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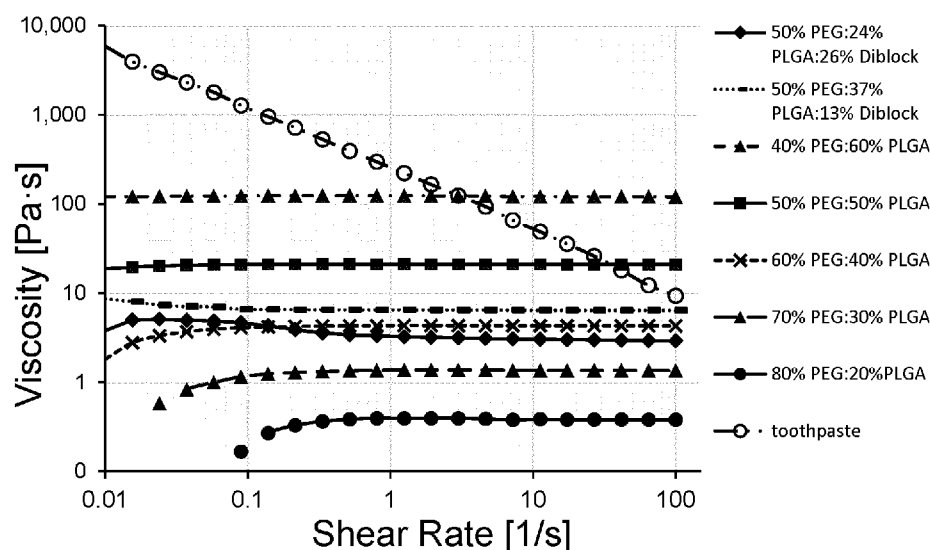
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FIGURE 1



(57) Abstract: This invention provides compositions for controlled localized release of one or more drugs within a subject. More particularly, described herein are compositions comprising a hydrophobic water-insoluble polymer, a low molecular weight biocompatible glycol, and one or more drugs. The compositions described herein may also optionally include a di-block copolymer and/or a swelling agent.

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POLYMERIC PASTE COMPOSITIONS FOR DRUG DELIVERY

FIELD OF THE INVENTION

This invention relates to biodegradable polymeric pastes suitable for drug delivery. More particularly, the invention relates to injectable polymeric pastes that release drugs in a controlled manner.

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Serial Nos. 62/518,800 filed on 13 June 2017, entitled "POLYMERIC PASTES FOR DRUG DELIVERY".

BACKGROUND OF THE INVENTION

Prostate Cancer

The anatomy and pathogenesis of prostate cancer (PCa) lends itself to localized treatment modalities. Low risk early-stage localized PCa often has a low long-term likelihood of progression and metastases, and treatments such as surgery or radiation may unnecessarily expose patients to the risks of treatment without a concomitant meaningful cancer-specific benefit. While surgery and radiation lead to excellent long-term cancer-free rates, it is estimated that PCa-related death will be prevented in only one out of 5 to 48 patients undergoing treatment^{1, 2}. To minimize the risk of 'overtreatment', active surveillance (AS) without immediate treatment has become an increasingly utilized option for some men with appropriate low to intermediate-risk cancer characteristics.

Large population-based studies evaluating outcomes for PCa based on clinical and pathological parameters have established well defined PCa risk categories³. Low risk PCa, defined as cT1-cT2a, Gleason score ≤ 6 , PSA < 10 , is unlikely to progress and require radical treatment, and is readily amenable to AS. AS for low and low-tier intermediate risk PCa has demonstrated favourable outcomes, and can spare up to 50% of men from radical treatment at 5 years⁴. AS has provided insight into the natural history of lower risk PCa and also addresses the population health concerns arising from PCa over-detection and overtreatment. Triggers to come off AS and proceed to definitive intervention include rises in serum PSA values, histological progression on biopsy, development of lower urinary tract symptoms, or patient anxiety on follow up.

While AS aims to minimize the risk of overtreatment, it relies on the assumption that the cancer will not metastasize and requires biopsies every 1-2 years. Taking this strategy can cause anxiety over living with an untreated cancer and leads to delayed whole-gland treatment (radiation or surgery) in 30-40% of

patients⁵. For some men with low-risk and intermediate-risk PCa, AS may be undesirable, yet the short-term and long-term complications associated with surgery and radiation present unacceptable risks. Moreover, any benefits of curative treatment with surgery or radiotherapy are small at durations of follow up of less than 10 years, and are hence associated with adverse effects on quality of life without near-term benefits in disease control^{6,7}.

For this reason, there has been a growing interest in minimally invasive focal therapies for PCa⁸⁻¹⁰. The dual goals are to eradicate a focal area of cancer and maintain normal urinary, sexual, and bowel function. Several minimally invasive ablation methods, such as cryotherapy^{11, 12} and high-intensity focused ultrasound (HIFU)¹³, have been developed and are currently FDA approved. These are, however, ablative therapies that kill benign and cancer cells indiscriminately and can lead to erectile dysfunction and fistulae.

Upper Tract Urothelial Carcinoma

Urothelial carcinomas (UCs) may occur in the lower urinary zones (bladder or urethra) or in the upper urinary tract (UUT: pyelocaliceal cavities and ureter)¹⁴. Over 90 % of UCs are located in the bladder with under 10% occurring in the upper tract (UTC). Patients with bladder cancer are usually diagnosed with early stage disease and the cancer confined to the superficial urothelium. This is partly due to the easy access of diagnostic equipment via the urethra. However, many patients with UTCs are not diagnosed early and may have already progressed to invasive disease. Staging of UTCs may also be difficult as the tissue is fragile with only limited musculature so that biopsies do not always accurately describe the disease level.

Once diagnosed, radical nephroureterectomy (RNU) with bladder-cuff removal is considered the standard treatment of UTC^{15, 16}. This procedure involves full removal of the kidney, the ureter and the bladder cuff. Tumor cell spillage may be a problem with such procedures. Furthermore, many patients are not candidates for this treatment. Some patients with low-risk disease, may be offered a more conservative treatment such as endoscopic ablation or segmental removal¹⁴. Clearly, with later diagnosis, the prognosis for these patients with UTC is poor. Chemotherapeutic options are limited for these patients especially because cisplatin based regimens are associated with nephrotoxicity, which may be exacerbated, when one kidney is removed. Other drugs used to treat bladder cancer such as Mitomycin C and Gemcitabine may have a preferred toxicity profile. However, when used to treat bladder cancer these drugs may be delivered at high concentrations intravesically (directly into the bladder) so that a 2 hour retention allows reasonable drug uptake into the tissues after tumor resection. More recently, the drug docetaxel is under

investigation as a chemotherapeutic option to treat bladder cancer locally and UTC by systemic delivery. The combination of gemcitabine and docetaxel, is also being studied as an improvement to using either drug alone¹⁷.

Because the UUT tissues cannot be treated locally with a drug solution (the pelvis is accessible but drug solutions would quickly wash into the bladder) one company (Urogen™) has developed a gel formulation of mitomycin called Mitogel. This gel undergoes a thermos-reversible gel transition in the body so may be injected as a liquid to form a semi solid gel in the pelvis of the kidney. The pluronic-based gel dissolves slowly, but allows for some retention of the drug in the tissues at the target site.

Background Chronic Scrotal Pain

Chronic scrotal contents pain (CSCP) is a common entity afflicting men of all ages and has been reported to peak in the mid to late thirties^{18, 19}. A study conducted in Switzerland reported an estimated incidence of 350-400 cases per 100,000 men per year²⁰. CSCP is an intermittent or constant, unilateral or bilateral pain involving the testes, epididymis, vas deferens or para-testicular structures of at least three months duration²¹. The etiology for CSCP is varied and is divided into scrotal and extra-scrotal causes. Extra-scrotal causes involve irritation of the ilioinguinal, genitofemoral or pudendal nerves. This can include inguinal hernias/hernia repairs, urolithiasis, or retroperitoneal tumors among many others. Causes within the scrotum include infection, prior scrotal surgery, post vasectomy pain or anatomic abnormalities.

Effective treatment options for CSCP are limited and data consists primarily of non-randomized, small studies. Conservative therapies include rest, ice and scrotal supports along with pain education and counselling. There is no standardized protocol for treatment²¹, but the mainstay of medical therapy involves nonsteroidal anti-inflammatory drugs (NSAIDs) with tricyclic antidepressants or gabapentin as alternatives²². Antibiotics may be trialed, if epididymo-orchitis is in the differential diagnosis. Beyond this, non-invasive options include pelvic floor physiotherapy, acupuncture or transcutaneous electrical nerve stimulation (TENS), but these are not associated with frequent or durable control of CSCP. Lidocaine combined with steroid injections short term relief for men with testicular pain²³. A case report from 2009 indicated success with sacral nerve stimulation though no further studies have validated this response²⁴. In 2012 a case series reported on treatment of chronic orchialgia using pulsed radiofrequency ablation, but again are not associated with frequent or durable control²⁵. An open-label trial from 2014 on spermatic cord injections with Botulinum toxin showed modest results for up to 3 months, but with limited effect at six-month follow up²⁶. A very recent study reported that a subset of men with chronic

testicular pain can benefit from excess doses of vitamin B12 and testosterone, but this type of treatment may be associated with increased risk of prostate cancer associated with testosterone treatment²⁷.

Surgical management is reserved for those who have persistent scrotal pain despite adequate trials of conservative and medical therapies. In the past, surgery for scrotal pain has focused on the area of the scrotum thought to be the source of pain. Epididymectomy, vasovasostomy, varicocelectomy and orchiectomy have all been attempted, but are invasive, associated with risk of loss of the testicle, and have low long-term pain control. In a study by Polackwich *et al.*, vasovasostomy or vasoepididymostomy, in men with post vasectomy pain syndrome, provided a degree of relief in 82% of patients²⁸. Epididymectomy for post vasectomy pain was studied by Hori *et al.* and produced a mean decrease in pain score by 67%²⁹. Epididymectomy for epididymal pain led to significant reductions in pain which were more pronounced for epididymal cysts compared to chronic epididymitis³⁰.

In contrast to anatomically based surgical interventions, microsurgical spermatic cord denervation (MSCD) provides effective pain relief for multiple sources of intrascrotal pain in men who respond to initial spermatic cord block. Multiple studies have shown results for MSCD with complete response rates in approximately 70 percent of patients (range 49-96%)³¹⁻³⁵. MSCD can be utilized as an initial surgical management tool or after other surgical interventions have failed³⁶. As with other surgical procedures, MSCD does involve use of a general anesthetic and there are risks of testicular atrophy or loss of testicle, as well as persistent pain despite and expensive surgical procedure.

Overall, the treatment of CSCP is challenging due to its multifaceted etiology and indistinct presentation, which imposes a significant burden on the patient and physician. Many patients with CSCP are left with untreated pain, seeking consultation with multiple physicians, loss of work, and risk of narcotic exposure³¹. As highlighted in the European Urological Association 2013 guidelines, chronic scrotal pain is “often associated with negative cognitive, behavioural, sexual or emotional consequences.”³⁷. A study from 2011 found that men with orchialgia had decreased scores in orgasmic function, intercourse satisfaction and sexual desire compared to men with no pain. Overall sexual satisfaction and International Index of Erectile Function scores were also significantly lower in this group³⁸. Thus, there remains an unmet clinical need for effective delivery of therapeutics in the management of CSCP.

To provide pain relief for CSCP, spermatic cord block is a valuable treatment option. The single local injection of lidocaine to break the pain cycle³⁹ is suggested at a dose of 100 mg (10 mL of 1% lidocaine) for peripheral nerve block⁴⁰. This regional delivery of lidocaine is characterized by a quick onset (3 min)

and of short duration (60-120 min). A maximum dose of 4.5 mg/kg of lidocaine alone can be used and if epinephrine is added this amount can be further increased to 6 mg/kg. Epinephrine acts as a vasoconstrictor, slows the systemic absorption of lidocaine and prolongs its duration of action^{41, 42}.

Instead of using epinephrine, which produces the common unwanted sympathomimetic side effects including vasoconstriction and reduced blood flow, it is preferred to use a drug carrier for lidocaine, which resides locally and releases small amounts of the drug over a more extended period of time.

In traditional chemotherapy, drugs are delivered systemically following resection surgery or to treat metastatic disease. However, to treat local tumors, a better method might be to deliver a controlled release drug formulation to the disease site. Currently, there are few such formulations available, often because the target tissue is difficult to access and locally delivered solutions of drugs are cleared rather quickly from the area, offering little efficacy. Certain tissues (like the prostate or upper urothelial tract) are routinely accessed in patients (needle biopsy for prostate or by endoscopy for UUT) and offer potential sites for local drug delivery. For the prostate, where the target tissue is confined to an organ with defined boundaries, an injectable, slow release polymeric paste might be suitable. Delivering drugs directly to the pelvis of the kidney to treat UTC is problematic because the ureter cannot be blocked by a polymeric paste for a long time. Delivery to this area may require using an injectable that breaks up or dissolves over a reduced time-frame so that urine may flow but some the drug loaded formulations remains to allow for local tissue uptake.

Injectable Polymeric Paste

Drugs are normally delivered orally or by injection to allow systemic uptake and circulation to most parts of the body. For many drugs this route of administration is ideally suited, for example, insulin for diabetes or statins for heart disease. However, many diseases are localized and the preferred method is to deliver the drug directly to the site of action. For example, painkillers for chronic localized pain, anticancer drugs for local tumors and anti-arthritis drugs to relieve symptoms of arthritis and joint pain. Accordingly, there have been numerous attempts to design locally injectable systems to deliver drugs to specific body sites. This targeted approach may also minimize systemic toxicity often associated with conventional methods of delivering drugs. The intravenous delivery of anticancer drugs often causes severe side effects and systemic toxicities usually limit drug dose. Local polymeric drug delivery systems could mitigate systemic side effects and allow for the delivery of high local doses.

PLGA is a common constituent of polymeric drug delivery systems. It is an FDA-approved biopolymer of lactic acid (D,L-LA) and glycolic acid (GA) and has been used both as a drug delivery carrier and as a scaffold for tissue engineering^{43, 44}. The degradation of PLGA depends on many factors including, but not limited to, the ratio of LA to GA, crystallinity, weight average molecular weight of the polymer, shape of the matrix, and type and amount of drug incorporated^{45, 46}. The ratio of LA to GA is a major player in degradation and polymers with a higher amount of the more hydrophilic GA generally degrade faster. The degradation products of PLGA are the hydrolysis products LA and GA. Both can enter the citric acid cycle and can be excreted as water and carbon dioxide, or in the case of GA, mainly excreted unchanged by the kidney⁴⁶. Minor toxicities like transient inflammation have been reported for some PLGA based implants⁴⁷, but they likely reflect increased exposure times and reduced clearance of the degradation products.

Injectable, drug loaded polymeric pastes are attractive for local drug delivery because ultrasound or MRI-guided systems allow pinpoint accuracy in directing a needle or catheter system to a target area. Others have described injectable liquids (e.g., Atrigel™)⁴⁸ composed of an organic solvent like acetone or polyvinyl-pyrrolidone and a drug that when injected into the body solidified as the solvent dissolved away. Such a system is flawed because introducing an organic solvent into potentially sensitive tissue areas may induce unwanted local toxicity. Local drug delivery systems ranging from drug loaded polymeric coatings of stents, injectable microspheres⁴⁹, perivascular films⁵⁰ and injectable polymeric pastes have been described⁵¹. In these examples, the antiproliferative drug paclitaxel was used to inhibit proliferative events associated with restenosis, cancer and arthritis.

An early polymeric paste system described in the literature was based on a blend of polycaprolactone and methoxypolyethylene glycol that was injectable (molten) at above body temperatures, but set to an implant at 37°C to release drug⁵². The implant was brittle and hard and the high temperature delivery was inappropriate for the injection into sensitive locations. Injectable paclitaxel-loaded polymeric paste made from a mixture of a triblock copolymer and methoxypolyethylene glycol that was injectable at room temperature and formed a solid implant *in vivo* has also been described⁵¹. This paste performed poorly in so far as the release rate of the drug paclitaxel and other hydrophobic drugs was too slow to achieve adequate tissue levels of active drug and the degradation profile of the polymer was too long potentially interfering with re-treatment injections. The inclusion of diblock copolymers of various compositions in solid (not paste) microspheres has been previously described⁴⁹. In this case, the dissolution of the diblock from the microspheres allowed for increased hydrophobic drug release as well as opening of the matrix to water and enhanced degradation. Microsphere formulations are quite different to pastes. They do

not flow under injection so must be injected in a liquid suspension. As such, they can disperse easily from a targeted tissue area.

SUMMARY OF THE INVENTION

This invention relates to improved polymeric pastes for controlled drug delivery. The compositions described herein allow for the formulation and injection of paste mixtures into the body of a subject whereby the paste mixture may form an implant at a localized site. In one aspect, the present invention provides for controlled drug release from polymeric paste delivery systems by using selected low-viscosity water-insoluble polymers to adjust the viscosity of the paste formulation and regulate release rates of drug(s) payload. The paste may be manufactured from simple polymers that form soft – hydrogel-like implants, which may degrade quickly where needed and the release of the drug and/or drug combinations may be controlled. This invention is based on the surprising discovery that only defined ratios and compositions of PEG and PLGA can be used effectively to form a waxy drug delivery deposit *in vivo*. Furthermore, it was discovered that the addition of a diblock copolymer may further control the release or fine tune the release of drug from the composition *in situ*.

Provided herein are non-solvent based, biodegradable polymeric pastes with controlled drug release properties. Furthermore, some of the paste compositions described herein have a low enough viscosity for injection, but set *in vivo* to a more solid formulation to allow controlled release by drug diffusion. Alternatively, the inclusion of a mucoadhesive swelling agent may further slow down the wash out time of the formulation for bladder uses.

When placed in an aqueous environment such as a body compartment, the low molecular weight biocompatible glycol can dissolve out of the matrix and the hydrophobic water-insoluble polymer can partially solidify in a semi-hydrated state that renders the implant waxy. The low molecular weight biocompatible glycols used herein are water-soluble polymer, but may not dissolve entirely out of the matrix over the lifetime of the implant, which may result in a waxy form. A further aspect of the invention includes compositions comprising a low molecular weight biocompatible glycol; a hydrophobic water-insoluble polymer; a drug; and optionally, a biocompatible diblock co-polymer such that the composition is a semi-solid at temperatures at or about room temperature and are capable of being injected into a subject through a syringe. This aspect of the invention has the advantage of being soft, comfortable, non-

compressing of tissues whilst providing long-term, controlled release of a drug at a specific site of injection in a subject.

This invention also provides methods for using the aforementioned compositions to form implants *in vitro* and *in vivo*. *In vivo* methodologies include injection of the composition to a site in a subject's body where the drug-containing implant is formed.

This invention also provides injection devices containing an implant forming composition according to this invention.

In a first aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having an inherent viscosity (IV) of about 0.15 to about 0.5 dL/g; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having an inherent viscosity (IV) of about 0.15 to about 0.55 dL/g; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having an inherent viscosity up to and including about 0.55 dL/g; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having an inherent viscosity up to an including about 0.50 dL/g; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having a molecular weight up to and including about 60,000 Daltons; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having a molecular weight up to and including about 76,000 Daltons; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having a molecular weight between about 4,300 daltons and about 60,000 Daltons; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having a molecular weight between about 4,200 daltons and 76,000 Daltons; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having a molecular weight between about 3,200 daltons and 80,000 Daltons; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having a molecular weight between about 2,200 daltons and 76,000 Daltons; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having a molecular weight between about 2,200 daltons and 70,000 Daltons; (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a composition, the composition including: (a) a hydrophobic water-insoluble polymer having a molecular weight between about 2,200 daltons and 60,000 Daltons; (b) a low

molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.

In a further aspect, there is provided a pharmaceutical composition comprising a compositions as described herein, together with a pharmaceutically acceptable diluent or carrier.

In a further aspect, there is provided a use of a composition as described herein, for the manufacture of a medicament.

In a further aspect, there is provided a use of a composition as described herein, for the treatment of a medical condition for which the drug is used.

In a further aspect, there is provided a composition as described herein, for use in the treatment of a medical condition.

In a further aspect, there is provided a commercial package comprising: (a) composition as described herein; and (b) instructions for the use.

The composition may further include a di-block copolymer. The composition may further include a swelling agent. The composition may further include a di-block copolymer and a swelling agent.

The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) of about 0.15 to about 0.5 dL/g is polylactic-co-glycolic acid (PLGA). The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) of about 0.15 to about 0.25 dL/g is polylactic-co-glycolic acid (PLGA). The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) of about 0.25 to about 0.5 dL/g is polylactic-co-glycolic acid (PLGA). The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) of about 0.15 to about 0.55 dL/g is polylactic-co-glycolic acid (PLGA). The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) of about 0.15 to about 0.60 dL/g is polylactic-co-glycolic acid (PLGA). The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) of about 0.10 to about 0.5 dL/g is polylactic-co-glycolic acid (PLGA). The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) of about 0.10 to about 0.6 dL/g is polylactic-co-glycolic acid (PLGA). The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) of about 0.15 to about 0.45 dL/g is polylactic-co-glycolic acid (PLGA). The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) at of below about 0.3 dL/g is polylactic-co-glycolic acid (PLGA).

