprolactone fumarate) implants

Poly(ε-caprolactone fumarate) is a relatively new photo-crosslinkable polymer that possesses both biocompatibility and good fluidity making it an ideal candidate for the development of an injectable ISFI [76]. This polymer was used by Sharifi *et al.* [76] to develop an ISFI for the delivery of tamoxifen citrate to breast cancer patients. *In vitro* studies conducted showed extremely slow release of the drug (less than 5% of drug after 400 h) and 40 – 60% of MCF-7 (breast cancer) cells incubated with the formulation were killed [76]. This formulation has potential for further development and *in vivo* work should be completed.

4.5 Polyethylene glycol

4.5.1 In situ *forming PEG implants*

Qiu *et al.* [77] synthesized a PEG-based co-polymer that was capable of *in situ* gelling. This was achieved as a result of chemical crosslinking of the multiple thiol groups that lie on the polymer backbone. However, the polymer as well as the crosslinking agent must be injected into the area [77]. Although hydrogel formation was achieved *in vivo*, the loaded hydrophilic anticancer drug, topotecan, was released very rapidly, probably due to the large pores in the hydrogel [77]. As a result, Lalloo *et al.* [78] formulated a two-phase drug release system. A portion of the drug was entrapped in the PEG hydrogel and some within liposomes, which were then loaded into the hydrogel. The drug release profile showed a quick initial release followed by a longer controlled release over several days [78]. Tumor masses (MAT BIII breast cancer cells) in rats were also significantly reduced with the use of this hydrogel [78].

4.5.2 *Preformed PEG implants*

Tauro *et al.* [79] proposed a PEG hydrogel system for the treatment of glioblastoma multiforme. Highly invasive tumors are often associated with higher amounts of matrix metalloproteases (MMPs) in the area surrounding the tumor. These proteins cause tumor invasion as well as neovascularization [77]. The developed system proposed the use of these proteases to control the release of the drug from the hydrogel matrix. The drug (cisplatin) was linked to the polymer backbone by means of peptide linkages. As the MMPs diffused through the hydrogel, the peptide bonds were cleaved by the MMPs and as the result the drug was released into the area surrounding the tumor. This allowed controlled release of the drug at the site of the tumor. The controlled release effect depended on the amount of MMPs present and hence the dose of drug delivered corresponded to the invasiveness of the tumor [79].

4.6 Preformed implants composed of PLG

PLGA is a well-known polymer, the use of which in the medical field is well documented. In the treatment of cancer, recent advances have been made into the use of this polymer as a foam or a nanofiber disc intended to be inserted intra- or peritumorally [80,81]. Lee *et al.* [80] formulated a micro-porous PLGA foam intended for the delivery of drug to the brain. The foams were loaded with paclitaxel and showed *in vitro* release of up to 8 weeks. The foams were also placed intracranially in healthy mice and assessment after 28 days revealed that therapeutic amounts of paclitaxel were found throughout the mouse brain [81]. Nanofiber discs were prepared by Ranganath and workers [81] and loaded with paclitaxel and implanted into the brains of mice bearing human glioblastoma. Paclitaxel was also found to have diffused from the disc to penetrate a large area of the brain and that the concentrations of paclitaxel were maintained for 42 days, which exceeds the release obtained by previous researchers [81]. This formulation seems extremely promising for further development.

4.7 Preformed polyanhydride polymeric implants

The most successful of the preformed implants are the Gliadel implants intended for the treatment of malignant human glioma [82-85]. These implants have been developed with the intention of delivering anticancer drugs following at least partial resection of the tumor (**Figure 3**) [86]. A study that was conducted by Brem *et al.* [82] using Gliadel showed that patients who received the implant containing an anticancer drug had a 6-month survival rate, which is 50% greater than those who received a placebo implant. In 1996, the FDA (USA) approved this implant. However, the implant has been shown to prolong the lives of patients only by 1 year [83,85]. Gliadel consists of poly(carboxyphenoxypropane/sebacic acid) anhydride, 20:80 (CPP–SA) (Biodel®) and the drug, carmustine (BCNU) co-dissolved in methylene chloride and spray dried into microspheres. The microspheres are then compressed into discs of dimensions 1.4 cm in diameter and 1.0 mm in thickness. The discs are sterilized by gamma irradiation.

Following the success of the Gliadel implant, Gopferich [87] aimed to develop an implant for release of at least two drugs, the release of one drug lasting 2 weeks and the second drug being released over the next week. This would decrease the resistance of cancer cells as they would be exposed to a number of different drugs over a certain period of time [87]. A surface-eroding polymer, poly(1,3-bis[*p*-carboxyphenoxy] propane-co-sebacic acid) (p(CPP–SA)), was used and two drugs were loaded into the implant. One drug was in the 'core' and the other was in the 'mantle'. Drug release from this implant was, therefore, a function of the erosion of the polymer. However, it was found that the release of the second drug occurred prematurely [87]. Thus, instead of increasing the thickness of the mantle, which would have caused the implant to be too large, a slow-eroding polymer namely poly (D,L-lactic acid) was used. A four-layer device was formulated as depicted in **Figure 4**. With this, implant release periods of up to 4 weeks were obtained [87].

Although the implant devised by Gopferich [87] was proven to allow release of drug from the core after 2 weeks,

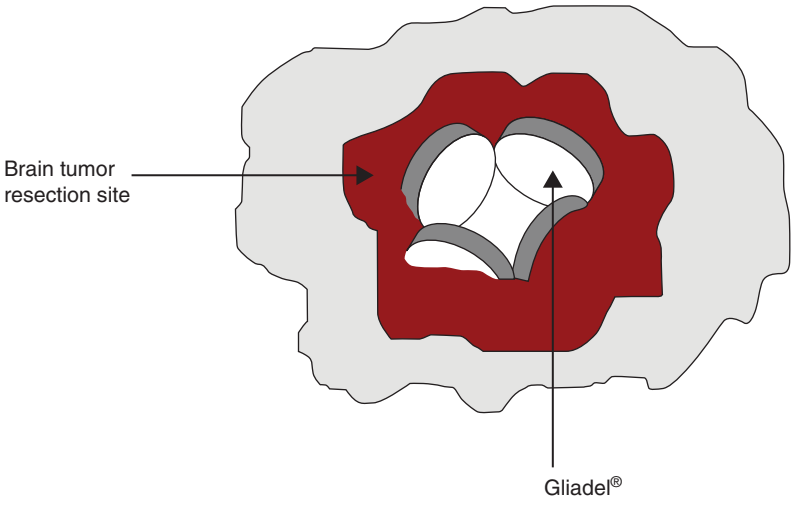

Figure 3. Implantation of Gliadel® at tumor resection site.
Adapted from Jain *et al.* [86].