The hydrophobic water-insoluble polymer may have a molecular weight between about 2,200 daltons and 70,000 Daltons. The hydrophobic water-insoluble polymer may have a molecular weight between about 4,300 daltons and 60,000 Daltons. The hydrophobic water-insoluble polymer may have a molecular weight between about 4,200 daltons and 60,000 Daltons. The hydrophobic water-insoluble polymer may have a molecular weight between about 4,300 daltons and 70,000 Daltons. The hydrophobic water-insoluble polymer may have a molecular weight between about 4,300 daltons and 75,000 Daltons. The hydrophobic water-insoluble polymer may have a molecular weight between about 4,300 daltons and 50,000 Daltons. The hydrophobic water-insoluble polymer may have a molecular weight between about 3,300 daltons and 60,000 Daltons. The hydrophobic water-insoluble polymer may have a molecular weight between about 2,300 daltons and 60,000 Daltons.

The PLGA may have a ratio of lactic acid (LA):glycolic acid (GA) at or below 75:25. The PLGA may have a ratio of lactic acid (LA):glycolic acid (GA) at or below 65:35. The PLGA may have a ratio of lactic acid (LA):glycolic acid (GA) at or below 50:50. The PLGA may have a ratio of lactic acid (LA):glycolic acid (GA) of between 50:50 and 75:25. The PLGA may have a ratio of lactic acid (LA):glycolic acid (GA) at or below 85:15.

The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) of about 0.15 to about 0.3 dL/g. The hydrophobic water-insoluble polymer may have an inherent viscosity (IV) of about 0.15 to about 0.25 dL/g.

The low molecular weight biocompatible glycol may have a molecular weight between about 76 Daltons and about 1,450 Daltons. The low molecular weight biocompatible glycol may have a molecular weight between about 300 Daltons and about 1,450 Daltons. The low molecular weight biocompatible glycol may have a molecular weight between about 76 Daltons and about 900 Daltons. The low molecular weight biocompatible glycol may have a molecular weight between about 300 Daltons and about 900 Daltons.

The low molecular weight biocompatible glycol may be selected from Polyethylene glycol (PEG), methoxypolyethylene glycol (mePEG) and propylene glycol. The low molecular weight biocompatible glycol may be PEG and mePEG. The PEG or mePEG may have an average molecular weight of between 300 Daltons and 1,450 Daltons.

The composition may include a hydrophobic water-insoluble polymer having an inherent viscosity (IV) of about 0.15 to about 0.5 dL/g is PLGA having a LA:GA ratio of 50:50 and a low molecular weight

biocompatible glycol is PEG or mePEG with a molecular weight of about 300 Daltons to about 1,450 Daltons. The composition may include a hydrophobic water-insoluble polymer having an inherent viscosity (IV) of about 0.15 to about 0.5 dL/g is PLGA having a LA:GA ratio of 65:35 and a low molecular weight biocompatible glycol is PEG or mePEG with a molecular weight of about 300 Daltons to about 1,450 Daltons. The composition may include a hydrophobic water-insoluble polymer having an inherent viscosity (IV) of about 0.15 to about 0.5 dL/g is PLGA having a LA:GA ratio of 75:25 and a low molecular weight biocompatible glycol is PEG or mePEG with a molecular weight of about 300 Daltons to about 1,450 Daltons. The composition may include a hydrophobic water-insoluble polymer having an inherent viscosity (IV) of about 0.15 to about 0.5 dL/g is PLGA having a LA:GA ratio at or below 75:25 and a low molecular weight biocompatible glycol is PEG or mePEG with a molecular weight of about 300 Daltons to about 1,450 Daltons. The composition may include a hydrophobic water-insoluble polymer having an inherent viscosity (IV) of about 0.15 to about 0.5 dL/g is PLGA having a LA:GA ratio of 50:50 and a low molecular weight biocompatible glycol is PEG or mePEG with a molecular weight of about 300 Daltons to about 900 Daltons.

The ratio of PEG or mePEG to PLGA may be between about 80%:20% and about 40%:60%. The ratio of PEG or mePEG to PLGA may be between about 70%:30% and about 40%:60%. The ratio of PEG or mePEG to PLGA may be between about 80%:20% and about 50%:50%. The ratio of PEG or mePEG to PLGA may be between about 60%:40% and about 40%:60%. The ratio of PEG or mePEG to PLGA may be between about 60%:40% and about 50%:50%.

The low molecular weight biocompatible glycol may be PEG 300. The low molecular weight biocompatible glycol may be PEG 600. The low molecular weight biocompatible glycol may be PEG 900.

The di-block copolymer may be between 13% and 26% of the total paste polymer, wherein the di-block copolymer substitutes for hydrophobic water-insoluble polymer. The di-block copolymer may be between 13% and 26% of the total paste polymer. The di-block copolymer may be between 10% and 30% of the total paste polymer, wherein the di-block copolymer substitutes for hydrophobic water-insoluble polymer. The di-block copolymer may be between 5% and 40% of the total paste polymer, wherein the di-block copolymer substitutes for hydrophobic water-insoluble polymer.

The di-block copolymer may have one hydrophobic monomer and one hydrophilic monomer.

The hydrophilic monomer may be selected from: PEG; and MePEG; and the hydrophobic monomer may be selected from: PLGA; polylactic acid (PLA); Poly-L-lactic Acid (PLLA); and Polycaprolactone (PCL). The

hydrophilic monomer may be selected from: PEG; and MePEG; and the hydrophobic monomer may be selected from: polylactic acid (PLA); Poly-L-lactic Acid (PLLA); and Polycaprolactone (PCL). The hydrophilic monomer may be selected from: PEG; and MePEG; and the hydrophobic monomer may be selected from: PLGA; polylactic acid (PLA); and Poly-L-lactic Acid (PLLA). The hydrophilic monomer may be MePEG; and the hydrophobic monomer may be PLGA. The hydrophilic monomer may be PEG; and the hydrophobic monomer may be PLLA. The hydrophilic monomer may be PEG; and the hydrophobic monomer may be PLGA. The di-block copolymer may be amphiphilic. The di-block copolymer may be PLLA-mePEG. The di-block copolymer may be PLLA-PEG. The di-block copolymer may be PLA-mePEG. The di-block copolymer may be PLA-PEG.

The one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof may be selected from one or more of the following categories: anti-cancer drugs; anti-inflammatory agents; anti-bacterial; anti-fibrotic; and analgesic. The one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof may be hydrophobic. The one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof may be hydrophilic.

The anti-cancer drug may be selected from one or more of the following: Actinomycin; All-trans retinoic acid; Azacitidine; Azathioprine; Bleomycin; Bortezomib; Carboplatin; Capecitabine; Cisplatin; Chlorambucil; Cyclophosphamide; Cytarabine; Daunorubicin; Docetaxel; Doxifluridine; Doxorubicin; Epirubicin; Epothilone; Etoposide; Fluorouracil; Gemcitabine; Hydroxyurea; Idarubicin; Imatinib; Irinotecan; Mechlorethamine; Mercaptopurine; Methotrexate; Mitoxantrone; Oxaliplatin; Paclitaxel; Pemetrexed; Teniposide; Tioguanine; Topotecan; Valrubicin; Vemurafenib; Vinblastine; Vincristine; Vindesine; and Vinorelbine.

The anesthetic drug may be a local anesthetic selected from one or more of the following: Procaine; Benzocaine; Chloroprocaine; Cocaine; Cyclomethycaine; Dimethocaine/Larocaine; Piperocaine; Propoxycaine; Procaine/Novocaine; Proparacaine; Tetracaine/Amethocaine; Articaine; Bupivacaine; Cinchocaine/Dibucaine; Etidocaine; Levobupivacaine; Lidocaine/Lignocaine/Xylocaine; Mepivacaine; Prilocaine; Ropivacaine; and Trimecaine. The anesthetic drug may be a local anesthetic selected from one or more of the following: Procaine; Benzocaine; Chloroprocaine; Cyclomethycaine; Dimethocaine; Piperocaine; Propoxycaine; Procaine; Proparacaine; Tetracaine; Articaine; Bupivacaine; Cinchocaine;

Etidocaine; Levobupivacaine; Lidocaine; Mepivacaine; Prilocaine; Ropivacaine; and Trimecaine. The anesthetic drug may be Lidocaine.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows the viscosity of polymeric pastes with different weight ratios of PLGA, PEG and diblock copolymer.

FIGURE 2 shows the release of PEG 300™ from several polymeric paste mixtures.

FIGURE 3 shows the release of docetaxel at 4%, bicalutamide at 4%, and VPC-27 at 10% (A) and 4% (B) from PEG:PLGA (50:50) polymeric pastes.

FIGURE 4 shows the release of docetaxel (A), bicalutamide (B), and VPC-27 (C) from PEG:PLGA:Diblock polymeric pastes (57:37:13 or 50:24:26).

FIGURE 5 shows the release of docetaxel at 0.25%, bicalutamide at 4%, and VPC-27 at 4% from PEG:PLGA:Diblock polymeric pastes (57:37:13 w/w%).

FIGURE 6 shows the effect of varying PLGA:Diblock ratios (A) 43%:7%, (B) 37%:13%, (C) 31%:19% (D) 25%:25% on the release rates of docetaxel (0.5%), bicalutamide (4%), and VPC-27 (4%) from PEG:PLGA:Diblock pastes.

FIGURE 7 shows the release of docetaxel (A), bicalutamide (B), and VPC-27 (C) from PEG:PLGA polymeric pastes (63:37 or 76:24).

FIGURE 8 shows the release of docetaxel (1%), bicalutamide (4%), and VPC-27 (4%) from PEG:PLGA polymeric pastes (50:50 (A) or 55:45 (B) or 60:40 (C)).

FIGURE 9 shows the release of rapamycin (1%), docetaxel (1%), and VPC-27 (4%) from PEG:PLGA:Diblock polymeric pastes (50:37:13 w/w%).

FIGURE 10 shows the release of Cephalexin (A) 2% and (B) 4%, 6%, 8% and 10% from PEG:PLGA:Diblock polymeric paste (50:37:13 w/w%).

FIGURE 11 shows the release of lidocaine from various paste shapes (cylinder, crescent and hemisphere (A)) and at different lidocaine concentrations (2%, 4%, 6%, 8% and 10% (B)) from PEG:PLGA:Diblock polymeric paste (50:37:13 w/w%).

FIGURE 12 shows the release of 1% docetaxel (A), 4% Enzalutamide (B), or 4% VPC-27 (C) from PEG:PLGA:Diblock polymeric pastes (63:37 w/w% or 50:37:13 w/w%).

FIGURE 13 shows the solubilization of docetaxel, bicalutamide, or VPC-27 by diblock copolymer (molecular weight 3333, PLLA 40%, MePEG 2000 60%).

FIGURE 14 shows the release of lidocaine (10%) and desoximetasone (1%) from PEG:PLGA:Diblock polymeric paste (50:37:13 w/w%).

FIGURE 15 shows the release of lidocaine (8%) from PEG:PLGA pastes (50:50, 55:45 and 60:40).

FIGURE 16 shows the release of sunitinib (1%) from PEG:PLGA:Diblock polymeric paste (50:37:13 w/w%).

FIGURE 17 shows the release of Tamsulosin (2%) from PEG:PLGA:Diblock polymeric paste (50:37:13 w/w%).

FIGURE 18 shows the release of lidocaine (8%), cephalexin (2%), and ibuprofen (5%) from PEG:PLGA:Diblock polymeric paste (50:37:13 w/w%).

FIGURE 19 shows the effect of drug-loaded (i.e. docetaxel (1%), bicalutamide (1%), and VPC-27 (4%)) PEG:PLGA:Diblock polymeric paste (50:37:13 w/w%) versus control paste (i.e. no drug) on mouse serum PSA (A) and absolute tumour size (B) as a representation of human prostate cancer tumors (ST-PC3) in mice. A study to determine the effect of variable concentrations of docetaxel.

FIGURE 20 shows the effect of varied amounts of Docetaxel (i.e. 0%, 0.25%, 0.5% and 1%) drug-loaded (i.e. Bicalutamide (4%), and VPC-27 (4%)) PEG:PLGA:Diblock polymeric paste (50:37:13 w/w%) on mouse serum PSA (A) and absolute tumour size (B) as a representation of human prostate cancer tumors in mice.

FIGURE 21 shows serum PSA concentrations (A) and tumour volume in cm³ (B) after intratumoral injection of drug-loaded pastes (1% Docetaxel and 4% Bicalutamide; 1% Docetaxel, 4% Bicalutamide and 4% VPC-27; 1% Docetaxel; and 1% Docetaxel and 4% VPC-27).

FIGURE 22 shows the systemic absorption of lidocaine after local injection of lidocaine pastes (in PEG/PLGA 50/50) subcutaneously in rats at different doses of lidocaine paste (i.e. 23mg/kg; 29 mg/kg; 36 mg/kg; 40 mg/kg; and 45 mg/kg) as a measure of serum concentration observed over time (A) and as a semi logarithmic plot (B).

FIGURE 23 shows the water absorption of pastes containing a swelling agent (i.e. 2% sodium hyaluronate (SH)) and variable amounts of diblock copolymer (i.e. 10%, 20%, 30% and 40%) as compared to no SH and no diblock.

FIGURE 24 shows the release of 5% Gemcitabine from pastes with (i.e. 2% sodium hyaluronate (SH)) and without swelling agent and with and without diblock copolymer. The pastes had a high PEG 300™ content (i.e. 53%, 58% and 76%).

FIGURE 25 shows the urinary excretion after injection of 5% gemcitabine pastes into pig kidney pelvis (A) and serum gemcitabine concentrations after injection of 5% gemcitabine pastes (68% PEG: 30% PLGA) into pig kidney pelvis (B) to show systemic absorption of gemcitabine paste containing a swelling agent (2% SH) in three pigs (administration of 1.5 mL of a 5% gemcitabine paste into kidney pelvis using 5F ureteral catheter).

DETAILED DESCRIPTION OF THE INVENTION

In embodiments of the invention hydrophobic water-insoluble polymers are used to control the consistency of biocompatible polymer pastes and subsequent release of a variety of drugs therefrom.

Inherent Viscosity (IV) is a viscometric method for measuring molecular size. IV is based on the flow time of a polymer solution through a narrow capillary relative to the flow time of the pure solvent through the capillary. The units of IV are typically reported in deciliters per gram (dL/g). IV is simple and inexpensive to obtain and reproducible. Gel Permeation Chromatography (GPC) may be used

as a chromatographic method for measuring molecular size. The molecular size can be expressed as molecular weight (MW) in Daltons obtained from calibration with a standard polymer (for example, polystyrene standards in chloroform). The molecular weight of styrene is 104 Daltons and standards of known polystyrene are readily available. MWs obtained by GPC are very method-dependent and are less reproducible between laboratories. Alternatively, molecular weight may be measured by size exclusion chromatography (SEC), high temperature gel permeation chromatography (HT-GPC) or mass spectrometry (MALDI TOF-MS).

The hydrophobic water-insoluble polymers may be a polyester. The hydrophobic water-insoluble polymers may be a polylactic-co-glycolic acid (PLGA), wherein, the ratio of LA:GA is equal to or below 75:25. The ratio of LA:GA may be about 50:50. Durect Corporation™ who supplied the PLGA used in these experiments graph inherent viscosity (IV) in dL/g in hexafluoroisopropanol (HFIP) against molecular weight in Daltons for their 50:50 and 65:35 LA:GA polymers. Similarly, when Durect™ calculated the IV values in dL/g for 75:25 PLGA and 85:15 PLGA, chloroform, was used as the solvent. The relationship between IV and molecular weight in Daltons is different depending on the ratio of LA:GA. As described herein an inherent viscosity of between 0.15 to 0.25 dL/g is an optional range, but an IV in the range 0.25-0.5 dL/g would also be suitable. Alternatively, the range may be between about 0.15 dL/g and about 0.5 dL/g.

Using a 50:50 PLGA a range of 0.15 to 0.25 dL/g is approximately equivalent to a range of about 4,300 Daltons to about 6,700 Daltons and a range of 0.25 to 0.5 dL/g is approximately equivalent to a range of about 6,700 Daltons to about 26,600 Daltons. Using a 65:35 PLGA a range of 0.15 to 0.25 dL/g is approximately equivalent to a range of about 6,500 Daltons to about 14,200 Daltons and a range of 0.25 to 0.5 dL/g is approximately equivalent to a range of about 14,200 Daltons to about 39,000 Daltons. The broader range of 0.15 to 0.5 dL/g is equivalent to about 4,300 Daltons to about 26,600 daltons for 50:50 PLGA and about 6,500 Daltons to about 39,000 daltons for 65:35 PLGA. Accordingly, the Dalton range for PLGA may be anywhere between 4,300 and about 39,000. Alternatively, the Dalton range for PLGA may be anywhere between 4,300 and about 40,000 or higher if using 75:25 (i.e. up to a molecular weight of 56,500 Dalton). For the 50:50, 65:35 and 75:25 LA:GA polymers, an IV of 0.5 g/dL approximately corresponds to molecular weights of 26,600, 39,000, and 56,500. As tested the Durect™ 50:50 having an IV of 0.25 dL/g is about 6,700 Daltons, Durect™ 75:25 having an IV of 0.47 dL/g is about 55,000 Daltons and Durect™ 85:15 having an IV of 0.55 dL/g to 0.75 dL/g is in the range of about 76,000 Daltons to about 117,000 Daltons.

Calculations of IV to Dalton's provided by Durect Corporation™ are as follows (for each ratio of LA:GA). For 50:50 an IV of 0.25 dL/g is about 6,700 Daltons, an IV of 0.35 dL/g is about 12,900, Daltons, an IV of 0.45 dL/g is about 21,100, an IV of 0.55 dL/g is about 31,100 Daltons and an IV of 0.65 dL/g is about 43,500 Daltons. For 65:35 an IV of 0.15 dL/g is about 6,500 Daltons, an IV of 0.25 dL/g is about 14,200 Daltons, an IV of 0.35 dL/g is about 23,700 Daltons, an IV of 0.45 dL/g is about 34,600 Daltons, an IV of 0.55 dL/g is about 47,000 Daltons and an IV of 0.65 dL/g is about 60,500 Daltons. For 75:25 an IV of 0.15 dL/g is about 11,200 Daltons, an IV of 0.25/0.3 dL/g is about 23,800 Daltons, an IV of 0.35/0.4 dL/g is about 39,000 Daltons, an IV of 0.45/0.5 dL/g is about 56,500 Daltons and an IV of 0.55/0.6 dL/g is about 76,000 Daltons.

Of particular interest are PLGA pastes having a ratio of LA:GA of 50:50 with an IV of between 0.15 dL/g to 0.25 dL/g (i.e. molecular weights of between 4,300 Daltons to 6,700 Daltons). However, PLGA pastes having a ratio of LA:GA of 50:50 with an IV of 0.25 dL/g to 0.5 dL/g (i.e. a molecular weight of about 6,700 to about 26,600 Daltons) is also useful.

The PLGA polymer molecular weight may be reported as inherent viscosity (IV)) may be IV = 0.15-0.5 dL/g. The PLGA polymer IV may be < 0.3 dL/g. The PLGA polymer density may lie between 0.15-0.25 dL/g. Low molecular weight versions of PLGA with a 50:50 ratio of LA:GA and an inherent viscosity under 0.3 dL/g may be rendered fully miscible with a low molecular weight biocompatible glycol using mild heating to form either a viscous or fluid paste at room temperature. For high viscosity pastes, the 50:50 ratio PLGA materials with an inherent viscosity up to 0.5 dL/g may be used with poly ethylene glycol (PEG). PEG or mePEG with a molecular weight below 1450 may be used in these applications. The low molecular weight biocompatible glycol may have a molecular weight between about 76 and about 1450. The PEG or mePEG may have an average molecular weight of between 300 and 1450.

Low molecular weight biocompatible glycol may be used to fluidize PLGA to a paste and set to an implant. Examples of a low molecular weight biocompatible glycol may include PEG, mePEG and propylene glycol. A PEG-based glycol (i.e. mePEG or PEG) may have a molecular weight of up to 1450. Alternatively, the PEG-based excipient may have a molecular weight ≤ 900 . In a further alternative, a PEG-based excipient may have a molecular weight of about 300. PEG 300™ is biocompatible and is directly cleared via the kidneys without liver or other degradation required.

PLGA:PEG pastes may be loaded with a variety of drugs and allow for controlled release of the loaded drug(s) over periods of approximately 1-2 months. Low molecular weight diblock copolymers may also be optionally incorporated without phase separation into the PLGA:PEG compositions with only minor changes in viscosity of the total composition. The presence of diblock copolymers may allow further control (acceleration) of drug release from the polymer matrix so that certain drugs that release slowly may be released more rapidly.

Diblock copolymers may consist of two different types of monomers. The monomers may be hydrophobic. The monomers may be hydrophilic. The diblock copolymer may have one hydrophobic monomer and one hydrophilic monomer. The diblock copolymer may be amphiphilic. The hydrophilic monomer for example, may be PEG or MePEG. The hydrophobic monomer for example, may be PLGA, PLA, PLLA or PCL. **TABLE 1** below provides a range of compositions that were made and tested to determine their characteristics and useful features.

TABLE 1 provides examples of various polymer formulations as tested.

PLGA IV or alternative	%	Glycol	%	Optional Diblock Copolymer	%	Form at injection	Injectability (needle size/force)	Set time in water starts
0.15-0.25	25	PEG 300™	75			Fluid paste	23 gauge /easy	1 minute
0.15-0.25	37	PEG 300™	63			paste	22 gauge/easy	1 minute
0.15-0.25	50	PEG 300™	50			paste	22 gauge/moderate	1 minute
0.15-0.25	24	PEG 300™	50	Diblock	26	paste	22 gauge/moderate	1-2 minutes
0.15-0.25	37	PEG 300™	50	Diblock	13	paste	22 gauge/easy-moderate	1-2 minutes
0.15-0.25	40	PEG 750™	60			paste	22 gauge/moderate	1-2 minutes
0.15-0.25	40	PEG 900™	60			paste	22 gauge/difficult	3-5 minutes
0.15-0.25	30	PEG 1450™	70			Wax/paste	16 gauge/difficult/needs 37°C	1 minute
0.15-0.25	40	MethoxyPEG 750	60			paste	22 gauge/moderate	1-2 minutes
0.15-0.25	50	Propylene Glycol	50			Very viscous paste	16 gauge /difficult	1 hour
0.25-0.50	35	PEG 300™	65			Medium viscous paste	18 gauge/e 16 gauge/easy	5 minutes

0.47-0.55*	50	PEG 300™	50			Very viscous paste	16 gauge/difficult	1 hour
0.47-0.55*	40	PEG 300™	60			viscous paste	16 gauge easy	0.5-1 hour
0.47-0.55*	30	PEG 300™	70			paste	16 gauge easy	3-5 min
0.47-0.55*	20	PEG 300™	80			liquid paste	16 gauge/very easy	1 minute, but dissolves away
* the PLGA was not from Durect™ and the IV values for these PLGAs were estimated based on the ratio of LA:GA of 75:25.								
More viscous injectables (needs pressure for injection - waxy prior to injection, delayed set time)								
0.25-0.50	35	Propylene glycol	65			Almost solid/paste	16 gauge/extreme force	1-2 hour
0.15-0.25	50	Pluronic L101™	50			Very viscous paste	16 gauge/difficult	1 hour
PLLA 2K	40	PEG 300™	60			Wax	16 gauge/extreme	5 minutes
PCLdiol 1250	60	PEG 300™	40			Wax	18 gauge/difficult	2 minutes sets to v hard implant
Not injectable using normal gauge needles or a reasonable amount of force								
0.55-0.75	20	PEG 300™	80			No homogenous paste	Not injectable	n/a
0.55-0.75	30	PEG 300™	70			No homogenous paste	Not injectable	n/a
0.55-0.75	40	PEG 300™	60			No homogenous paste	Not injectable	n/a
0.55-0.75	50	PEG 300™	50			No homogenous paste	Not injectable	n/a

Drug delivery compositions described herein may exist in a variety of “paste” forms. Examples of paste forms may include liquid paste, paste or wax-like paste, depending on to polymers used, the amount of the polymers used and the temperature.

Drug delivery compositions described herein may release one or more drugs over a period of several hours or over several months, depending on the need. Compositions described herein may be used for localized delivery of one or more drugs to a subject. Examples of drugs that may be delivered using these compositions are not limited, and may include anti-cancer drugs, anti-inflammatory agents, anti-bacterial, anti-fibrotic, analgesic. Examples of anti-cancer drugs that may be used with the compositions of the present invention include docetaxel, paclitaxel, mitomycin, cisplatin, etoposide vinca drugs, doxorubicin drugs, rapamycin, camptothecins, gemcitabine, finasteride (or other cytotoxics); bicalutamide, enzalutamide, VPC-27, tamoxifen, sunitinib, erlotinib. Anti-cancer biological agents may also be used in the formulation such as antibody based therapies e.g. Herceptin, Avastin, Erbitux or radiolabelled antibodies or targeted radiotherapies such as PSMA-radioligands. Anti-inflammatory agents may include non-steroidal drugs like ibuprofen, steroids like prednisone. Local analgesia or local anesthetic medications may include, for example, one or more of the following: Procaine; Benzocaine; Chloroprocaine; Cocaine; Cyclomethycaine; Dimethocaine/Larocaine; Piperocaine; Propoxycaine; Procaine/Novocaine; Proparacaine; Tetracaine/Amethocaine, Articaine; Bupivacaine; Cinchocaine/Dibucaine; Etidocaine; Levobupivacaine; Lidocaine/Lignocaine/Xylocaine; Mepivacaine; Prilocaine; Ropivacaine; and Trimecaine. Antibiotic medications may include penicillin, cephalexin, gentamicin, ciprofloxacin, clindamycin, macrodantin, and others. The drugs may be hydrophobic or may be hydrophilic. Specific drugs may be selected from one of more of the following: Docetaxel; VPC-27; Bicalutamide; Cephalexin (A); Sunitinib; Tamsulosin; Desoximetasone; Gemcitabine; Rapamycin; and Ibuprofen.

Hydrophobic drugs may be able to bind with strong affinity to the hydrophobic water-insoluble polymer (ex. PLGA) allowing slow dissociation and controlled release from the implant. Such drugs tend to dissolve (at least partially) in the paste mixture. Hydrophilic drugs may be blended into the paste but because the matrix is partially hydrated in aqueous environments, these drugs may dissolve out of the implant quickly. In some situations this may be desirable, such as when an antibacterial drug may be included in the paste to treat a local infection and it is preferred if all the drug is cleared from the paste in 7 days to suit an antibacterial drug treatment regime.

Drug delivery compositions may be prepared and utilized to treat or prevent a variety of diseases or conditions. Examples of diseases or conditions that may be treated, may for example, include cancer, pain, inflammatory conditions, fibrotic conditions, benign tumors (including benign prostate hyperplasia), and infections.

Local anesthetics usually fall into one of two classes: aminoamide and aminoester. Most local anesthetics have the suffix “-caine”. The local anesthetics in the aminoester group may be selected from one or more of the following: Procaine; Benzocaine; Chlorprocaine; Cocaine; Cyclomethycaine; Dimethocaine/Larocaine; Piperocaine; Propoxycaine; Procaine/Novocaine; Proparacaine and Tetracaine/Amethocaine. The local anesthetics in the aminoamide group may be selected from one or more of the following: Articaine; Bupivacaine; Cinchocaine/Dibucaine; Etidocaine; Levobupivacaine; Lidocaine/Lignocaine/Xylocaine; Mepivacaine; Prilocaine; Ropivacaine; and Trimecaine. Local anesthetics may also be combined (for example, Lidocaine/prilocaine or Lidocaine/tetracaine).

Furthermore, local anesthetics used for injection may be mixed with vasoconstrictors to increase residence time, and the maximum doses of local anesthetics may be higher when used in combination with a vasoconstrictor (for example, prilocaine hydrochloride and epinephrine; lidocaine, bupivacaine, and epinephrine; lidocaine and epinephrine; or articaine and epinephrine).

Anti-cancer drugs as may be used in the composition described herein, may be categorized as alkylating agents (bi and mono-functional), anthracyclines, cytoskeletal disruptors, epothilone, topoisomerase inhibitors (I and II), kinase inhibitors, nucleotide analogs and precursor analogs, peptide antibiotics, platinum-based agents, vinka alkaloids, and retinoids. Alkylating agents, may be bifunctional alkylators (for example, Cyclophosphamide, Mechlorethamine, Chlorambucil and Melphalan) or monofunctional alkylators (for example, Dacarbazine(DTIC), Nitrosoureas and Temozolomide). Examples of anthracyclines are Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone, and Valrubicin. Cytoskeletal disruptors or taxanes are Paclitaxel, Docetaxel, Abraxane and Taxotere. Epothilones may be epothilone or related analogs. Histone deacetylase inhibitors may be Vorinostat or Romidepsin. Inhibitors of topoisomerase I may include Irinotecan and Topotecan. Inhibitors of topoisomerase II may include Etoposide, Teniposide or Tafluposide. Kinase inhibitors may be selected from Bortezomib, Erlotinib, Gefitinib, Imatinib, Vemurafenib or Vismodegib. Nucleotide analogs and precursor analogs may be selected from Azacitidine, Azathioprine, Capecitabine, Cytarabine, Doxifluridine, Fluorouracil, Gemcitabine, Hydroxyurea, Mercaptopurine, Methotrexate or Tioguanine/Thioguanine. Peptide antibiotics like Bleomycin or Actinomycin. Platinum-based agents may be selected from Carboplatin, Cisplatin or Oxaliplatin. Retinoids may be Tretinoin, Alitretinoin or Bexarotene. The Vinca alkaloids and derivatives may be selected from Vinblastine, Vincristine, Vindesine and Vinorelbine.

An anti-cancer drug that may be used with the compositions described herein, may be selected from one or more of: Actinomycin; All-trans retinoic acid; Azacitidine; Azathioprine; Bleomycin; Bortezomib; Carboplatin; Capecitabine; Cisplatin; Chlorambucil; Cyclophosphamide; Cytarabine; Daunorubicin; Docetaxel; Doxifluridine; Doxorubicin; Epirubicin; Epothilone; Etoposide; Fluorouracil; Gemcitabine; Hydroxyurea; Idarubicin; Imatinib; Irinotecan; Mechlorethamine; Mercaptopurine; Methotrexate; Mitoxantrone; Oxaliplatin; Paclitaxel; Pemetrexed; Teniposide; Tioguanine; Topotecan; Valrubicin; Vemurafenib; Vinblastine; Vincristine; Vindesine; and Vinorelbine. Alternatively, the anti-cancer drug may be a biological agent and may be selected from Herceptin (Trastuzumab), Ado-trastuzumab, Lapatinib, Neratinib, Pertuzumab, Avastin, Erbitux or radiolabelled antibodies or targeted radiotherapies such as PSMA-radioligands. The anti-cancer drug may be an Androgen Receptor, an Estrogen Receptor, epidermal growth factor receptor (EGFR) antagonists, or tyrosine kinase inhibitor (TKI). An anti-angiogenesis agent may be selected from avastin, an epidermal growth factor receptor (EGFR) antagonists or tyrosine kinase inhibitor (TKI). An Immune modulator such as Bacillus Calmette-Guerin (BCG).

As used herein a “drug” refers to any therapeutic moiety, which includes small molecules and biological agents (for example, proteins, peptides, nucleic acids). Furthermore, a biological agent is meant to include antibodies and antigens. As used herein, the term drug may in certain embodiments include any therapeutic moiety, or a subset of therapeutic moieties. For example, but not limited to one or more of the potentially overlapping subsets and one or more drugs, as follows: hydrophobic drugs, hydrophilic drugs; a cancer therapeutic drug; a local anesthetic drug; an anti-biotic drug; an anti-viral drug; an anti-inflammatory drug; a pain drug; an anti-fibrotic drug; or any drug that might benefit from a localized and/or sustained release.

As used herein, “an antibody” is a polypeptide belonging to the immunoglobulin superfamily. In particular, “an antibody” includes an immunoglobulin molecule or an immunologically active fragment of an immunoglobulin molecule (i.e., a molecule(s) that contains an antigen binding site), an immunoglobulin heavy chain (alpha (α), mu (μ), delta (δ) or epsilon (ϵ)) or a variable domain thereof (VH domain), an immunoglobulin light chain (kappa (κ) or lambda (λ)) or a variable domain thereof (VL domain), or a polynucleotide encoding an immunoglobulin molecule or an immunologically active fragment of the immunoglobulin molecule. Antibodies includes a single chain antibody (e.g., an immunoglobulin light chain or an immunoglobulin heavy chain), a single-domain antibody, an antibody variable fragment (Fv), a single-chain variable fragment (scFv), an

scFv-zipper, an scFv-Fc, a disulfide-linked Fv (sdFv), a Fab fragment (e.g., CLVL or CHVH), a F(ab') fragment, monoclonal antibodies, polyclonal antibodies. As used herein "antigen" refers to any epitope-binding fragment and a polynucleotide (DNA or RNA) encoding any of the above.

As used herein, a "paste" is any composition described herein that has the characteristics of a solid and of a liquid depending on applied load and the temperature. Specifically, the viscosity of a paste may be anywhere in the range of about 0.1 to about 200 pascal seconds (Pa·s) at room temperature and may be measured by any number of methods known to those of skill in the art. Numerous types of viscometers and rheometers are known in the art. For example, a cone and plate rheometer (i.e. Anton Paar™, MCR 502).

As used herein a "swelling agent" is meant to encompass any biocompatible agent that will increase the volume of a paste as described herein, once the paste with swelling agent incorporated is placed in an aqueous environment. A swelling agent may be selected from: salts of hyaluronic acid (e.g., sodium hyaluronate); cellulose derivatives (e.g., carboxymethylcellulose); or polyacrylic acid derivatives (e.g., Carbomers). A swelling agent may advantageously be approved for use in injectable compositions. Also having a swelling agent that does not interfere with the injectability of the paste (for example, is not too grainy, does not precipitate and is easy to disperse again) would be of benefit. It may also be advantageous, if the swelling agent is able to provide a suitable amount of swelling without reducing the overall % of the polymers of the paste as described herein (i.e. be a small percentage of the overall paste). Furthermore, a swelling agent that exhibits high rate of swelling and quick swelling characteristics (for example, swell within minutes of injection) would be beneficial.

METHODS

Paste preparation

The paste was prepared by weighing the polymers into a glass vial and stirring at 60°C. The polymers formed a homogenous melt. If drug is to be added, it is added following the polymer paste preparation. The values for the paste polymers (i.e. hydrophobic water-insoluble polymer; low molecular weight biocompatible glycol; and, if used, the di-block copolymer and/or swelling) is prepared as a total % out of 100% before mixing with drug. When the drug is added the % associated therewith is a percent of the total composition with drug and the "pre-drug paste" component %s are based on their proportions prior

to adding the drug. For example, 4% means 4g of drug in 100 g paste. Drug(s) were incorporated using levigation or a mortar and pestle.

The injectability of a paste will depend on many parameters (i.e. needle size, needle lengths, volume, tissue backpressure, strength of the person administering the paste). Normally it is preferred that a paste be easily drawn up into a syringe using a 14 gauge needle and easily injected into a tissue zone using an 18 gauge or even smaller needle with a small amount of extra pressure. However, for particular uses and depending on the gauge of the needle, having a more viscous paste (i.e. more difficult to inject), may be desirable.

Viscosity measurement

Viscosity measurements were taken using a cone plate rheometer (Anton Paar™, MCR 502) and recorded as a function of shear rate at constant temperature.

Water absorption by pastes containing a swelling agent

Pastes containing a swelling agent were prepared by incorporating increasing amounts of a base paste (PEG:PLGA) into the swelling agent (sodium hyaluronate) using mortar and pestle. Around 20 mg of paste samples (n=3) for each paste formulation were weighed on filter membranes (0.45 µm) and repeatedly weighed after soaking in water at 37°C. For each time point, excess water was carefully removed using a vacuum pump.

In vitro drug release assays

The drug-loaded paste can be aliquoted for *in vitro* release studies. Paste (50-100 mg) is deposited at the bottom of a test tube and release medium is added (5-10 mL, sink conditions). Release medium is phosphate buffered saline (PBS, 10mM, pH 7.4) or PBS containing 1% Albumin. The test tubes are kept in a 37°C incubator until the end of the study. Release samples are taken at appropriate time points by replacing the complete release medium (supernatant) and analyzing it for total drug using Reversed phase high-performance liquid chromatography with ultraviolet (UV) detection (RP-HPLC-UV).

TABLE 1. Chromatographic parameters used in RP-HPLC

Parameter	Specification

HPLC	Waters (1525 Binary HPLC Pump, 2489 UV/Visible Detector, 717 plus Autosampler)
Detector	UV/Visible
Flow rate	1 mL/min
Column	C-18, Nova-Pak, 4 μ m, 3.9 x 150 mm
Column Temperature	Ambient, no temperature control
Injection Volume	20 μ L
Elution	isocratic

TABLE 2. Mobile phase, retention times and UV detection wavelength for studied drugs.

Drug	Mobile phase composition (v/v)	Retention time (min)	UV detection wavelength (nm)
Bicalutamide/ enzalutamide	30/30/40 Acetonitrile/methanol/water (adjusted to pH 3.4 with glacial acetic acid)	3 min	272
Docetaxel	30/30/40 Acetonitrile/methanol/water (adjusted to pH 3.4 with glacial acetic acid)	6 min	228
VPC-27	300/180/35 Acetonitrile/methanol/water + 200 μ L glacial acetic acid	4.3 min	244
Rapamycin	200/175/125 Acetonitrile/methanol/water	2.9 min	278
Cephalexin	20/80 Acetonitrile/water (adjusted to pH 3.4 with glacial acetic acid)	5 min	254

Lidocaine	50/50 Acetonitrile/ammoniumacetate 20 mM (pH 6.4)	3.2 min	220
Desoximetasone	50/50 Acetonitrile/ammoniumacetate 20 mM (pH 6.4)	2 min	244
Sunitinib	55/45 Acetonitrile/ammoniumacetate 20 mM (pH 6.4)	4 min	431
Tamsulosin	50/50 Acetonitrile/ammoniumacetate 20 mM (pH 6.4)	2.3 min	220
Ibuprofen	50/50 Acetonitrile/ammoniumacetate 20 mM (pH 6.4)	1.9 min	220
Gemcitabine	3/97 methanol/water (adjusted to pH 3.4 with glacial acetic acid)	2.3min	272

Intratumoral paste injection

Athymic male nu/nu mice (uncastrated) have been injected with 4×10^6 LNCap cells suspended in Matrigel™ subcutaneously in the left flank. Treatment allocation began once a single site tumor reached 150-200mm³ via caliper measurement. Drug-loaded paste (30 µL) was injected into the tumor using a 21 gauge needle. Serum prostate specific antigen (PSA) levels were measured over time and tumor size was monitored.

In another experiment, groups of five to six animals received 30-40 µL paste intratumorally once the tumor had reached a size of 100 mm³. Tumor growth and serum PSA levels were monitored for the following 12 weeks. Local delivery of paste subcutaneously in rats.

Five groups of rats (male, Sprague Dawley™) with six animals in each group received one injection of paste formulation (0.1 mL) subcutaneously in their flank. The paste formulation was based on a

50:50 mixture of PEG 300™ and PLGA. Lidocaine was incorporated into the paste at 80, 100, 120, 140, and 160 mg per g of paste. The corresponding doses for each group were 23, 29, 36, 40 and 45 mg of Lidocaine per kg.

Blood was collected from the saphenous vein over four weeks at 0, 0.25, 1, 4, 24, 48, 168 336, 504 and 672 hours after injection. Lidocaine concentrations in rat serum were determined using ultra high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS). A non-compartmental analysis was then applied to each data set using Phoenix 64™ (Build 6.3.0.395) WinNonlin 6.3™ to determine relevant pharmacokinetic parameters.

Kidney Pelvis Injection of Paste

After placement of a ureteral catheter, three pigs received an injection of 1-2 mL of polymeric paste into the kidney pelvis. After removal of the ureteral catheter, a urinary catheter was placed and urine collected for 3h intervals over 24h. Blood was collected from an ear vein over 24 h and gemcitabine concentrations were determined using ultra high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS).

EXAMPLES

EXAMPLE 1. Viscosity of polymeric pastes manufactured using different ratios of PLGA, PEG and diblock copolymer.

The polymeric paste is a biocompatible formulation comprised of two or three constituents: poly-(lactic-co-glycolic) acid (PLGA), a diblock copolymer of DL-lactide (DLLA) (optional) and methoxy polyethylene glycol (mePEG) termed poly(DL-lactide)-methoxy polyethylene glycol (PDLLA-mePEG), and polyethylene glycol with a molecular weight of 300 Da (PEG 300™). Drug or drug mixtures can be incorporated into the paste through levigation with a spatula and the paste can be injected through a 20G needle. The PLGA is comprised of equal amounts of LA and GA (50:50 Poly[DL-lactide-co-glycolide]) and may have a degradation time of 1-2 months. The polymeric drug delivery paste may be an injectable viscous solution at 37°C. After injection into an aqueous tissue environment, the paste may transform into a waxy solid, which may serve as a sustained release platform for incorporated drug(s).

Polymeric pastes were manufactured using different weight ratios of PLGA (Durect™, Alabama) (IV = 0.15-0.25 dL/g, 50:50 ratio of LA to GA), PEG with a molecular weight of 300 Da (Polysciences™, USA) and diblock copolymer (synthesized in house, MW = 3333 Da, comprising 40% PLLA and 60% methoxypolyethylene glycol (w:w)). The diblock copolymer may be used to adjust the degradation profile of the polymeric paste and the release profile of the drug(s). The diblock copolymer can help to encapsulate hydrophobic drugs due to its amphiphilic characteristics. In aqueous solution, the diblock can spontaneously arrange itself in micelles that can host hydrophobic drug in the poly (DL lactic acid) (PDLLA) core surrounded by the hydrophilic PEG or mePEG chains⁵³⁻⁵⁵.

The components were weighed into a glass vial and stirred overnight at 37°C to form a homogenous mixture. Viscosity measurements were taken using a cone plate rheometer (Anton Paar™, MCR 502) and recorded as a shear rate at constant temperature. Pastes comprised of PEG and PLGA had very low viscosities at low PLGA content such that the viscosity of pastes at 80% PEG were less than 1 Pa·s. **FIGURE 1** shows that as the concentration of PLGA increased, paste viscosity rose very quickly to over 100 Pa s for the 40% PEG and 60% PLGA composition. **FIGURE 1** also shows that the addition of diblock copolymer in place of PLGA reduced the viscosity considerably so that at 13% diblock with 50% PEG and 37% PLGA the viscosity was less than 10 Pas, and was reduced even further using 26% diblock.

EXAMPLE 2. The release of PEG 300™ from polymeric paste.