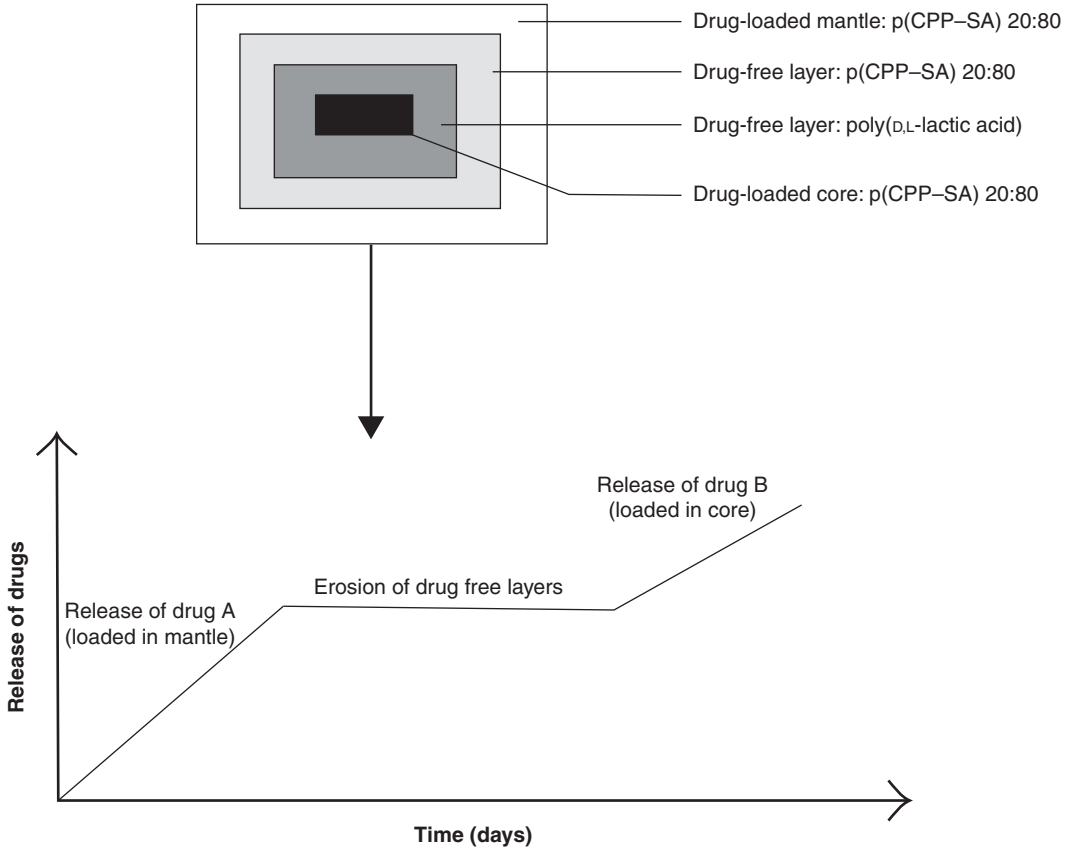

Figure 4. Schematic depicting a longitudinal section through the disc-shaped implant with the loading of two drugs and ideal release pattern clearly illustrated.
Adapted from data in Gopferich, [87].
CPP: Carboxyphenoxypropane; SA: Sebacic acid.

Vogelhuber *et al.* [88] attempted to create an implant that had a greater lag phase before the release of the drug. This was meant to allow the implant to have more applications as a drug delivery system. Furthermore, this implant would also address the problem of the low survival rate of patients with human glioblastoma despite therapy with Gliadel, as this implant would be capable of delivering a number of drugs to the tumor region in a controlled manner. This attempt registered some promising results [88].

The greatest challenge that was faced during the attempt to improve the implant designed by Gopferich [87] was the size of the implant. The implant had dimensions of 8 mm diameter and 4 mm height and this made the *in vivo* testing in a rat model impossible [88]. As a result Vogelhuber *et al.* [88] investigated the drug release from an implant consisting two layers one containing the drug (drug-loaded core) and the other containing no drug (drug-free mantle) (**Figure 5**). This reduced the size of the implant to a diameter of 2 mm and a height of 1.8 mm [88].

The mantle consisted of either PLA or PLGA while the core consisted of polyanhydride, p(CPP: SA) 20:80 loaded with the drug. The effect of tempering the implant in silicon oil was also investigated. Delayed onset of drug release with this implant was achieved with the release being delayed by 10 days post-implantation when $PLGA50_{17}$ was used and by 58 days when $PLA50_{30}$ formed the mantle layer [88]. Furthermore, it was shown that tempering of the implant allowed for erosion and drug release to be controlled by the type of polymer used and the effects of pores and other defects in the polymer mantle affected the release of the drug far more than the polymer erosion [88].

More recently, Hiremath *et al.* [71] have synthesized cylindrical biodegradable implants intended for the delivery of tamoxifen citrate to breast cancers by the placement of the implant into the affected area. The employed polyanhydride polymer was poly(sebacic acid-co-rinoleic-ester anhydride) in a ratio of 70:30 w/w (poly(SA–RA) 70:30 w/w). The implants were prepared using the standard melt manufacturing method and *in vitro* studies revealed that the release of drug from 10- and 20%-loaded implants was 42.36 and 62.60% after 30 days, indicating prolonged delivery of the drug to the tumor. It was also estimated that drug release would be complete after 72 days for the 10%-loaded implant and 100 days for the 20%-loaded implant [71].

5. Synthetic, biodegradable triblock polymers used for implants

5.1 Triblock copolymer from PLG and PEG (PLG–PEG–PLG)

ReGel® (MacroMed) is a triblock polymer (ABA or BAB) whereby the A block is PLG and the B block is PEG. The triblock polymer is water soluble at room temperature but insoluble at body temperature (37°C) [14]. It has been established that due to its insoluble gel state *in vivo*, the implant can remain intact at the site of application for at least 1 month [15]. The implant is also biodegradable. The rate of degradation of the polymer, the permeability of the matrix of the hydrogel, the sol–gel transition temperature as well as the burst release rate depend on the molecular weight of the polymers and the ratio of PLGA to PEG [15]. In addition, the above-mentioned polymer characteristics are also influenced by the ratio of lactide:glycolide as well as the concentration of these elements and the end group of the PLGA polymer component. Formulations of ReGel-containing paclitaxel have been trademarked OncoGel®. This triblock polymer has also been used to develop a drug delivery system for the delivery of testosterone [71] and the delivery of interleukin 2 or cancer immunotherapy and this formulation is trademarked Cytoryn® [89]. More recently, the polymer has been used in a formulation containing PEGylated camptothecin [90]. The purpose of adding a PEG group to the camptothecin was to enhance the release of the drug in a controlled manner. This was achieved and, in addition, the solubility of the drug was also enhanced [90]. Furthermore, the sol–gel transition temperature was decreased and the viscosity of the implant with the PEGylated drug was higher than that of the implant without the PEGylated drug. Ostensibly, this will improve the implants' behavior *in situ*.

5.2 Poloxamers/Pluronics®

These are triblock co-polymers consisting of poly(ethylene oxide)-b–poly(propylene oxide)-b–poly(ethylene oxide) (PEO–PPO–PEO). Poloxamers have also been investigated as potential implant-forming systems due to their thermoreversible nature [71]. Sol to gel transitions occur at 5 – 30°C and gel to sol transitions at 35 – 50oC [15]. Alteration of the molecular weights, composition and concentration of the polymer results in a change in the sol to gel transition (gelation) temperature of the polymer [21]. However, the actual formation of the gel phase is poorly understood [21]. Pluronic products include Pluronic F127, P85 and L61. The cytotoxicity of these polymers has been investigated and the study revealed that F127 had no cytotoxic potential while both P85 and L61 decreased the growth of the tumor cells [91]. Amiji *et al.* [92] created a paclitaxel-containing implant using Pluronic F127, which was administered to melanoma-bearing mice. The results were promising as 91% of rats survived up to 15 days post-implantation compared with 58% in the control group [21]. This study seems to be an exception as other formulations containing Pluronics rarely released drugs for more than a period of a few days [36].

More recently, Bae and co-workers (2011) have developed a conjugated linoleic acid-coupled poloxamer (Pluronic F127) (Plu-CLA) [93]. Utilization of this thermoresponsive polymer in the delivery of 5-fluorouracil (a drug with a short half-life) led to significant reduction in metastatic masses. In addition, the implant itself (Plu-CLA) was shown to have tumor inhibitory properties [93]. The Plu-CLA was injected intraperitoneally and in this way the drug was able to reach the hepatic metastatic