Seven compositions of polymeric pastes were manufactured from PLGA, PEG and diblock copolymer as described in EXAMPLE 1. For each of the seven different polymeric pastes, 8 × 100 mg each were weighed into the corner of 8 × 20 ml pre-weighed scintillation vials by holding each vial at a slight angle. 10 ml of water was added to each vial with the vial still held at an angle so the paste remained in the vial corner whilst exposed to water. After 10 minutes the outer surface of each paste whitened slightly indicating setting of the paste and the vials were then reoriented to the vertical position. This procedure prevented a premature disruption of the setting paste upon exposure to water turbulences. The vials were capped and placed in a 37°C oven. At various time points the vials were removed, water was aspirated and the contents dried for one hour in a 37°C incubator followed by one day of vacuum drying at room temperature. The vials were then re-weighed to determine the weight loss of water-soluble polymer (PEG or diblock) that dissolved into the water from the polymer paste. **FIGURE 2** shows that most of the PEG or diblock was released by 2 days.

The values of % polymer released approximately matched the initial weight of PEG and diblock present by % in each formulation.

EXAMPLE 3. Release of docetaxel, VPC-27 and bicalutamide from polymeric pastes.

Polymeric pastes were manufactured from 50:50, 55:45, 60:40 weight ratio compositions of PLGA (50:50 IV = 0.15-0.25 dL/g) and PEG 300™, 50:37:13 ratios of PEG:PLGA:Diblock, or 50:24:26 ratios of PEG:PLGA:Diblock using the methods described in EXAMPLE 1. The presence of the diblock copolymer allows more detailed control of drug release. This diblock copolymer has been previously described to increase the water solubility of hydrophobic drugs by forming diblock micelles with hydrophobic cores that allows the drugs to partition into the core and increase the apparent solubility. In the paste application as water enters the paste matrix the water soluble diblock begins to dissolve out and any drug dispersed at the molecular level may become “micellized” in the diblock milieu to increase drug release. The drugs VPC-27, bicalutamide or docetaxel were added at various weight ratios directly into the paste with mixing by standard spatula levigation techniques. The drug release was studied according to the descriptions found in the general methods section (*In vitro* drug release assays, **TABLE 1** and **TABLE 2**).

FIGURE 3 shows the release of VPC-27, docetaxel and bicalutamide from a 50:50 (PEG:PLGA) paste. Docetaxel (at 4% w/w) and bicalutamide (at 4% w/w) released with similar profiles showing a fast burst of release over 5 days (10% drug released) followed by a slower more sustained release over the next 40 days where a further 20% of encapsulated drug was released (**FIGURE 3A**). VPC-27 (at 10% w/w) released slowly from the paste reaching about 15% of total encapsulated drug released by day 45 (**FIGURE 3A**). When the concentration of VPC-27 was reduced to 4%, the release profiles of docetaxel and bicalutamide were similar to each other but a little slower overall than from the paste containing 10% VPC-27. However, the release rate of VPC-27 was almost the same as the other two drugs using a 4% w/w drug loading (**FIGURE 3B**).

FIGURE 4 shows the release of docetaxel, Bicalutamide, and VPC-27 from PEG:PLGA:Diblock pastes 50:37:13 w/w % or 50:24:26 w/w %. **FIGURE 4A** shows that the release rate of docetaxel from 13% and 26% diblock loaded pastes is increased in comparison to the 50:50 paste mixtures shown in **FIGURE 3** (no diblock). **FIGURE 4A** further shows that by day 10, between 40 and 60% of encapsulated docetaxel was released from the 13% and 26% diblock pastes as compared to less than 17% being released from the 50:50 pastes shown in **FIGURE 3**. The addition of diblock

copolymer to the PEG:PLGA paste had a similar effect on the release rates of bicalutamide (**FIGURE 4B**) and VPC-27 (**FIGURE 4C**). By day 10, the release was approximately 60% for both drugs at a diblock loading of 13%, and approximately 100% for pastes containing 26% diblock compared to less than 17% release for either drug from 50:50 pastes with no diblock.

FIGURE 5 shows the release of docetaxel (0.25%), bicalutamide (4%), and VPC-27 (4%) w/w from a PEG:PLGA:Diblock paste (50:37:13 w/w %). Drug release was characterized by a small burst release within the first day and a slower release of drug over the next 35 days. After one day, 24% docetaxel, 8% bicalutamide and 12% VPC-27 were released, followed by a slow release reaching 32% docetaxel, 16% bicalutamide and 19% VPC-27, on day 35 (**FIGURE 5**).

FIGURE 6 shows the effect of varying PLGA:Diblock ratios on the release rates of docetaxel (0.5%), bicalutamide (4%) and VPC-27 (4%) from PEG:PLGA:Diblock pastes (50:Y:X w/w %). Diblock (X) varied from 7, 13, 19 to 25% and PLGA (Y) varied accordingly from 43, 37, 31 to 25% w/w %.

FIGURE 6 shows that by increasing diblock paste content (7%, 13%, 19%, 25%) and decreasing PLGA content, drug release rates increased. For example, at the low diblock concentration, docetaxel was released in a burst of 20% on day 1 and reached 34% on day 21 (**FIGURE 6A**); while at the high diblock concentration, docetaxel was released in a burst of 67% on day 1 and reached 78% on day 21 (**FIGURE 6D**). The effect was similarly pronounced for bicalutamide and more pronounced for VPC-27 (**FIGURE 6**).

FIGURE 7 shows how high amounts of PEG affects the release rates of docetaxel (4%), bicalutamide (4%) and VPC-27 (4%) from PEG:PLGA pastes (63:37 or 76:24). At too high a ratio of PEG to PLGA the paste may be very fluid and tends to disintegrate *in vivo* because the PLGA is over dispersed and unable to form a cohesive solid. Docetaxel released quickly from the high PEG content pastes reaching between 40% and 50% released drug at day 11 (**FIGURE 7A**). Neither bicalutamide nor VPC-27 released quickly from either of the high PEG pastes, but release was steady and continuous even after 28 days (**FIGURE 7B** and **7C**). At 11 days, drug release from either high PEG paste formulation was below 22% for both bicalutamide and VPC-27.

FIGURE 8 shows more release profiles of docetaxel (1%), bicalutamide (4%), and VPC-27 (4%) from PEG:PLGA pastes without diblock. Three pastes were prepared with 50:50, 55:45, 60:40 PEG:PLGA (w/w %). The pastes stayed cohesive and the release of the drugs increased with increasing PEG

content. The release of the three drugs in the 50:50 paste was around 2-5%, for the 55:45 paste around 10% and for the 60:40 paste between 10 and 20% on day 18.

EXAMPLE 4. Release of rapamycin from polymeric pastes.

Polymeric pastes comprised of 50% PEG300, 37% PLGA (IV 0.15, 50:50 ratio) and 13% diblock copolymer containing a drug mixture of docetaxel, rapamycin and VPC-27 (at 1%, 1% and 4% w/w, respectively) were manufactured as described in the general methods section. Drug release experiments were performed as described previously (*In vitro* drug release assays, **TABLE 1** and **TABLE 2**).

FIGURE 9 shows the release rates for docetaxel, rapamycin, and VPC-27, from PEG:PLGA:Diblock pastes (50:37:13). Docetaxel released in a sustained manner reaching almost 45% drug release at day 8. VPC-27 released well, reaching almost 20% release at day 8. Rapamycin released very slowly with only 4% of the encapsulated drug being released at day 8.

EXAMPLE 5. Release of Cephalexin from polymeric paste.

Polymeric pastes comprised of 50% PEG300, 37% PLGA (IV 0.15, 50:50 ratio) and 13% diblock copolymer containing cephalexin at between 2 and 19% loading were prepared as described in Examples 1 and 3. For cephalexin, albumin was not included in the PBS as this drug is water soluble. The drug release was studied according to the descriptions found in the general methods section (*In vitro* drug release assays, **TABLE 1** and **TABLE 2**). **FIGURE 10** shows that Cephalexin released quickly from the polymeric pastes where almost all drug was released from drug loaded pastes at 1 day.

EXAMPLE 6. Effect of paste geometry and drug loading on the release of lidocaine from polymeric paste.

PEG:PLGA:Diblock paste (50:37:13) containing lidocaine (non-HCl form) at 2-10% w/w loading were mixed as previously described. To achieve different paste geometries, the 8% w/w paste was placed in a syringe and 100 mg samples were extruded through an 18 gauge needle onto the base of a cold (approximately 2°C) 20 ml glass scintillation vial as either a cylinder, a crescent shape in the lower corner of a tilted vial or as a hemisphere “blob” in the middle of the base of the vial. The cold temperature assisted in keeping the shape of the very viscous paste at this temperature. 10 ml of

cold PBS were very gently added and the vial was left for 10 minutes to allow the outer surface of the paste to whiten a little. The vials were then placed in a 37°C incubator. At dedicated time points the 10 ml of PBS were removed and replaced with another 10 ml of room temperature PBS. The drug release was studied according to the descriptions found in the general methods section (*In vitro* drug release assays, **TABLE 1** and **TABLE 2**).

Lidocaine released from all geometric forms with a burst phase between approximately 50% and 70% at day 2 (**FIGURE 11A**). After that the release rate slowed, especially for the hemisphere shape, such that by day 7 this shape had released approximately 65% of the drug as compared to 88% and 92% released from the crescent and cylinder shapes, respectively. All paste shapes released small amounts of lidocaine between 7 to 28 days. The release rates for lidocaine using different % w/w loadings were similar and are shown in **FIGURE 11B**.

EXAMPLE 7. Release of docetaxel, VPC-27 and enzalutamide from polymeric pastes.

Polymeric pastes were manufactured from 63:37 compositions of PEG 300™ and PLGA (50:50 IV=0.15) or from 50:37:13 ratios of PEG:PLGA:Diblock using the method described earlier. The drugs VPC-27, enzalutamide or docetaxel were added at various weight ratios directly into the paste with mixing by standard spatula levigation techniques. The drug release was studied according to the descriptions found in the general methods section (*In vitro* drug release assays, **TABLE 1** and **TABLE 2**). All drugs released more quickly from the diblock containing paste than the high PEG content paste as shown in **FIGURE 12**. From the high PEG content PEG:PLGA paste (63:37), VPC-27 released slowly without any apparent burst phase of release (**FIGURE 12C**) but a burst phase occurred from the PEG:PLGA:diblock containing paste (50:37:13), resulting in nearly 35% of drug released by day 50 (**FIGURE 12C**). Docetaxel released well from both pastes (approximately 50% released by day 50) (**FIGURE 12A**) and enzalutamide released approximately 40% of the total encapsulated drug by day 50 (**FIGURE 12B**).

EXAMPLE 8. Solubilization of drugs by diblock copolymer.

Diblock copolymer (molecular weight 3333, PLLA 40%, MePEG 2000 60%) was weighed out into 2 ml glass vials in various amounts at concentrations of 0 to 45 mg/ml. The drugs docetaxel, bicalutamide, and VPC-27 were added in a drug polymer ratio of 1:9 (one part drug, 9 parts diblock copolymer) from stock solutions in acetonitrile and topped up to approximately 1 ml. All contents were in solution and the vials were dried down under nitrogen with mild heat followed by vacuum

overnight. The vials were then warmed to 37°C and 1 ml of PBS at 37°C was added. The vials were vortexed to dissolve their contents and the contents were then centrifuged at 15000 rpm in a microfuge and filtered through a 0.2 µm filter to give a clear solution. The concentration of each drug in each solution was then measured using RP-HPLC described in the general methods section (*In vitro* drug release assays, **TABLE 1** and **TABLE 2**). Drugs were solubilized effectively by the diblock copolymer as shown in **FIGURE 13**. For VPC-27 and docetaxel, drug concentrations in the 3.5 to 5 mg/ml range were achieved. Above a diblock concentration of 20 mg/ml, bicalutamide did not stay in solution as shown in **FIGURE 13**.

EXAMPLE 9. Release of lidocaine (10%) and desoximetasone (1%) from PEG:PLGA:Diblock paste (50:37:13).

The paste was manufactured as in EXAMPLE 7 using lidocaine at 10% and desoximetasone at 1%. Drug release was measured using RP-HPLC as described earlier (*In vitro* drug release assays, **TABLE 1** and **TABLE 2**).

FIGURE 14 shows that lidocaine released in the same manner as previously observed with a 50% burst within the first day and an extended release reaching 80% by day 35. Similarly, desoximetasone released with a burst of 50% on day one and reached 100% release on day 35. The injectable lidocaine pastes keep the drug near the local injection site and delays systemic uptake of lidocaine. The suggested drug load is 10% and the maximum injectable volume should be 3 g of paste into the spermatic cord to stay below the maximum single dose of 300 mg. Lidocaine is released in a sustained fashion while the paste degrades.

EXAMPLE 10. Release of Lidocaine from various PEG:PLGA pastes without diblock.

Pastes were manufactured as described in EXAMPLE 1. **FIGURE 15** shows the lidocaine release from PEG:PLGA pastes without diblock. Three pastes were prepared with 50:50, 55:45, 60:40 PEG:PLGA (w/w %) and 8% lidocaine (w/w). The pastes stayed cohesive and drug release was faster in pastes with higher PEG content. Lower PEG content decreased the amount of burst release slightly and by day 18, 100% of lidocaine was released from all pastes.

EXAMPLE 11. Release of Sunitinib from PEG:PLGA:Diblock polymeric paste (50:37:13).

The paste was manufactured as in EXAMPLE 7 and the drug Sunitinib was added at 1% w/w. Drug release was measured using RP-HPLC as described earlier (*In vitro* drug release assays, **TABLE 1** and

TABLE 2). The release of Sunitinib is shown in **FIGURE 16** and is characterized by a burst phase on day 1 with a release of 35% and an extended release phase that reaches approximately 55% at day 44.

EXAMPLE 12. Release of Tamsulosin from PEG:PLGA:Diblock polymeric paste (50:37:13).

Tamsulosin was loaded at 2% w/w to PEG:PLGA:Diblock polymeric paste (50:37:13 PEG:PLGA:Diblock) as described in EXAMPLE 6. Drug release was measured using RP-HPLC as described earlier (*In vitro* drug release assays, **TABLE 1** and **TABLE 2**). The release of Tamsulosin is shown in **FIGURE 17** and is characterized by a burst phase of 47% on day 1. The release continues and reaches 70% by day 6 and 80% on day 21.

EXAMPLE 13: Release of Lidocaine (8%), Cephalexin (2%) and Ibuprofen (5%) from PEG:PLGA:Diblock polymeric paste (50:37:13).

The three drugs were loaded into the paste as previously described in EXAMPLE 3. HPLC analysis for lidocaine, cephalexin and ibuprofen was performed using the general chromatographic set up mentioned earlier (*In vitro* drug release assays, **TABLE 1** and **TABLE 2**). The release of the three drugs is shown in **FIGURE 18**. Cephalexin was released very quickly and reached its maximum at 80% on day 3. Lidocaine and Ibuprofen release was similar and characterized by a burst release of 54% drug by day one and a slower drug release over the next 10 to 15 days, reaching approximately 70% by day 35.

EXAMPLE 14: Effect of drug loaded polymeric paste on the growth of human prostate cancer tumors in mice.

PEG:PLGA:Diblock polymeric paste (50:37:13) containing docetaxel (1%), bicalutamide (1%), and VPC-27 (4%) was manufactured as previously described and injected intra-tumorally (see Intratumoral paste injection, **FIGURE 19**).

In a different experiment, groups of mice were treated with a formulation containing either docetaxel alone, bicalutamide and docetaxel, docetaxel and VPC-27 or all three drugs. Treatment groups that received both docetaxel and bicalutamide or docetaxel alone showed slower tumor growth and a delayed increase in serum PSA levels than groups that received pastes that contained also VPC-27.

EXAMPLE 16: Local release of Lidocaine and absence from serum *in vivo*.

Five groups of rats (male, Sprague Dawley) with six animals in each group received one injection of paste formulation (0.1 mL) subcutaneously in their flank. The paste formulation was based on a 50:50 mixture of PEG 300™ and PLGA. Lidocaine was incorporated into the paste at 80, 100, 120, 140, and 160 mg per g of paste. The corresponding doses for each group were 23, 29, 36, 40 and 45 mg of lidocaine per kg. Lidocaine dissolved at all concentrations to form a clear paste except at the 160 mg/g level, where small crystals were visible that dissolved when warming the paste to 37°C. All formulations were warmed to 37 °C before administration and the injection was smooth.

The concentrations of systemic lidocaine detected in serum were very low (see **FIGURES 22A and 22B**). The maximum concentrations detected in serum in each group were all below the upper limit of its therapeutic range of 5 µg/mL or 5000 ng/mL in all studied strengths. The maximum serum concentrations for the 80, 100, 120, 140, 160 mg/g paste formulations were 557.26 ± 81.15 , 578.90 ± 162.59 , 638.03 ± 190.61 , 855.98 ± 196.18 , 1148.88 ± 838.97 ng/mL respectively. Since the highest dosing level (160mg/g paste or 45 mg/kg) is 10 times above the locally administered lidocaine dose in humans (4.5 mg/kg) using a conventional lidocaine solution.

EXAMPLE 17: Use of swelling agents in paste.

Pastes were manufactured using 68% PEG 300™, 30% PLGA and 2% of a swelling agent. The agents included carboxymethylcellulose, carbomer or sodium hyaluronate. These pastes were effectively injected through a 5F ureteral catheter of 70 centimeters length. In water there was a clearly observed swelling behavior.

The drug gemcitabine was incorporated at 5% (m/m) in the sodium hyaluronate containing paste. This paste was injected through the 5F catheter into the kidney pelvis of a pig. Gemcitabine levels in urine were initially high and levelled off after 5-7 hours (see **FIGURE 25A**). Serum gemcitabine levels were very low, but detectable in all pigs (see **FIGURE 25B**). The paste did not result in any blockage of the ureter and paste fragments were found on the urinary catheter after removal.

EXAMPLE 18: Use of swelling agent, sodium hyaluronate, for Gemcitabine release.

Pastes containing 2% of sodium hyaluronate (SH) and increasing amounts of diblock copolymer were prepared to observe swelling and degradation of these pastes over one hour. The inclusion of SH was associated with a rapid swelling of the paste in water.

As shown in **FIGURE 23**, pastes with 2% SH were swelling rapidly after contact with water. Pastes with 0 and 10% of diblock absorbed less water than pastes with higher diblock copolymer content. Furthermore, these pastes did also not disintegrate over the monitored time. Pastes that contained 20, 30 and 40% diblock copolymer immediately absorbed water to roughly double their initial weight. The 20% paste hold its weight at least over one hour, whereas the 30% and 40% DB pastes lost 30 and 100% of their initial weight over one hour. Overall, a higher amount of DB allows for more rapid water absorption and swelling and quick paste disintegration.

EXAMPLE 19. Release of Gemcitabine from various polymeric pastes.

As shown in **FIGURE 24**, pastes having no diblock copolymer showed delayed release of gemcitabine, except where there was a high PEG 300 level (i.e. 76%) and low PLGA (i.e. 22%). All other compositions showed a burst release at between 0 and 4.5 hours and sustained release thereafter.

Although various embodiments of the invention are disclosed herein, many adaptations and modifications may be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the substitution of known equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. Numeric ranges are inclusive of the numbers defining the range. The word “comprising” is used herein as an open-ended term, substantially equivalent to the phrase “including, but not limited to”, and the word “comprises” has a corresponding meaning. As used herein, the singular forms “a”, “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a thing” includes more than one such thing. Citation of references herein is not an admission that such references are prior art to an embodiment of the present invention. The invention includes all embodiments and variations substantially as hereinbefore described and with reference to the examples and drawings.

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What is Claimed Is:

1. A composition, the composition comprising:
 - (a) a hydrophobic water-insoluble polymer having an inherent viscosity (IV) of about 0.15 to about 0.5 dL/g;
 - (b) a low molecular weight biocompatible glycol; with a molecular weight at or below 1,450 Daltons; and
 - (c) one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof.
2. The composition of claim 1, further comprising a di-block copolymer.
3. The composition of claim 1 or 2, wherein the hydrophobic water-insoluble polymer having an inherent viscosity (IV) of about 0.15 to about 0.5 dL/g is polylactic-co-glycolic acid (PLGA).
4. The composition of claim 1, 2 or 3, wherein the PLGA has a ratio of lactic acid (LA):glycolic acid (GA) at or below 75:25.
5. The composition of any one of claims 1-4, wherein the hydrophobic water-insoluble polymer has an inherent viscosity (IV) of about 0.15 to about 0.3 dL/g.
6. The composition of any one of claims 1-5, wherein the hydrophobic water-insoluble polymer has an inherent viscosity (IV) of about 0.15 to about 0.25 dL/g.
7. The composition of any one of claims 1-6, wherein the low molecular weight biocompatible glycol has a molecular weight between about 76 Daltons and about 1,450 Daltons.
8. The composition of any one of claims 1-7, wherein the low molecular weight biocompatible glycol is selected from Polyethylene glycol (PEG), methoxypolyethylene glycol (mePEG) and propylene glycol.
9. The composition of any one of claims 1-8, wherein the low molecular weight biocompatible glycol is selected from PEG and mePEG.
10. The composition of claim 9, wherein the PEG or mePEG has an average molecular weight of between 300 Daltons and 1,450 Daltons.