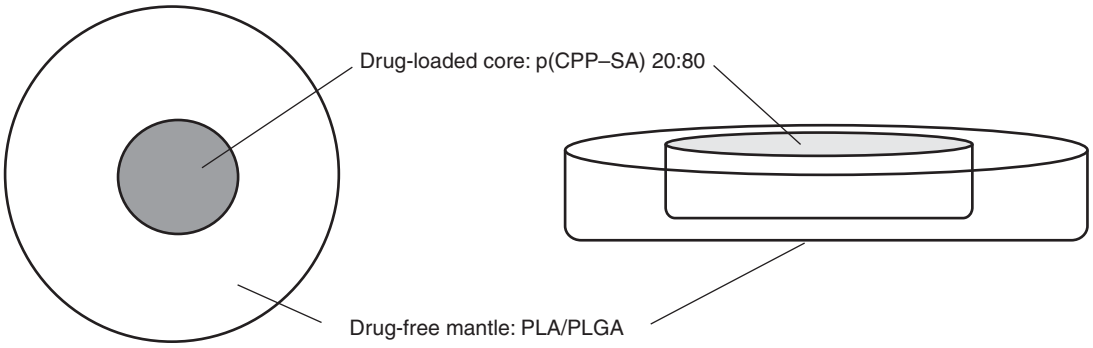

Figure 5. Schematic depicting a cross-section through the implant.
Adapted from data in Vogelhuber *et al.* [88].
CPP: Carboxyphenoxypropane; PLA: Poly lactic acid; PLGA: Poly(lactic-co-glycolic acid); SA: Sebacic acid.

masses. The implant significantly reduced the metastatic score in treated animals when compared with animals receiving intraperitoneal injections of 5-fluorouracil. As the treatment of metastases is usually considered to be a drawback for the treatment of solid tumors using an implant *in situ* [94], the intraperitoneal use of the ISFI in addition to intratumoral delivery of drug via an ISFI for the treatment of metastatic masses is one that should be researched more thoroughly.

5.3 Triblock polymer composed of poly (ϵ-caprolactone) and PEG

A novel thermosensitive polymer composed of poly(ε-caprolactone) and PEG was synthesized [95] (Gong *et al.*, 2009). The implant-forming system showed promise in the local delivery of anesthetic agents [95] and was subsequently used in combination with drug-loaded nanoparticles for the delivery of an extremely hydrophobic chemotherapeutic (Honokiol) in the treatment of malignant pleural effusion [96]. The entrapment of the drug within the nanoparticles, which were then suspended in the *in situ* forming hydrogel, slowed the release of the entrapped drug considerably, as expected, and also allowed easy dispersion of the hydrophobic drug and a reduction in side effects. The formulation is promising as the *in vivo* work showed a definite improvement as well as the use of polymers that are biocompatible.

6. Synthetic non-biodegradable polymers

6.1 Silicone

The use of silicone in the formulation of implants has not been investigated extensively as silicone is not biodegradable [97]. He *et al.* [97] investigated the effects of silastic implants loaded with 5-fluorouracil (5FU) – a drug that has an extremely short half-life (10 min). The dimensions of the implants were 2 mm (outer diameter), 0.5 mm (wall thickness) and 25 mm in length. Each pellet contained 13.2 mg of 5FU. These implants were surgically implanted into the livers of Wistar rats bearing Walker-256 carcinosarcoma. When the implant was placed in the left lobe of the liver at the site where the tumor had been implanted, the tumor inhibition was found to be as high as 96.3%, with one of the animals in this group surviving the entire length of the experiment and no viable tumor was detected in this animal [97]. Biodistribution results showed a high concentration of 5FU in the tissues adjacent to the area in which the implant was placed but the amount of 5FU found in other tissues was lower, indicating a lower toxicity of this implant than when administered parenterally. In addition, 5FU was found in the blood for 1 – 8 weeks, despite its short half-life, indicating that there was a controlled release of the drug from the implant [97]. Pathological studies were also carried out on the tissue surrounding the implant and no fibrous capsule was found around the implant, indicating the lack of immunological attack on the implant [97]. While these results seem to indicate the feasibility of the system for cancer treatment, the lack of biodegradability potential in silicone cannot be ignored. Non-biodegradation necessitates the removal of the implant following the drug release. This is not likely to have high patient acceptability and also multiple operations may lead to further complications.

7. Surgical pastes

Most of the pastes developed for use in cancer have been formulated prior to 2005 and include those developed by Winternitz *et al.* [98], Jackson *et al.* [14,99] and Dordunoo *et al.* [100]. Dordunoo *et al.* [100] investigated the impact of a paclitaxel-containing surgical paste composed of poly(caprolactone). This polymer has a biodegradation lifetime of between 6 and 9 months, making it an ideal polymer for sustained drug release. The paste was to be delivered by heating the paste to temperatures of between 50 and 55°C and delivering it via injection or application to the tumor area following the resection of the tumor. This paste showed tumor regression in 63% of the mice treated [100]. The same polymer and drug were used by Hunter *et al.* [101]. The application of this paste was carried out on a murine tumor model. The results indicated that the implant delayed the regrowth of tumors that were not resected

entirely [101]. Blends of poly(ε-caprolactone) (PCL) and methoxypolyethylene glycol were also investigated by Winternitz *et al.* [98], obtaining drug release over a number of days.

A paclitaxel-containing paste formulation was also prepared by Jackson *et al.* [14] by dissolving the drug in a combination of biodegradable triblock co-polymer of a random co-polymer of D,L-lactide and PCL with PEG (PLC–PEG–PLC) blended with methoxypoly(ethylene glycol) in a 40:60 ratio. This formulation was intended for the treatment of non-metastatic human tumors and was tested in the rat model [14]. In 2004, Jackson *et al.* [99] formulated another paste consisting of a triblock polymer also with paclitaxel as the anticancer drug. The triblock used was poly(D,L-lactide-co-caprolactone)-block–polyethylene glycol-block–poly(D,L-lactide-co-caprolactone) (PLC–PEG–PLC) or triblock blended with a low-molecular weight polymer methoxypolyethylene glycol (MePEG) [97]. Jackson *et al.* [99] also prepared a paste of taxol using PCL (poly(ε-caprolactone) as a polymer. All these formulations showed controlled release of the incorporated drug over a number of days.

8. Other implants

Numerous other implants also exist, which are intended for the treatment of cancer but cannot be implanted locally. These include Zoladex (AstraZeneca PLC), which consists of PLGA rods containing goserelin, a leutinizing hormone-releasing hormone analog that is injected subcutaneously and is used in the treatment of advanced prostate cancer [102]. Results from clinical studies have revealed that the implant may be effective over at least 14 weeks when injected into the upper arm of patients [102]. An implant of a gonadotropin-releasing hormone agonist namely histrelin (administered subdermally) has also shown efficacy in the treatment of prostate cancer [103]. Implanted devices that carry radiopharmaceuticals to the site of the tumor have also been synthesized [79].

9. Conclusions

The use of implants in cancer chemotherapy has been researched extensively but the ideal system has not been developed as yet. Thus far, a good number of *in vivo* animal studies have been conducted on various *in situ* forming and preformed implants, as summarized in **Tables 2** and **3**. Such studies must be pursued further in the interest of determining the long-term safety of these implants. As the drug therapy of cancer evolves to encompass immunomodulators and other such proteins, delivery systems for these molecules must be developed. The use of implants at tumor sites to deliver these molecules may be beneficial due to limited systemic toxicity, as well as the 'protection' imposed on the proteins. Research in this field must continue not only to overcome the obstacles outlined above but also to discover new uses for these systems. Furthermore, the development of such implants would have far-reaching consequences as these systems would then have the potential for application in other fields such as gene delivery and hormonal therapies.

10. Expert opinion

Considering the current intravenous and oral systems that are mainly used in the treatment of solid tumors, the necessity for an implantable system that is able to deliver high doses of chemotherapeutics to the tumor site, over prolonged periods with relatively few side effects on normal tissue, cannot be denied. Furthermore, drug penetration into solid tumors is hindered due to the low blood perfusion in the necrotic center of the three-dimensional cancerous tissue thus requiring the implantation of drug delivery devices in the form of minimally invasive injectable. ISFIs employing different environmental cues such as temperature, pH and phase separation as stimulus or in the form of preformed implants are a potential strategy in this regard. As summarized in this review, numerous attempts using natural and synthesized polymers have been made to formulate these devices.