11. The composition of any one of claims 1-10, wherein the hydrophobic water-insoluble polymer having an inherent viscosity (IV) of about 0.15 to about 0.5 dL/g is PLGA having an LA:GA ratio of 50:50 and the low molecular weight biocompatible glycol is PEG or mePEG with a molecular weight of about 300 Daltons to about 1,450 Daltons.
12. The composition of claim 11, wherein the ratio of PEG or mePEG to PLGA is between about 80%:20% and about 40%:60%.
13. The composition of claim 12, wherein the ratio of PEG or mePEG to PLGA is between about 80%:20% and about 40%:60%.
14. The composition of any one of claims 1-13, wherein the low molecular weight biocompatible glycol is PEG 300.
15. The composition of any one of claims 2-14, wherein the di-block copolymer is between 13% and 26% of the total, wherein the di-block copolymer substitutes for hydrophobic water-insoluble polymer.
16. The composition of claims 15, wherein the di-block copolymer has one hydrophobic monomer and one hydrophilic monomer.
17. The composition of claims 16, wherein the hydrophilic monomer is selected from: PEG; and MePEG; and the hydrophobic monomer is selected from: PLGA; polylactic acid (PLA); Poly-L-lactic Acid (PLLA); and Polycaprolactone (PCL).
18. The composition of claims 15, wherein the di-block copolymer is amphiphilic.
19. The composition of claims 16 or 17, wherein di-block copolymer is PLLA-mePEG.
20. The composition of any one of claims 1-19, wherein the one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof is selected from one or more of the following categories: anti-cancer drugs; anti-inflammatory agents; anti-bacterial; anti-fibrotic; and analgesic.
21. The composition of any one of claims 1-20, wherein the one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof is hydrophobic.

22. The composition of any one of claims 1-20, wherein the one or more drug compounds or pharmaceutically acceptable salt, solvate or solvate of the salt thereof is hydrophilic.
23. The composition of claim 20, wherein the anti-cancer drug is selected from one or more of the following: Actinomycin; All-trans retinoic acid; Azacitidine; Azathioprine; Bleomycin; Bortezomib; Carboplatin; Capecitabine; Cisplatin; Chlorambucil; Cyclophosphamide; Cytarabine; Daunorubicin; Docetaxel; Doxifluridine; Doxorubicin; Epirubicin; Epothilone; Etoposide; Fluorouracil; Gemcitabine; Hydroxyurea; Idarubicin; Imatinib; Irinotecan; Mechlorethamine; Mercaptopurine; Methotrexate; Mitoxantrone; Oxaliplatin; Paclitaxel; Pemetrexed; Teniposide; Tioguanine; Topotecan; Valrubicin; Vemurafenib; Vinblastine; Vincristine; Vindesine; and Vinorelbine.
24. The composition of claim 20, wherein the anesthetic drug is a local anesthetic selected from one or more of the following: Procaine; Benzocaine; Chloroprocaine; Cocaine; Cyclomethycaine; Dimethocaine/Larocaine; Piperocaine; Propoxycaine; Procaine/Novocaine; Proparacaine; Tetracaine/Amethocaine; Articaine; Bupivacaine; Cinchocaine/Dibucaine; Etidocaine; Levobupivacaine; Lidocaine/Lignocaine/Xylocaine; Mepivacaine; Prilocaine; Ropivacaine; and Trimecaine.
25. A pharmaceutical composition comprising a composition of any one of claims 1-24, together with a pharmaceutically acceptable diluent or carrier.
26. Use of a composition of any one of claims 1-24, for the manufacture of a medicament.
27. Use of a composition of any one of claims 1-24, for the treatment of a medical condition for which the drug is used.
28. A composition of any one of claims 1-24, for use in the treatment of a medical condition.
29. A commercial package comprising: (a) composition of any one of claims 1-24; and (b) instructions for the use.