The ideal characteristics of an ideal polymer for an implant include responsiveness to a stimuli such as temperature, pH (~ 6.75) or light (photopolymerizable), biocompatibility, biodegradability, low cytotoxicity, mucoadhesivity, low concentration effectiveness, easily sterilizable, long storage capability, the ability to form mechanically robust hydrogels, oxidizable to form lower molecular weight oligomers, easily modifiable and, lastly, high LCST. An appropriately designed and defined implant should provide a sustained delivery of drugs (beneficial in reducing the development of multi-drug resistance), retention of activity of the bioactive molecules such as IL2, controlled rate of degradation of the polymer, desirable permeability of the hydrogel matrix, desirable sol–gel transition temperature and finally feasibility of the drug delivery system, which also depends on the chemical nature of the drug. The most commonly cited problems with the polymer/polymeric implant include i) quick burst release or release of the bioactive at a lower pH (pH 5 – 6); ii) negatively charged entities, which may interact with bioactive components once in the body; and iii) formation of turbid gels thus necessitating the need of stabilizers during lyophilization. Quite often, this results in the formation of hydrogels with very low strength, which are also expensive to manufacture. Apart from these problems, there are some technical concerns that need to be addressed from fabrication point of view including an increase in tumor size indicating regrowth of the tumor due to the lack of drug release up to appropriate duration. The use of photo-crosslinking can as well be detrimental to the drug, for example, leading to degradation of the drug. In addition, smaller chemotherapeutics may not be as effective in cases where the time taken for a stable gel to form is quite lengthy, UV-induced polymerization can only be used during surgical resection of the tumor and usually the concentration of polymer is quite high for the gel formation to occur and hence the formed gel also takes a long period to dissolve.

Table 3. *In vivo* animal studies conducted on preformed implants in rats.

Polymer used	Drug/therapeutic substance	Shape and dimensions or weight	Model and cancer cell line	Ref.
Chitosan-ePC	Paclitaxel	Cubes, 1.5 – 50 mg	CD-1 Mouse; SKOV-3 Human ovarian carcinoma	[44]
Chitosan-ePC	Paclitaxel	Rectangular prism, 1×5 mm^3 $\times$ 0.15 mm thick	CD-1 Mouse; SKOV-3 Human ovarian carcinoma	[44]
Chitosan-ePC	Paclitaxel	Rectangular prism, 10×10 mm^3 $\times$ 1 mm thick	BALB/c Mouse; Healthy	[40]
Gelatin	Cisplatin	Rectangular prism, 1.2×1.2 mm^3 $\times$ 1 mm thick	CDF_1 Mouse; Meth-Ar1 Fibrosarcoma	[105]
Gelatin	Cisplatin, Adriamycin	Rectangular prism, 1.2×1.2 mm^3 $\times$ 1 mm thick	CDF_1 Mouse; Meth-Ar1 Fibrosarcoma	[55]
Gelatin	Interleukin-12	?	CMT-93 Colon carcinoma	[52]
pCPP:SA	-	Disc, 2 mm diam $\times$ 1.8 mm thick	NMRI (*nu/nu*) mice; healthy	[86]
pCPP:SA	Carmustine, Paclitaxel	Cylinders 2 mm diam. $\times$ 1.8 mm height	NMRI (*nu/nu*) mouse; U-87 MG Glioblastoma	[86]
PLGA	Paclitaxel	Discs 3 mm $\times$ 1 mm	BALB/c mice; U87 MG-luc2 Human glioblastoma	[79]

DOX: Doxorubicin; ePC: Egg phosphatidylcholine; pCPP:SA: Poly(carboxyphenoxypropane/sebacic acid) anhydride, 20:80.

Table 4. Comparison of the advantages and disadvantages of *in situ* forming implants.

System	Photo-crosslinkable systems	Local stimuli responsive systems	Solvent diffusion systems
How it works	Use of an initiator in the implant and an external light source	Responds to local environment, e.g., pH or temperature	Contains an organic solvent, which diffuses into surrounding body tissue leaving implant *in situ*
Advantages	Do not require surgical implantation and removal Cost of production (manufacturing is lower than that for similar targeted systems, e.g., micro- or nanoparticles) [106] Can be used in the delivery of 'sensitive' molecules, e.g., proteins [106]		
Disadvantages	Area of injection limited by penetration of the light source [107] Possibility of toxicity of the initiator [42] Drug may be damaged when crosslinking occurs [43]	Inter-patient variations Differences in injection techniques can result in differences in release kinetics Sterilization technique may pose challenge Initial burst release may occur[33,59]	Possibility of toxicity of the solvent Initial burst phase release [33,73]

In addition to the above ideal characteristics, the response of the implant to a local stimulus should also be taken into consideration, which can be detrimental in that inter-patient differences may become important. The temperature or pH at the site of the tumors is unlikely to be the same for every patient and is more likely to be a range when considering large numbers of patients. Hence formation of the implant or release of drug from the implant should be able to occur over a range of temperatures or pH values. The amount of variation between patients (if significant) can be ascertained only in a clinical trial. While *in vivo* studies have been conducted in a mouse or rat model in many cases, it should be noted that the induced cancer is of the same cell line, whereas in the human patient, variations based on

unique physiology are more likely. ISFIs also have a disadvantage in terms of the site of injection, as well as the injection technique. As the implant will form *in vivo*, and is not preformed, the shape of the implant at the site may differ and hence the release kinetics of the entrapped drug may differ. The technique of injection becomes important when the site of the tumor is considered, that is, the depth of the injection as well as the position of injection: intra- or peritumoral. The sterilization technique for ISFIs is also more challenging than that for preformed implants as the sterilization method has to be such that the formulation is not damaged; this is of special concern when considering thermoresponsive systems. These shortcomings of ISFIs are summarized in **Table 4**.

A few of the systems described herein such as Intradose, Atrigel, Eligard, Gliadel, ReGel, Cremophor EL-paclitaxel, OncoGel, Cytoryn and Zoladex have shown great potential, but further development of these systems are warranted for the effective treatment of solid tumors. Of the various implantable systems, the ISFIs are of particular interest and potential as they rule out the need for surgical interventions and hence have the benefit of both higher patient acceptability and reduction of multitude complications that may occur during surgery. These implant systems also allow delivery of the drugs intratumorally rather than peritumorally as is the case with preformed implants. The main challenge to overcome regarding the ISFIs is the initial burst release of the drug that often occurs due to the time taken for phase change to occur. Furthermore, ensuring the delivery of drug over prolonged periods of time at adequate levels for tumor reduction or elimination and to prolong patient survival is yet another challenge. The ISFIs that respond to stimuli at the site of the tumor are far more useful than those that require the use of organic solvents or the application of an external stimulus.

Declaration of interest

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Affiliation

Ameena Wadee[1], Viness Pillay[†3], Yahya E Choonara[1], Lisa C du Toit[1], Clement Penny[2], Valence MK Ndesendo[1], Pradeep Kumar[1] & Caragh S Murphy[1]
[†]Author for correspondence
[1]University of the Witwatersrand, Department of Pharmacy and Pharmacology, 7 York Road, Parktown, 2193, Johannesburg, South Africa
[2]University of the Witwatersrand, Department of Medical Oncology, 7 York Road, Parktown, 2193, Johannesburg, South Africa
[3]Professor, University of the Witwatersrand, Department of Pharmacy and Pharmacology, 7 York Road, Parktown, 2193, Johannesburg, South Africa
Tel: +011 717 2274; Fax: +27 86 553 4733; E-mail: viness.pillay@wits.ac.za