FIGURE 1

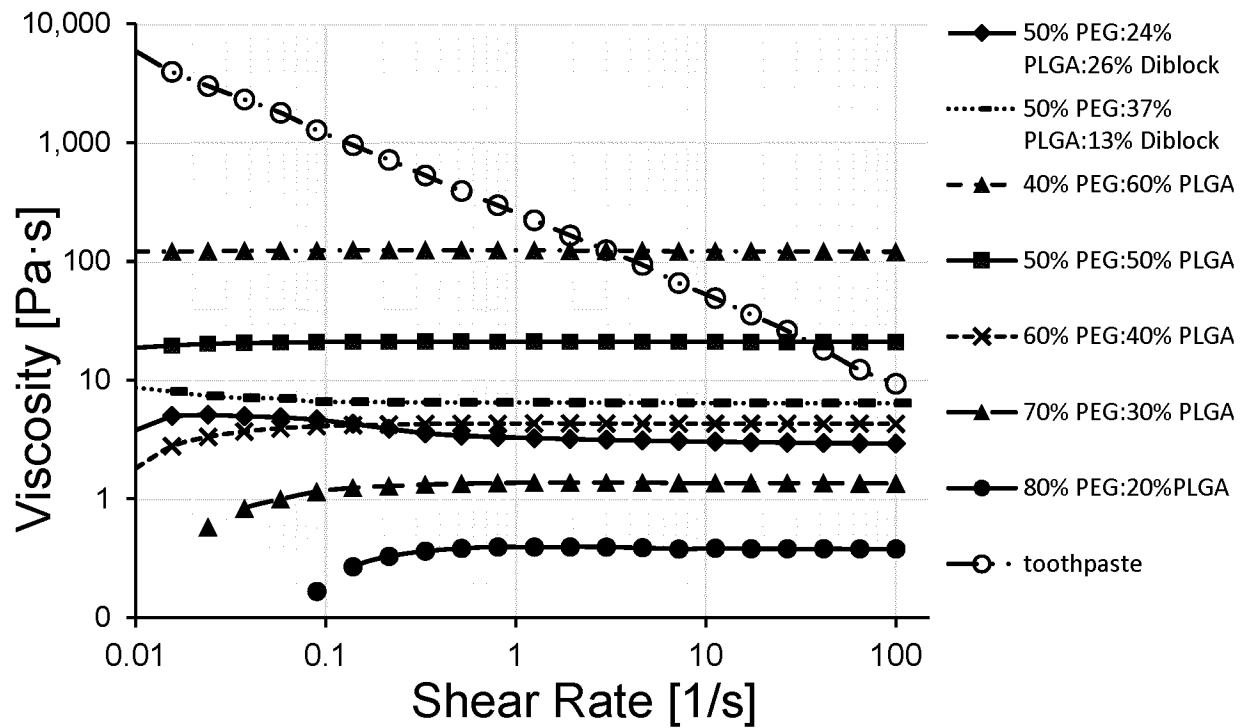


FIGURE 2

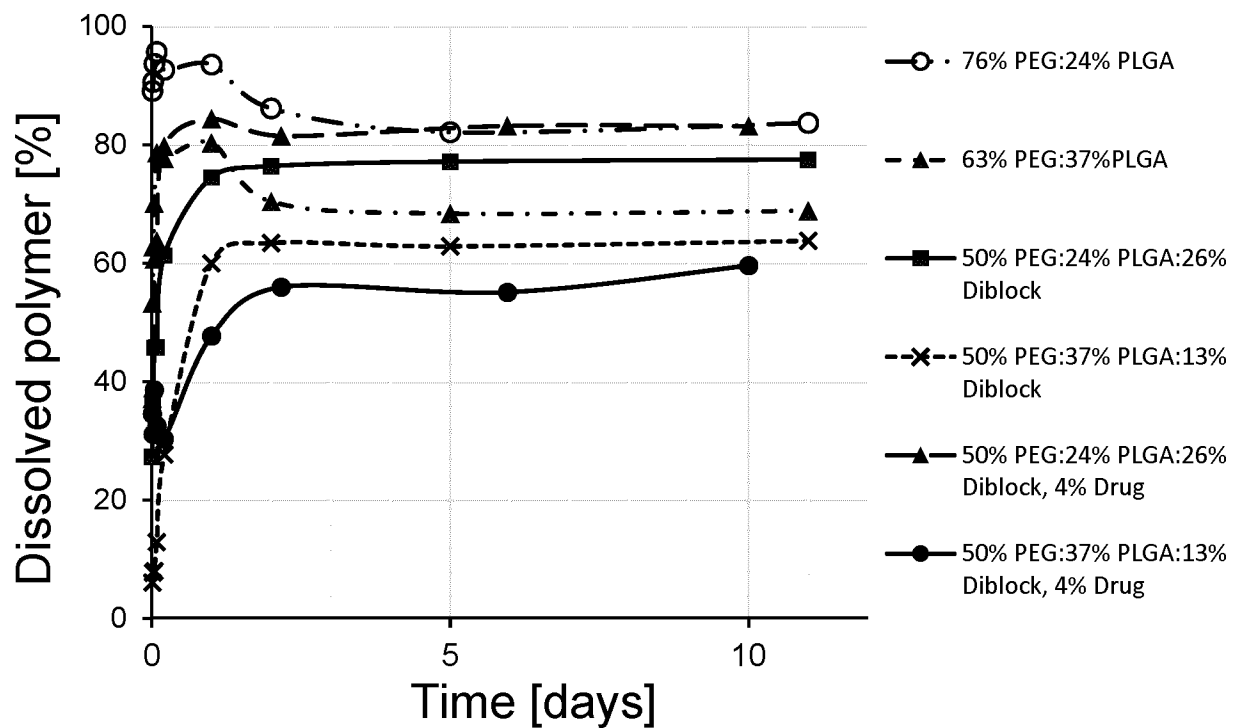


FIGURE 3A

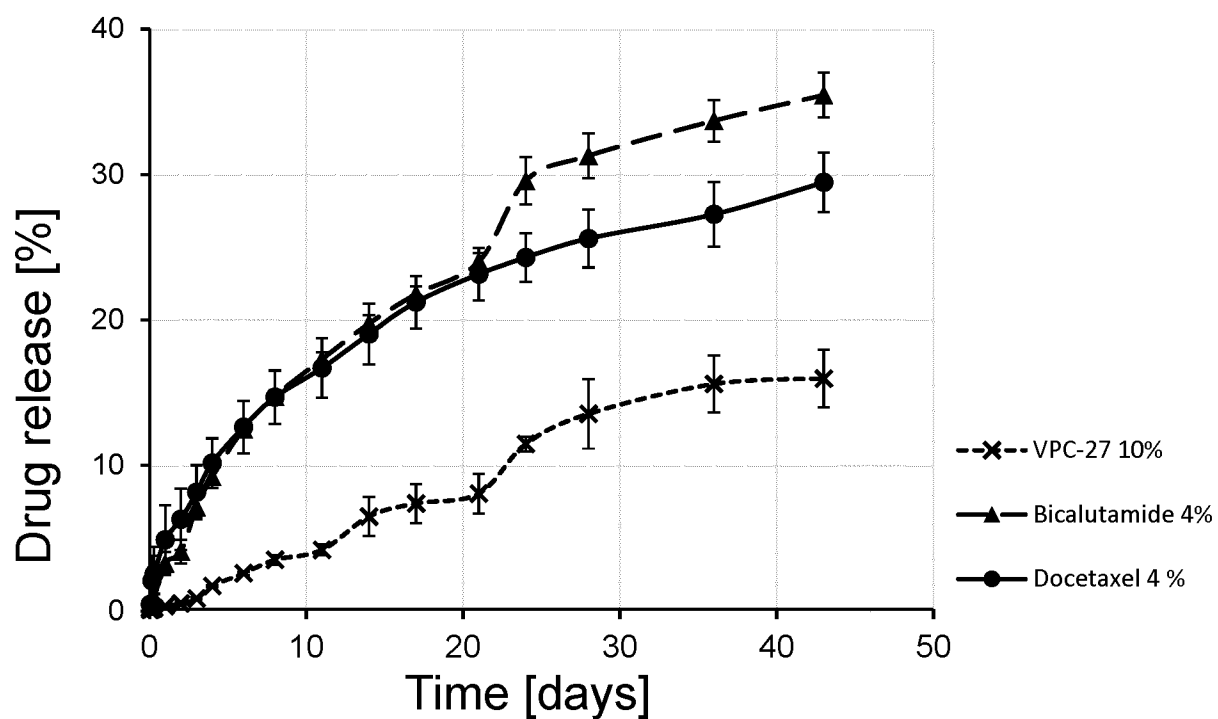


FIGURE 3B

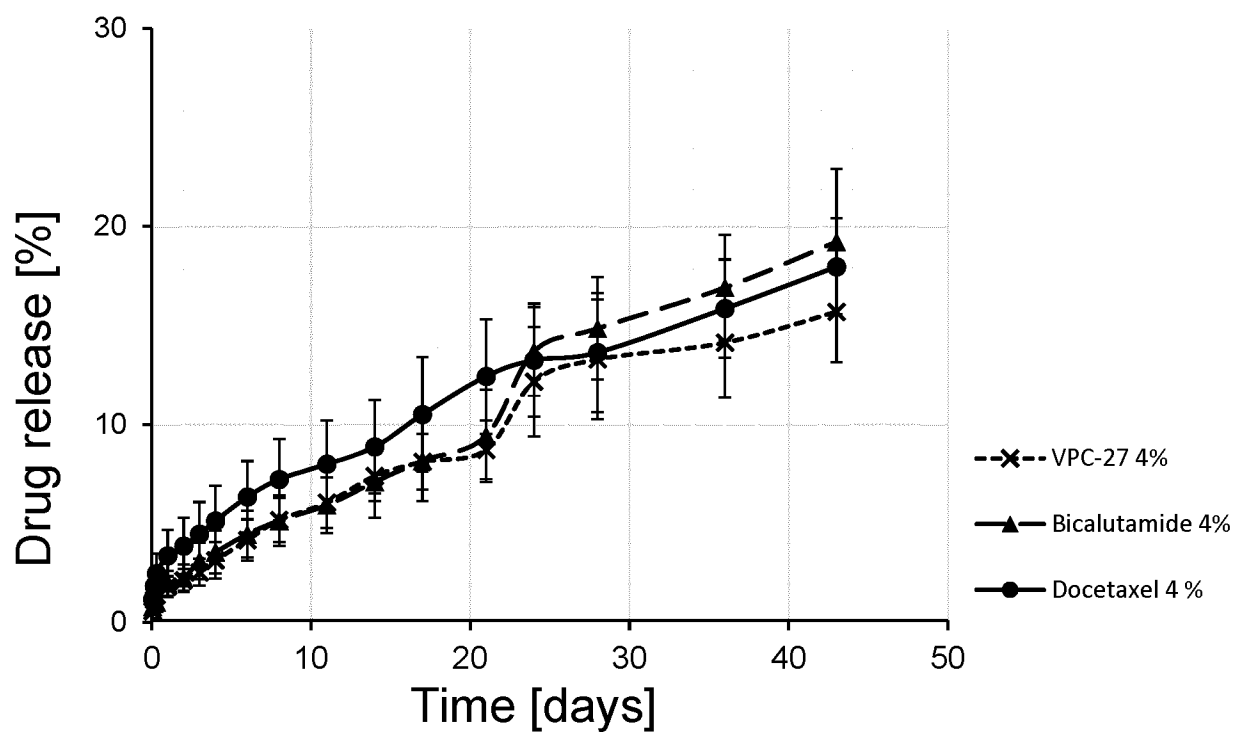


FIGURE 4A

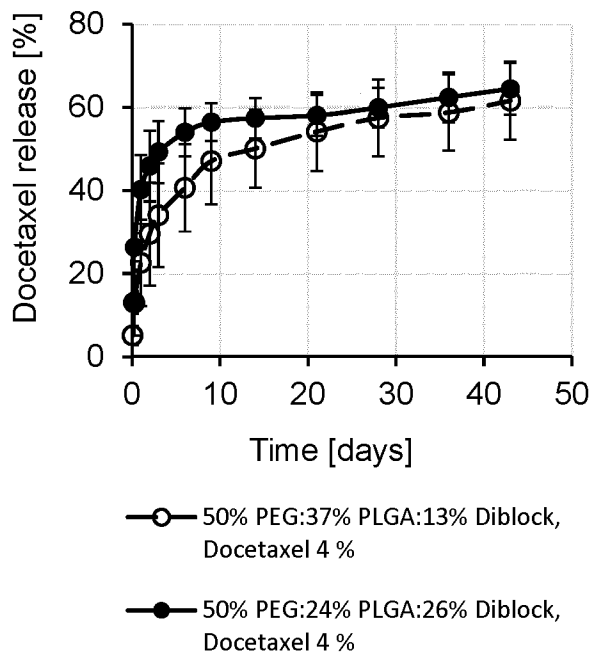


FIGURE 4B

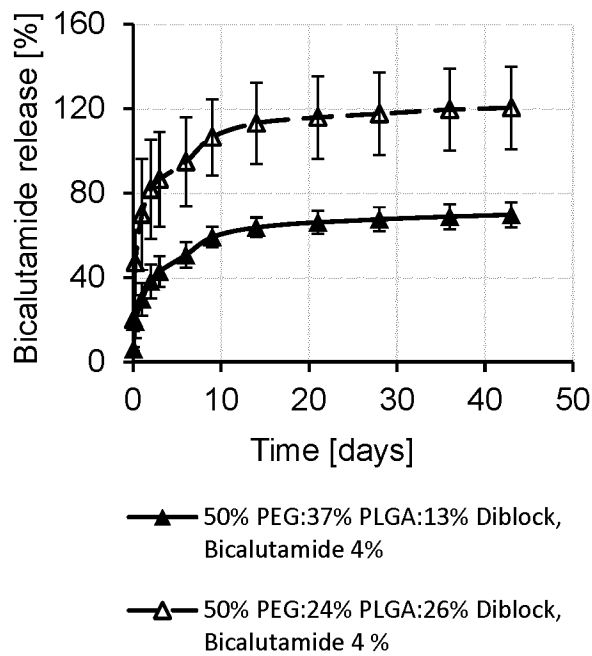


FIGURE 4C

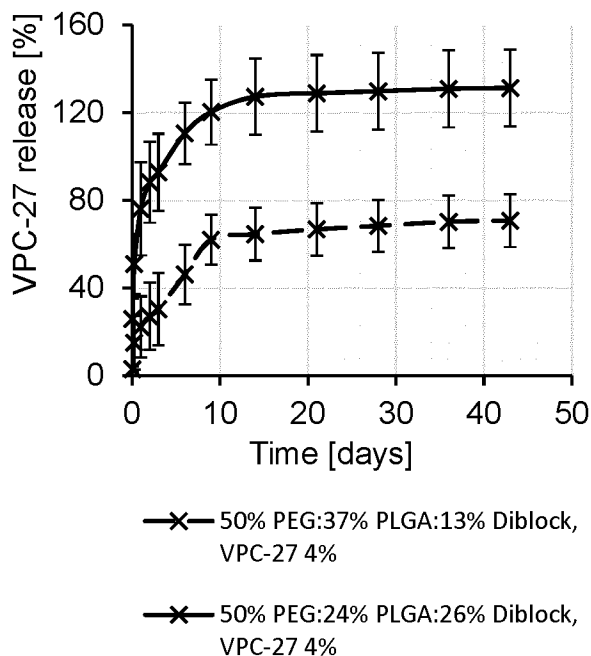


FIGURE 5

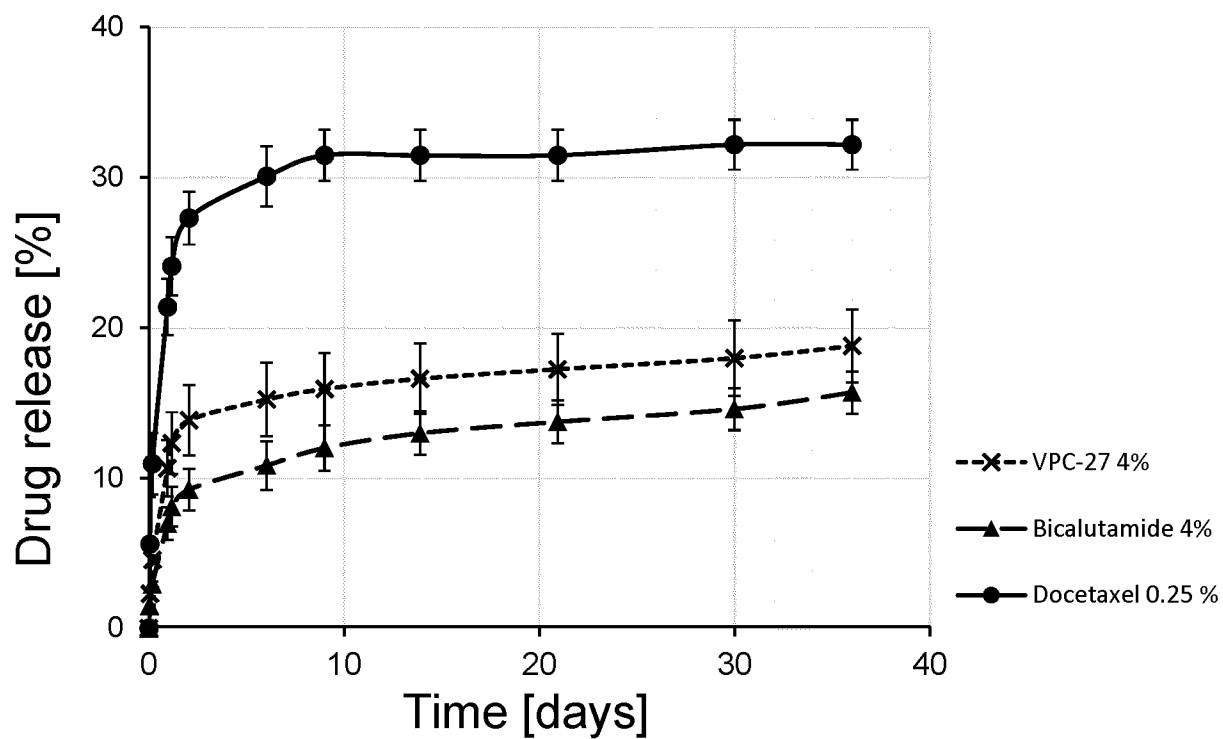


FIGURE 6A

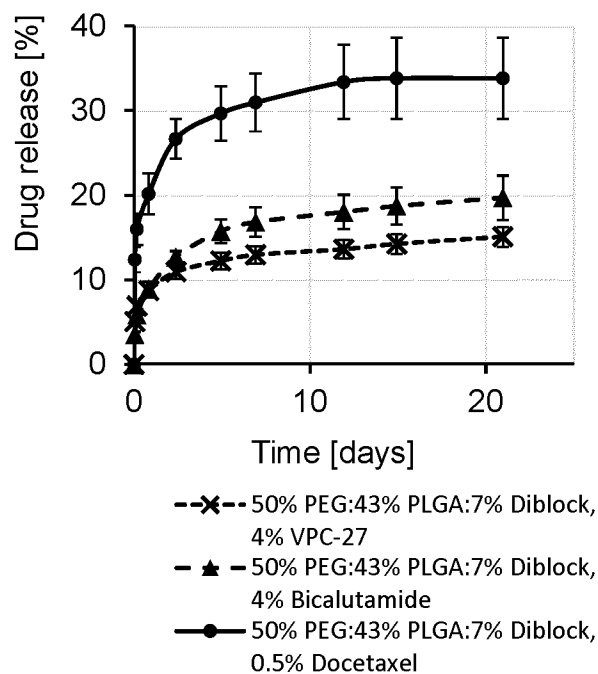


FIGURE 6B

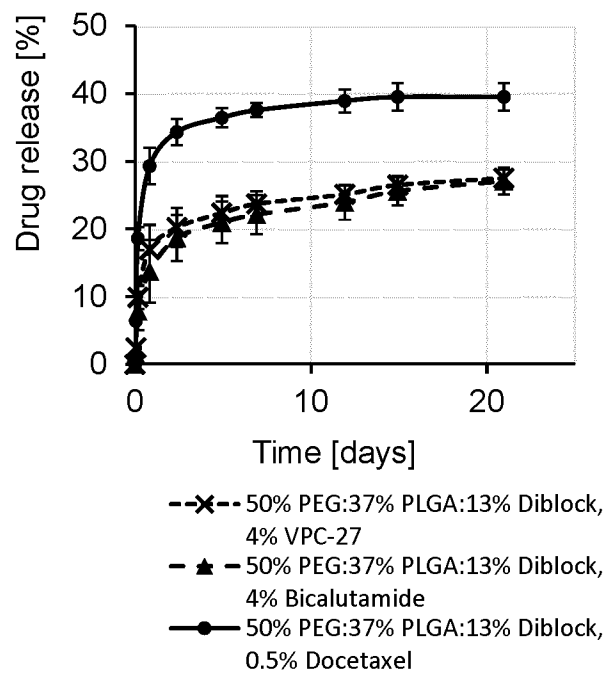


FIGURE 6C

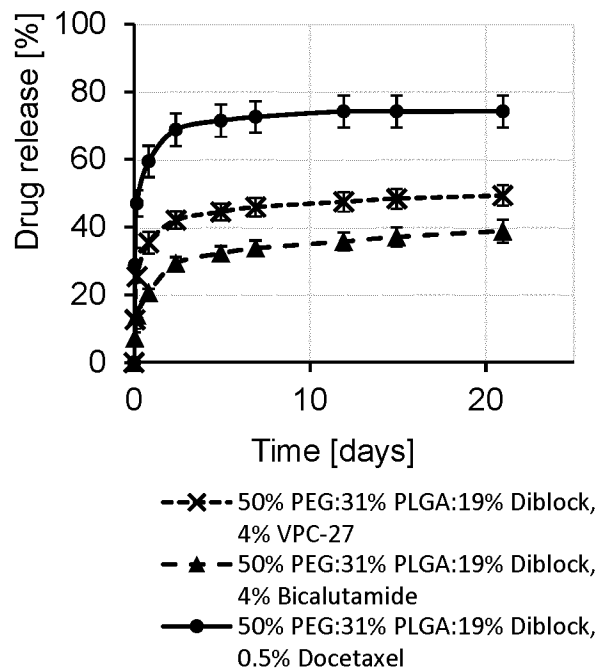


FIGURE 6D

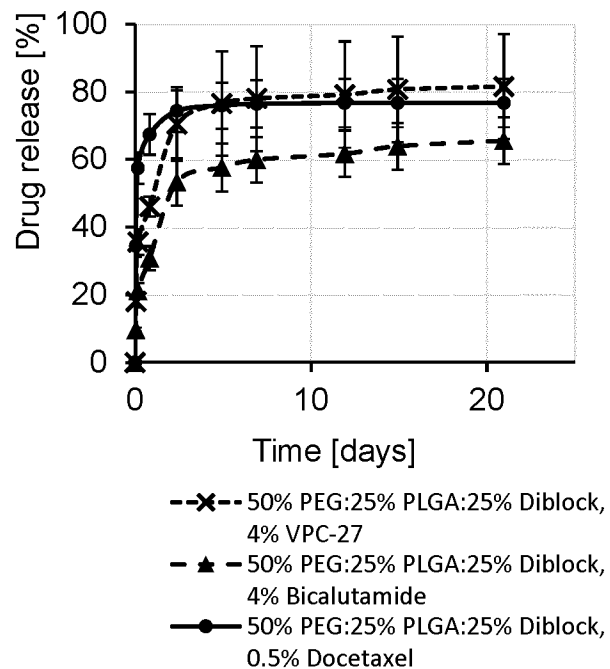


FIGURE 7A

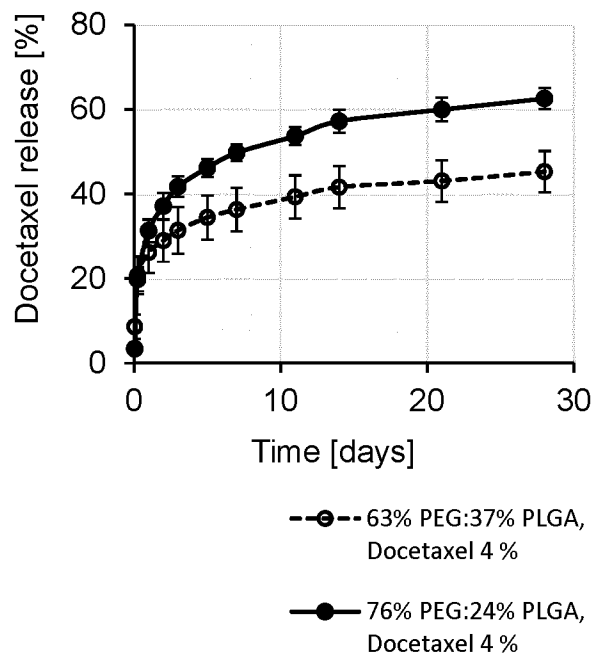


FIGURE 7B

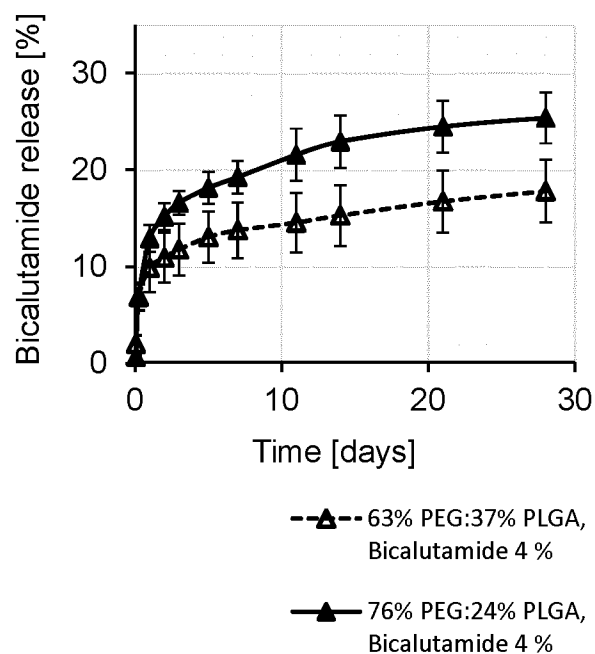


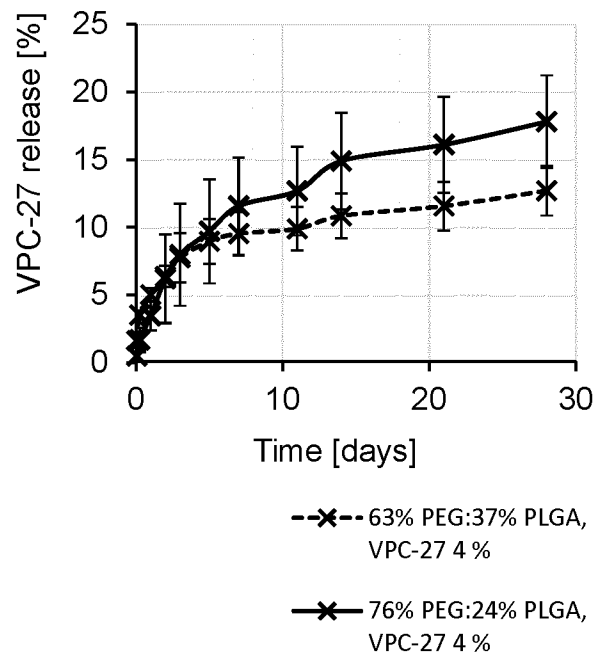
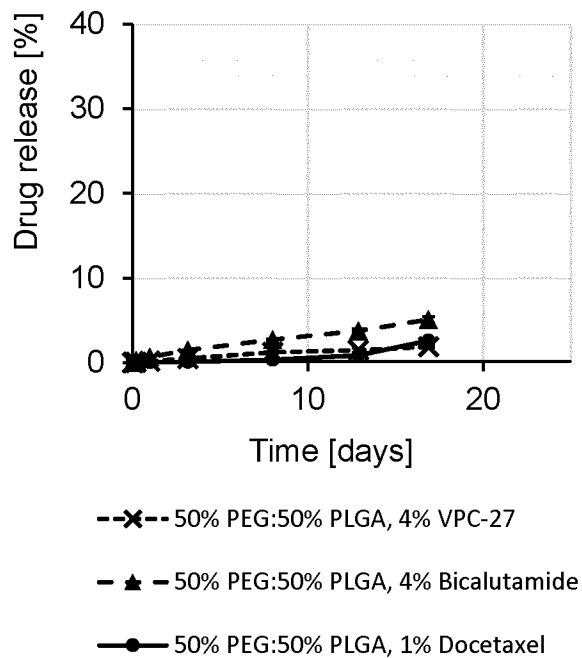
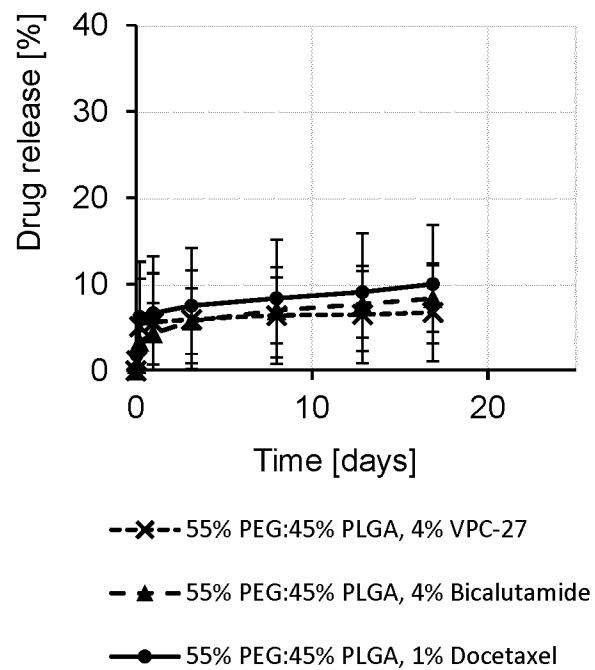
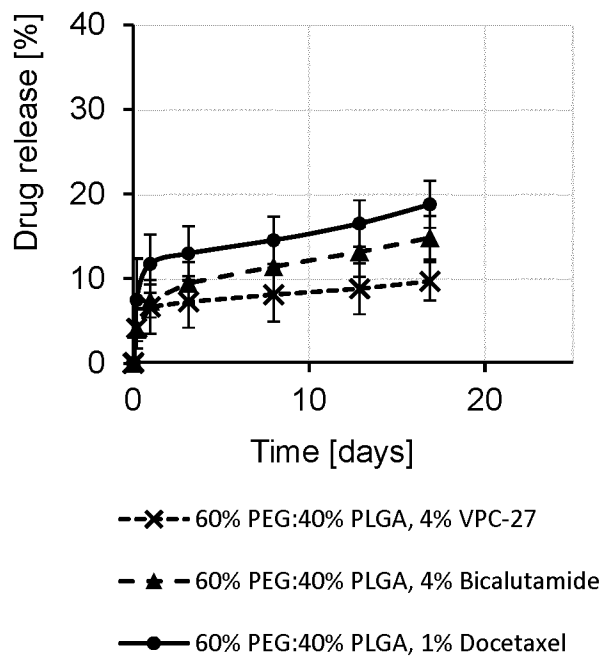
FIGURE 7C**FIGURE 8A****FIGURE 8B****FIGURE 8C**

FIGURE 9

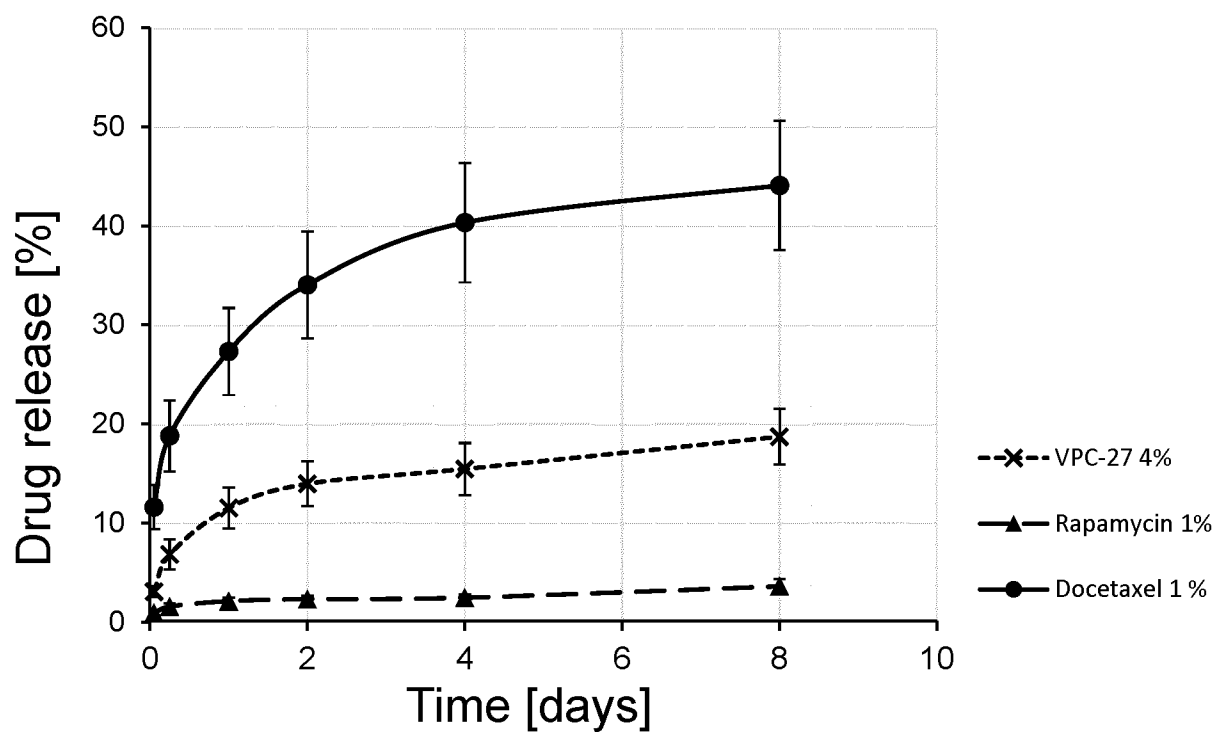


FIGURE 10A

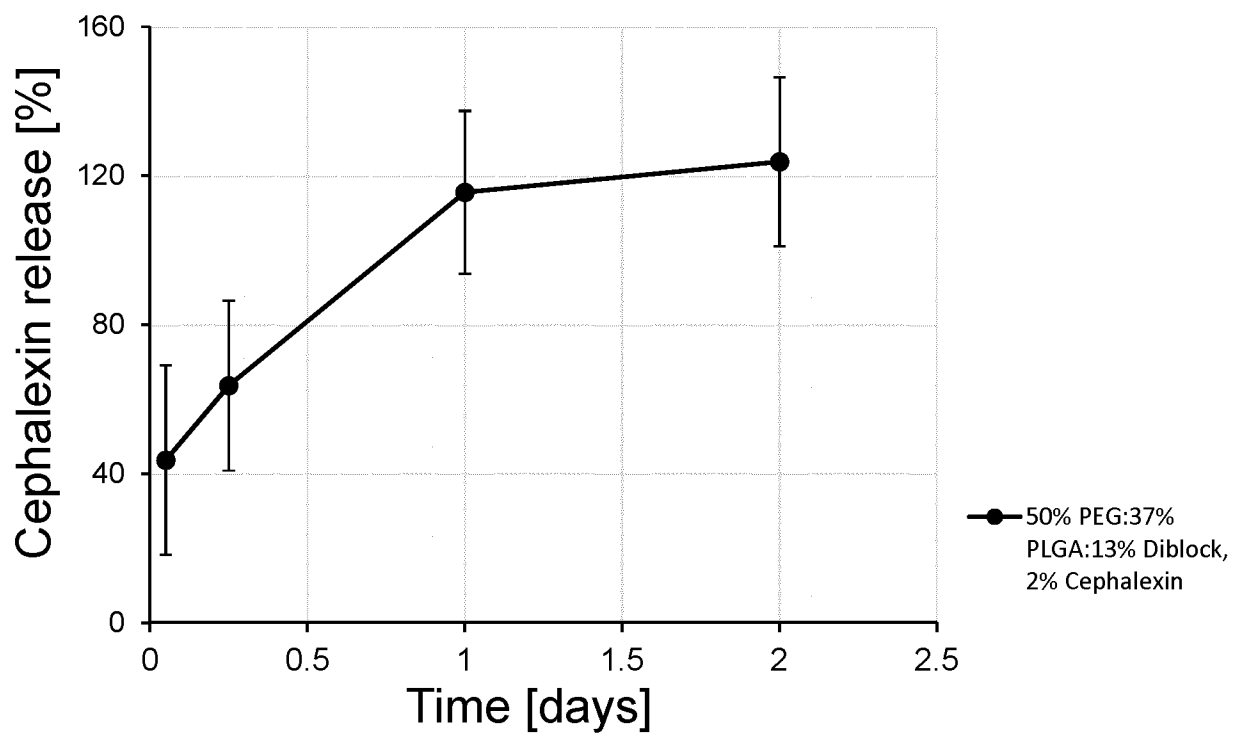


FIGURE 10B

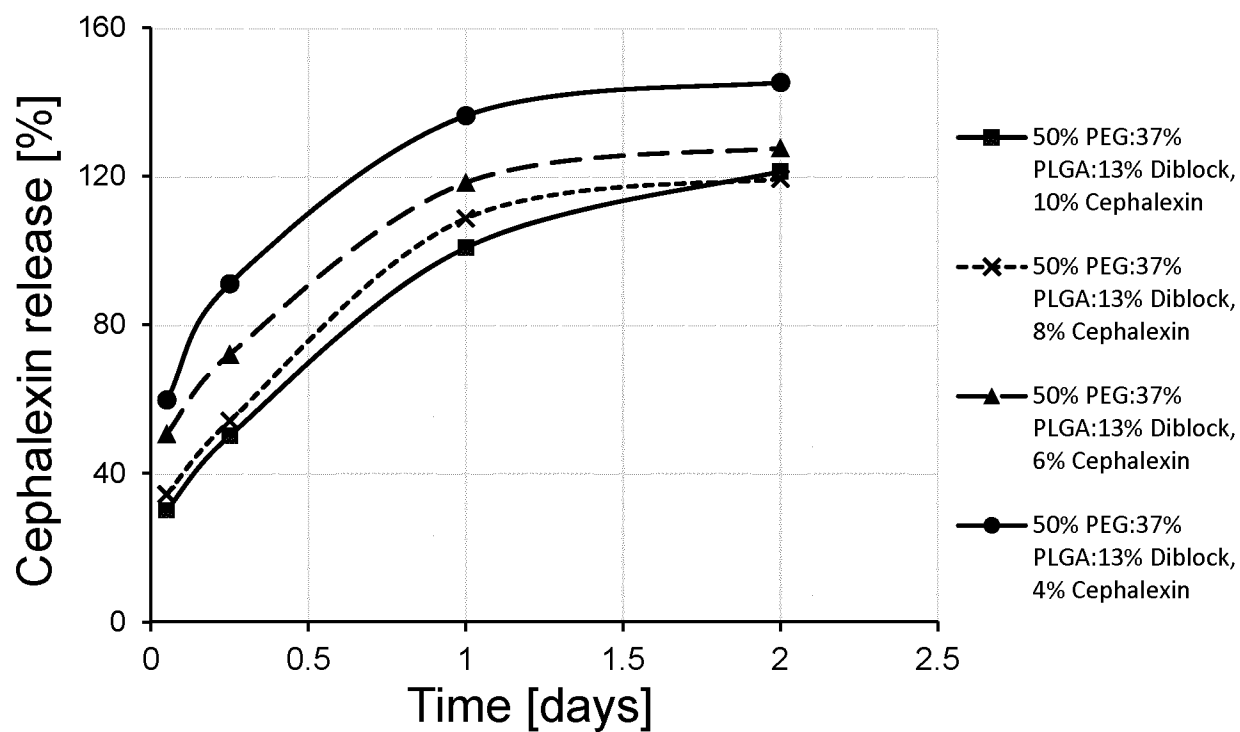


FIGURE 11A

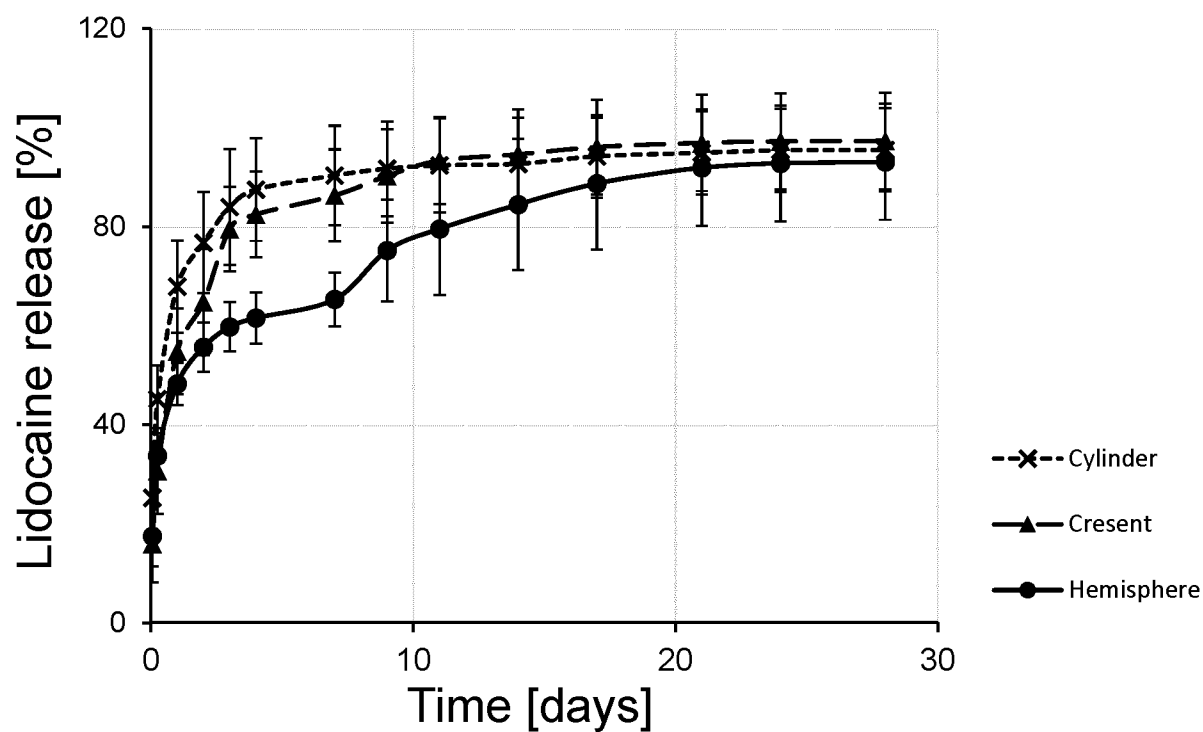


FIGURE 11B

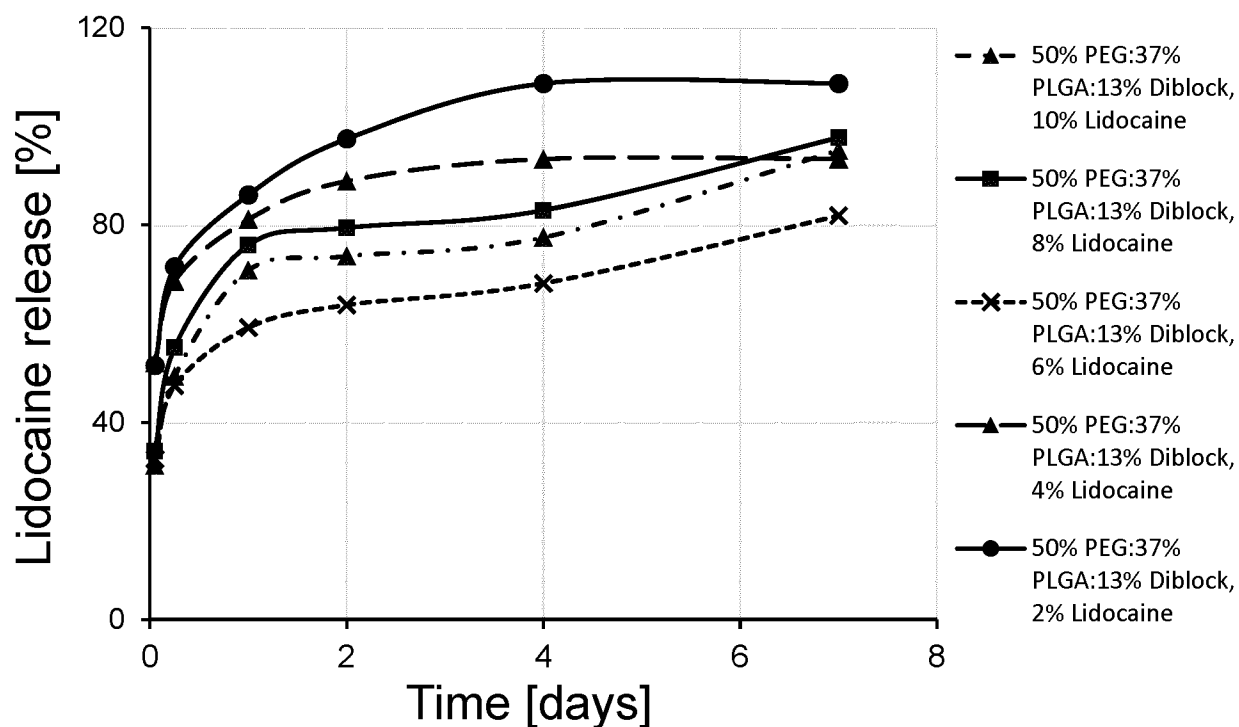


FIGURE 12A

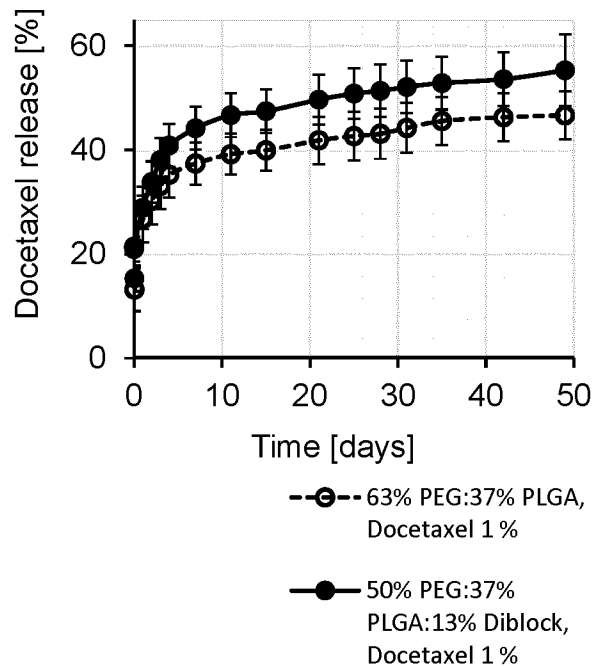


FIGURE 12B

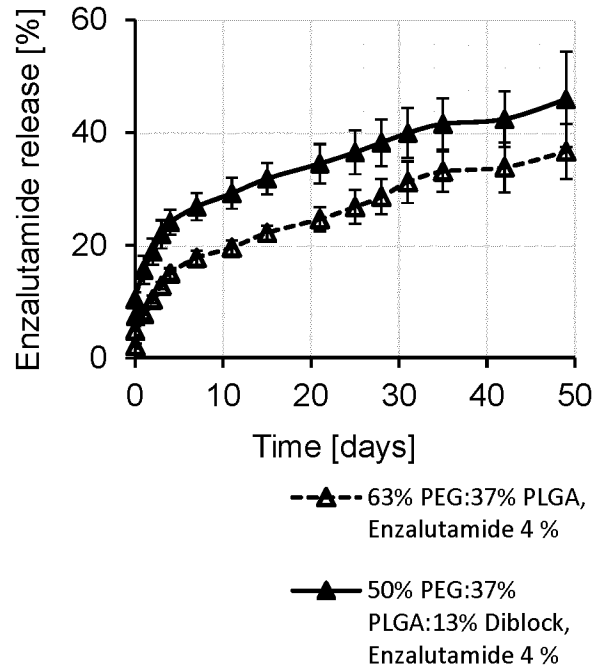


FIGURE 12C

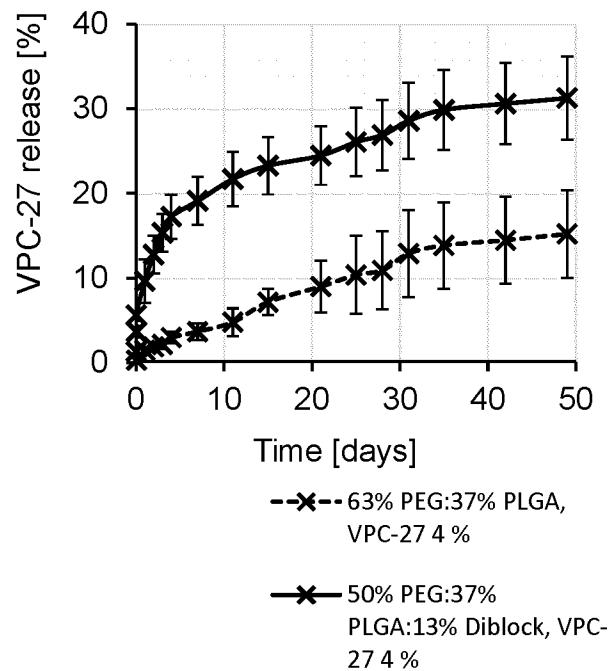


FIGURE 13

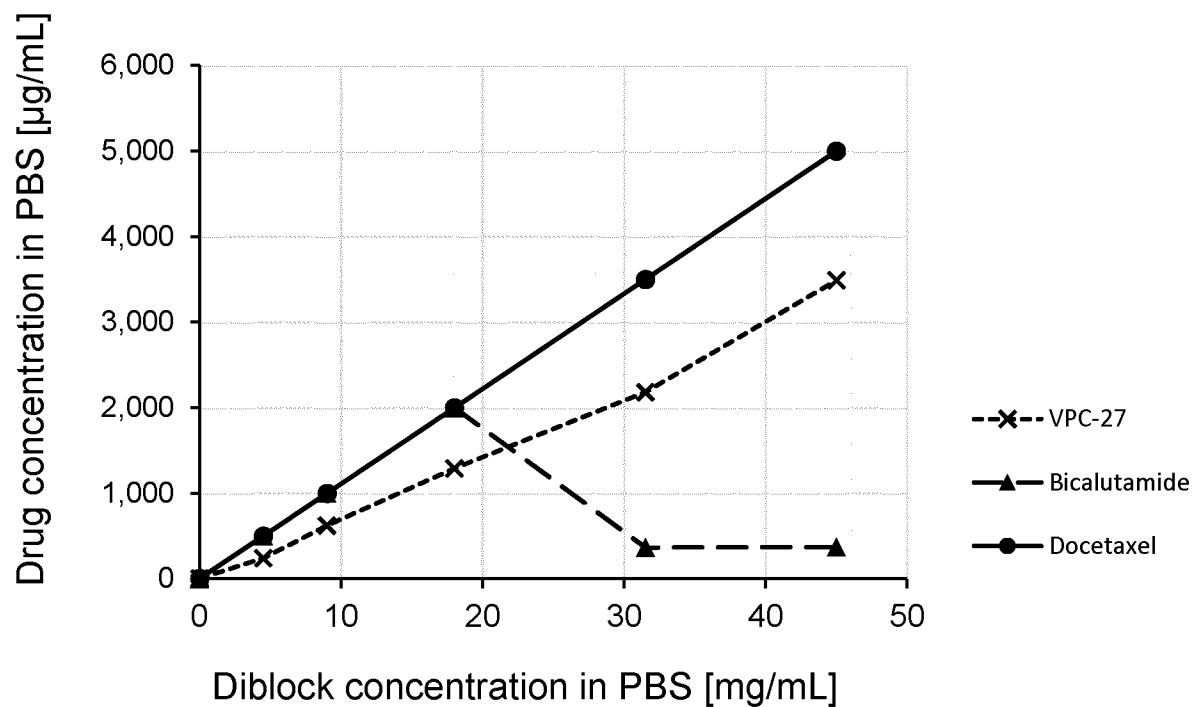


FIGURE 14

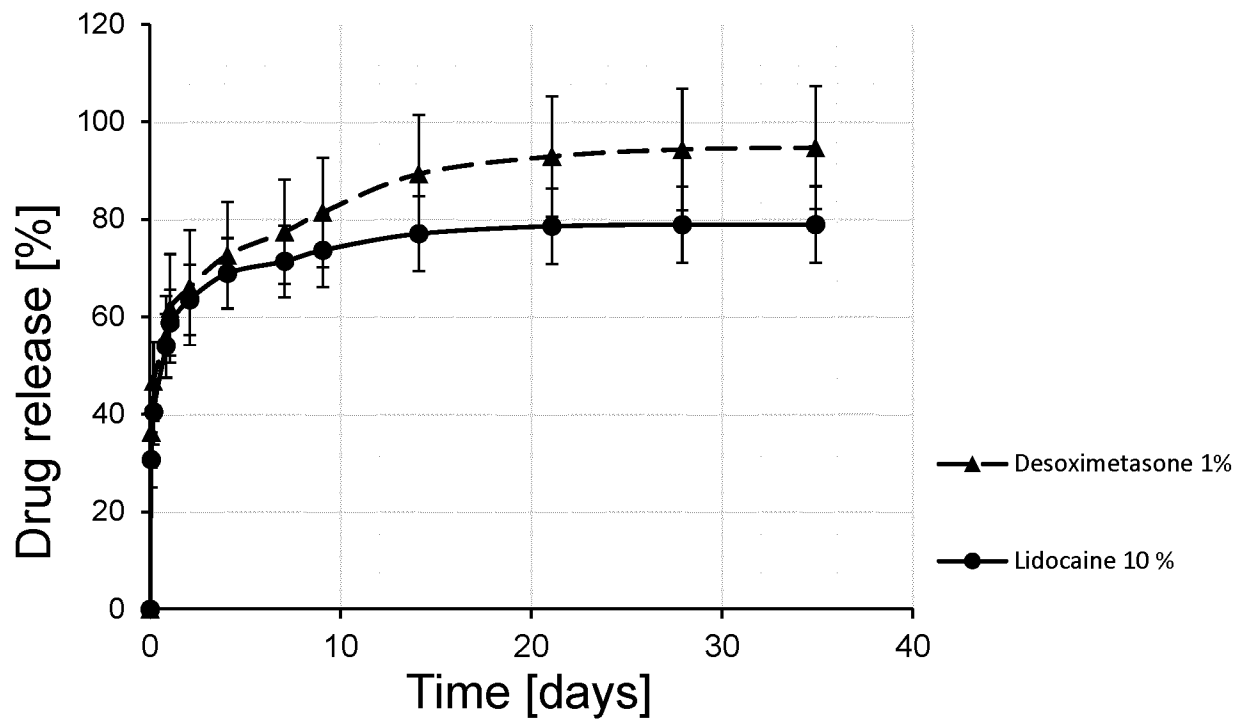


FIGURE 15

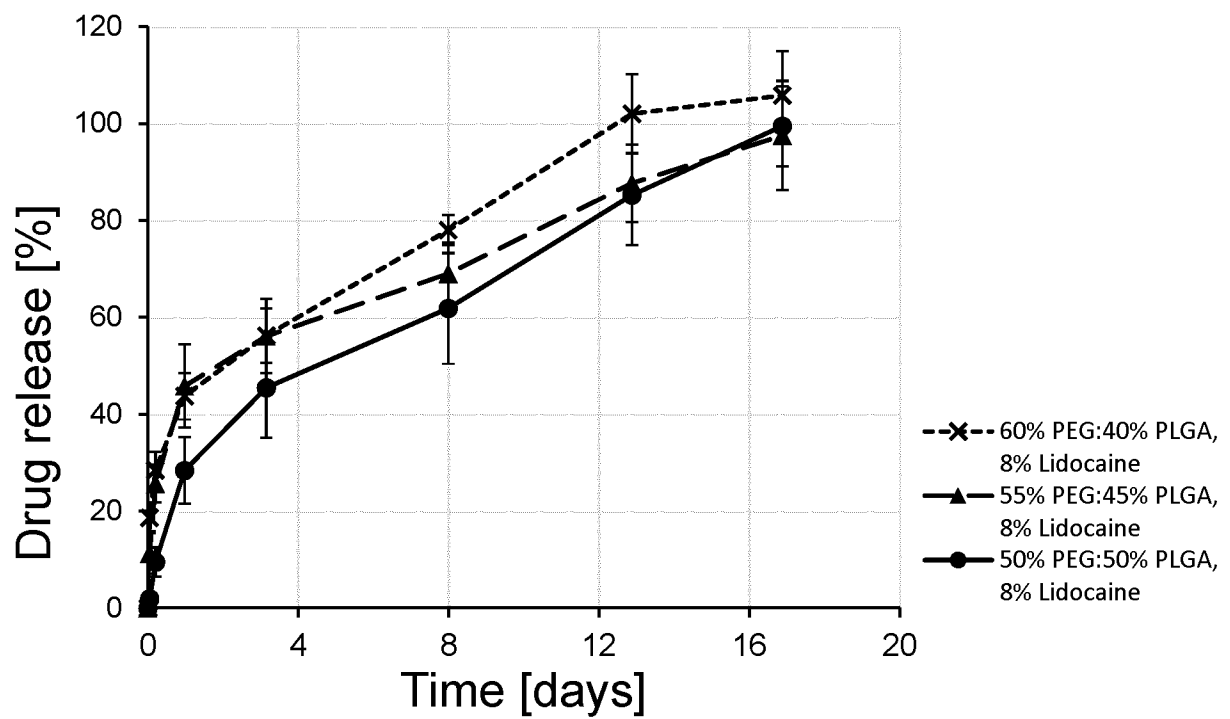


FIGURE 16

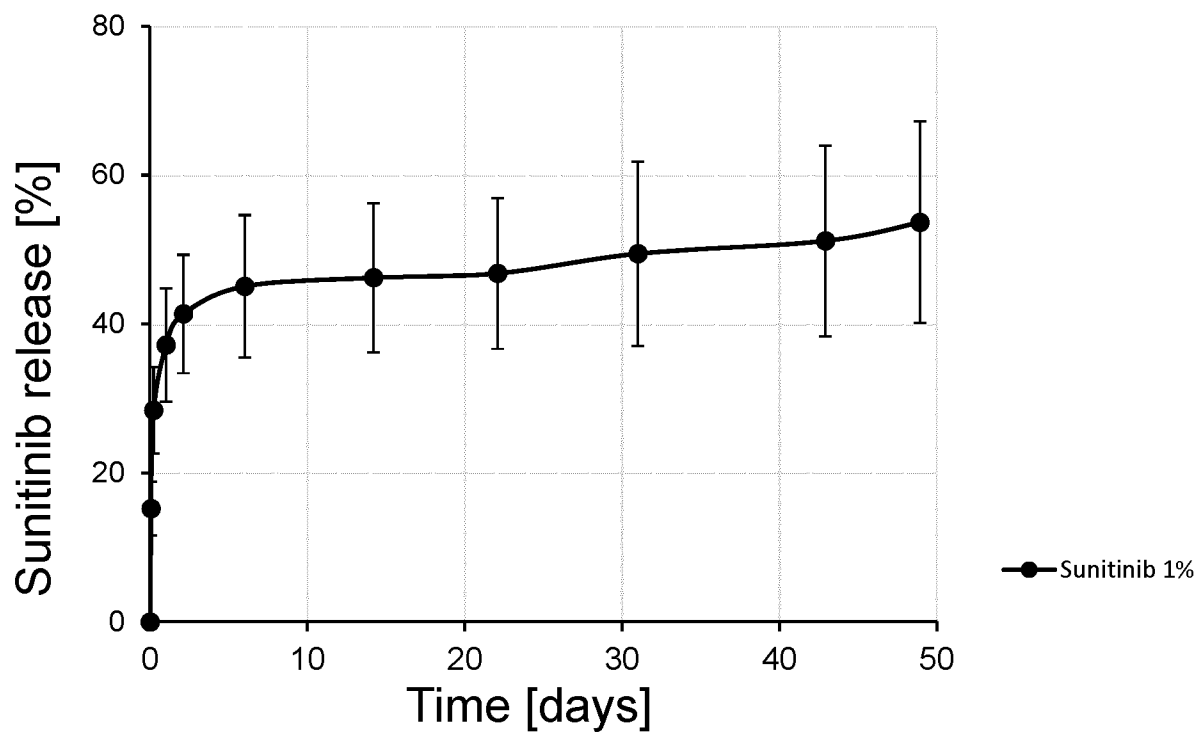


FIGURE 17

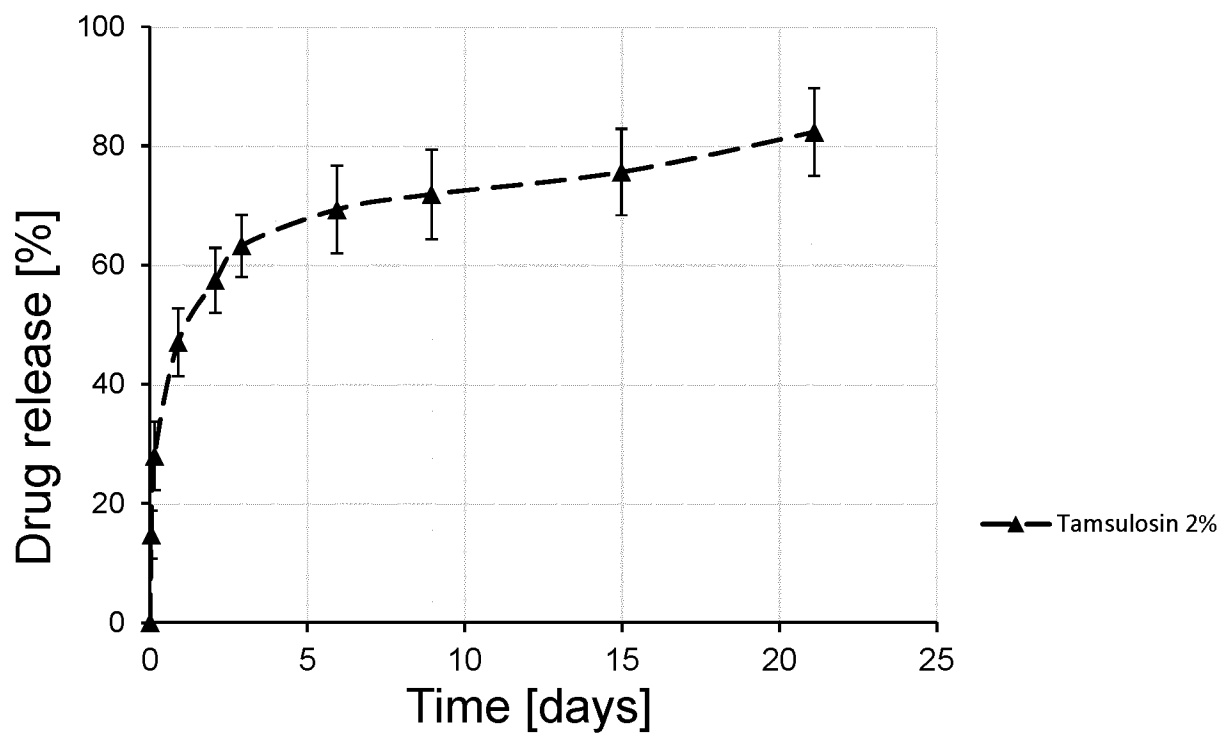


FIGURE 18

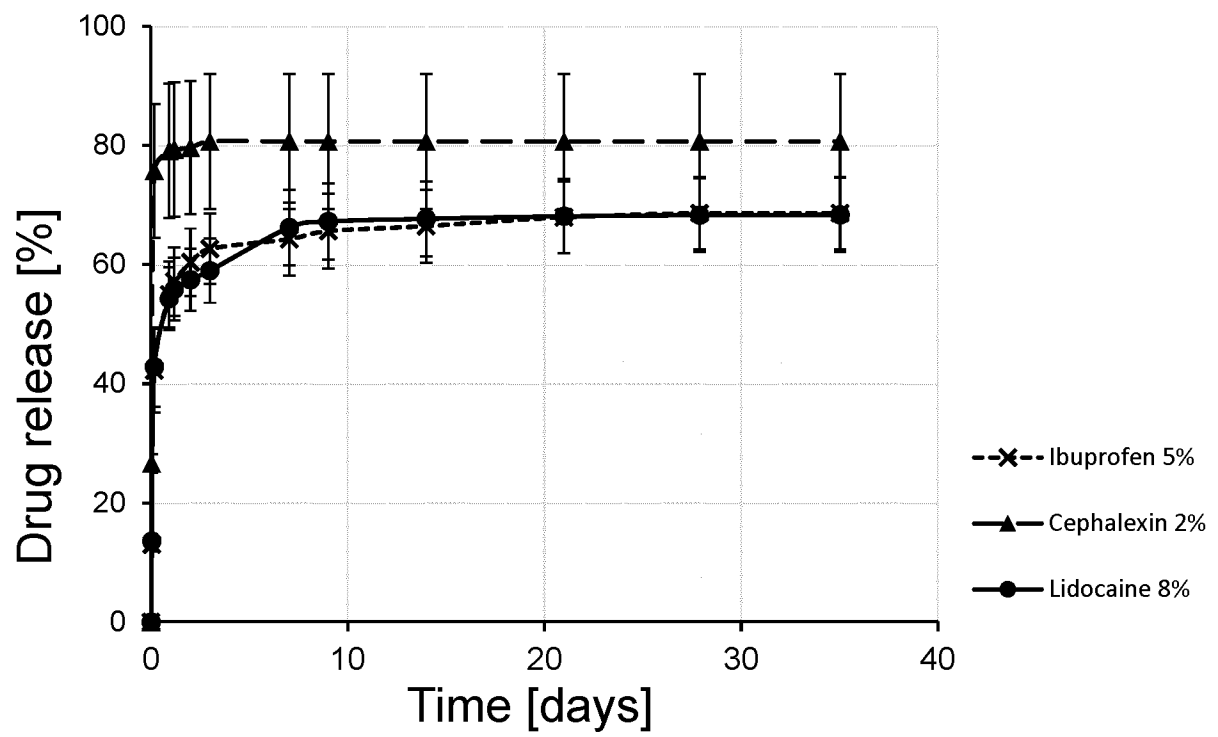


FIGURE 19A

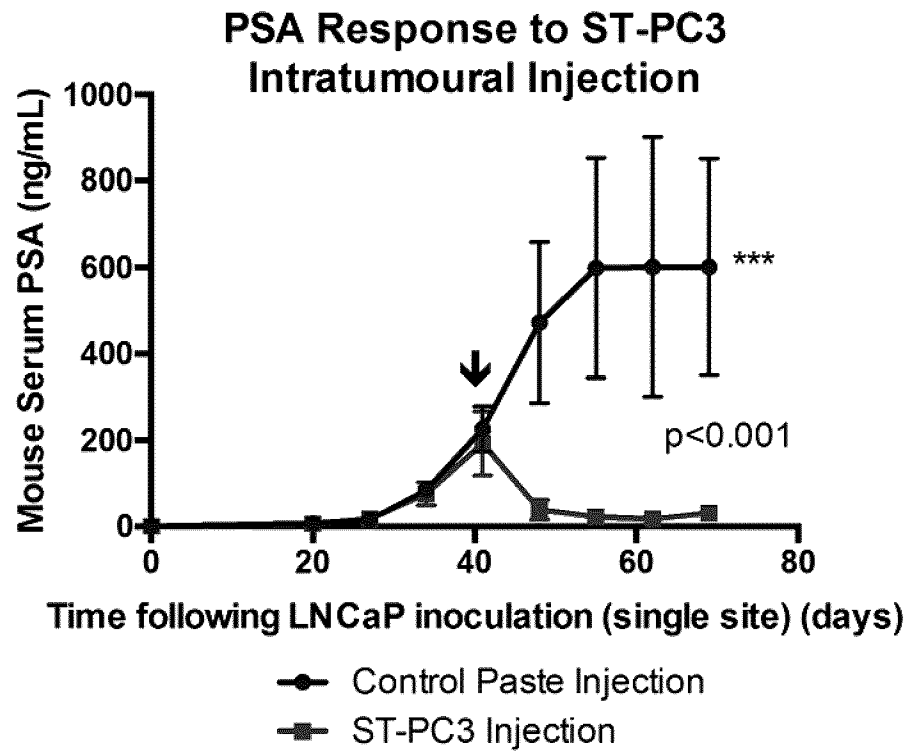


FIGURE 19B

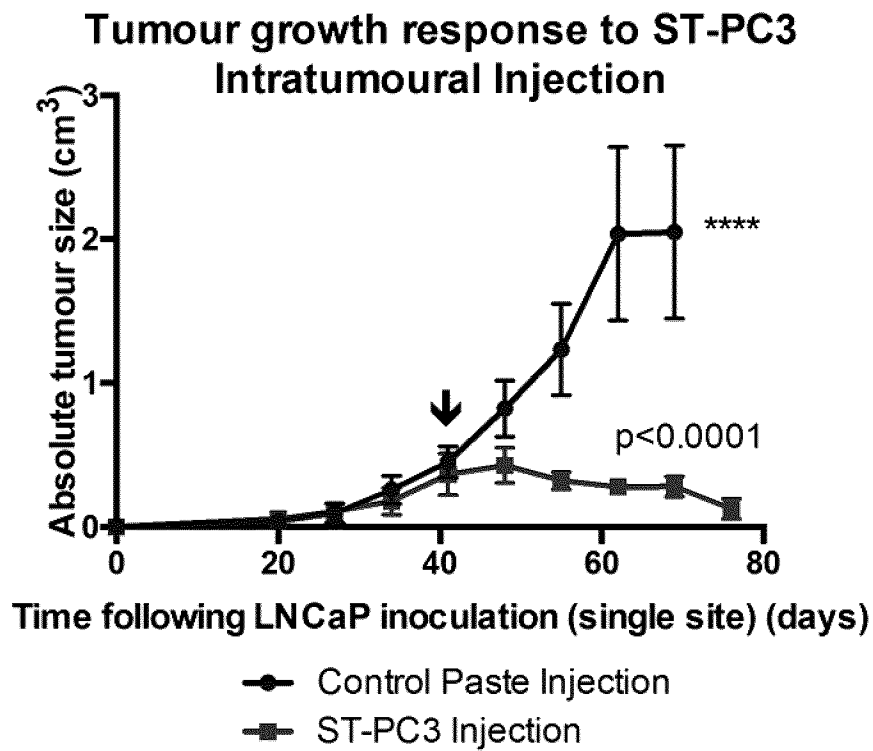


FIGURE 20A

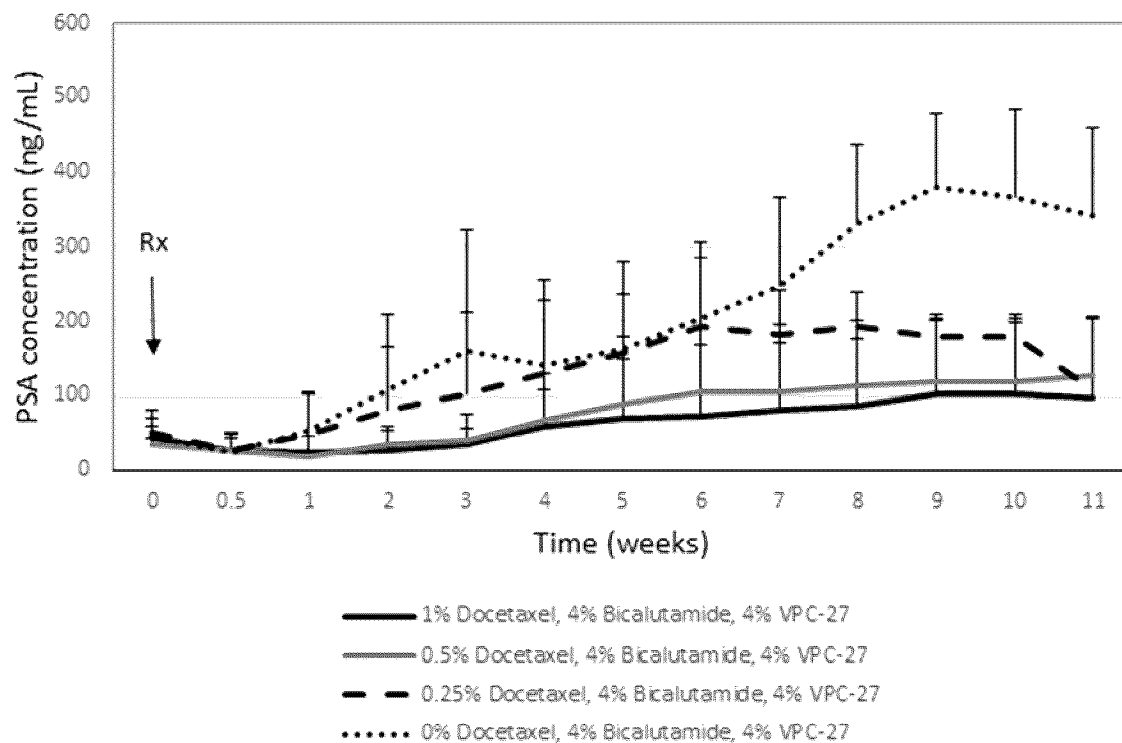


FIGURE 20B

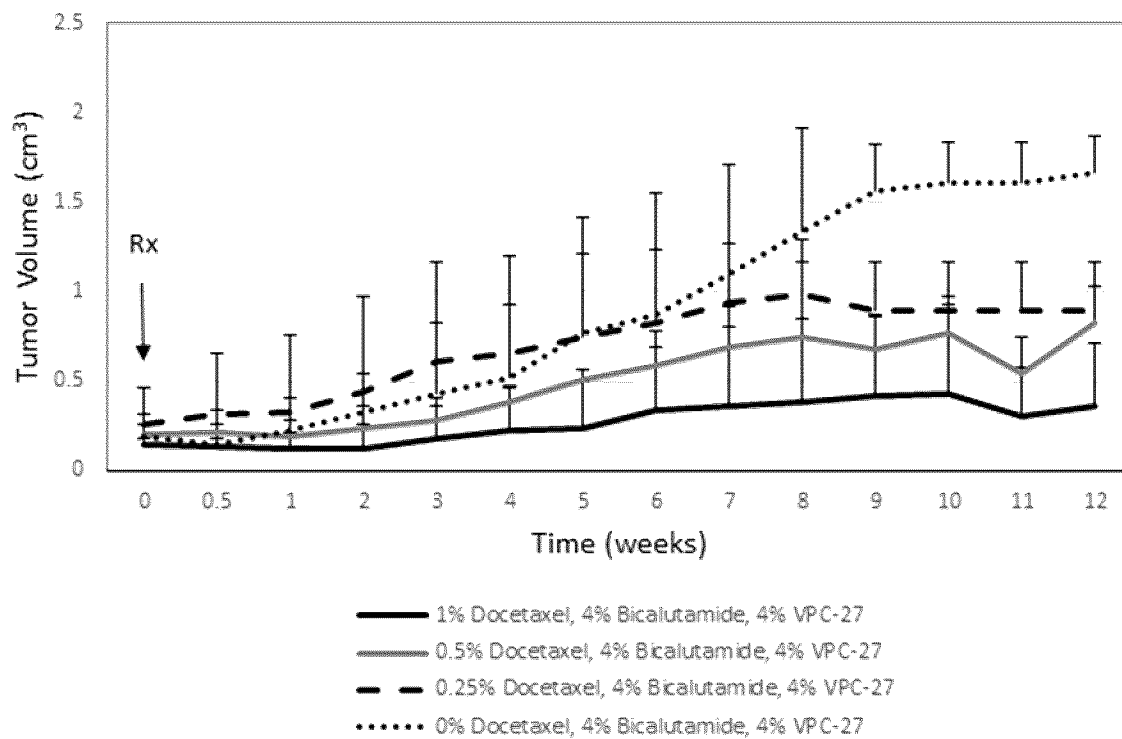


FIGURE 21A

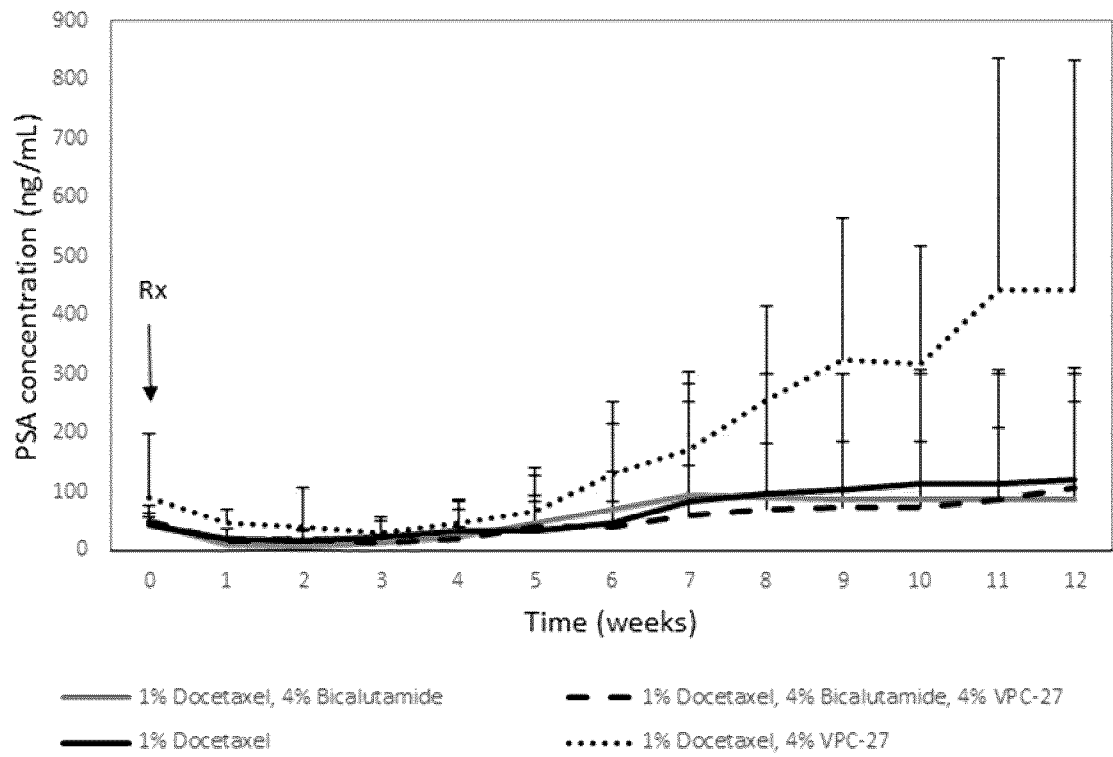


FIGURE 21B

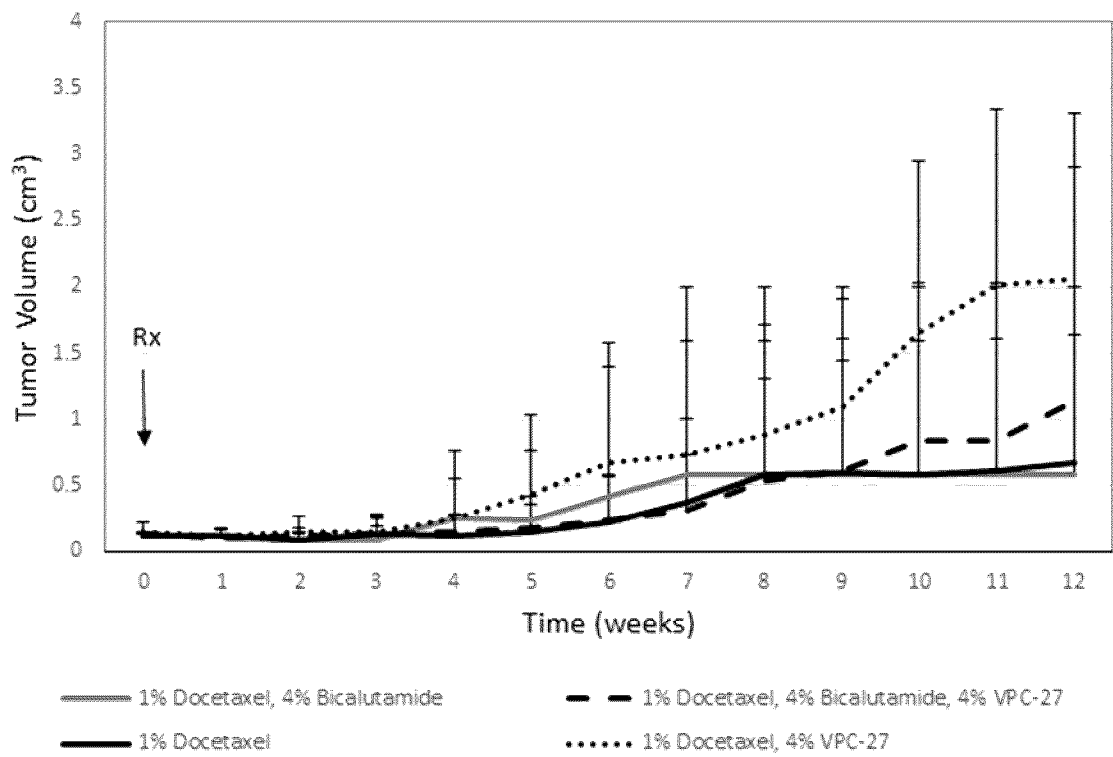


FIGURE 22A

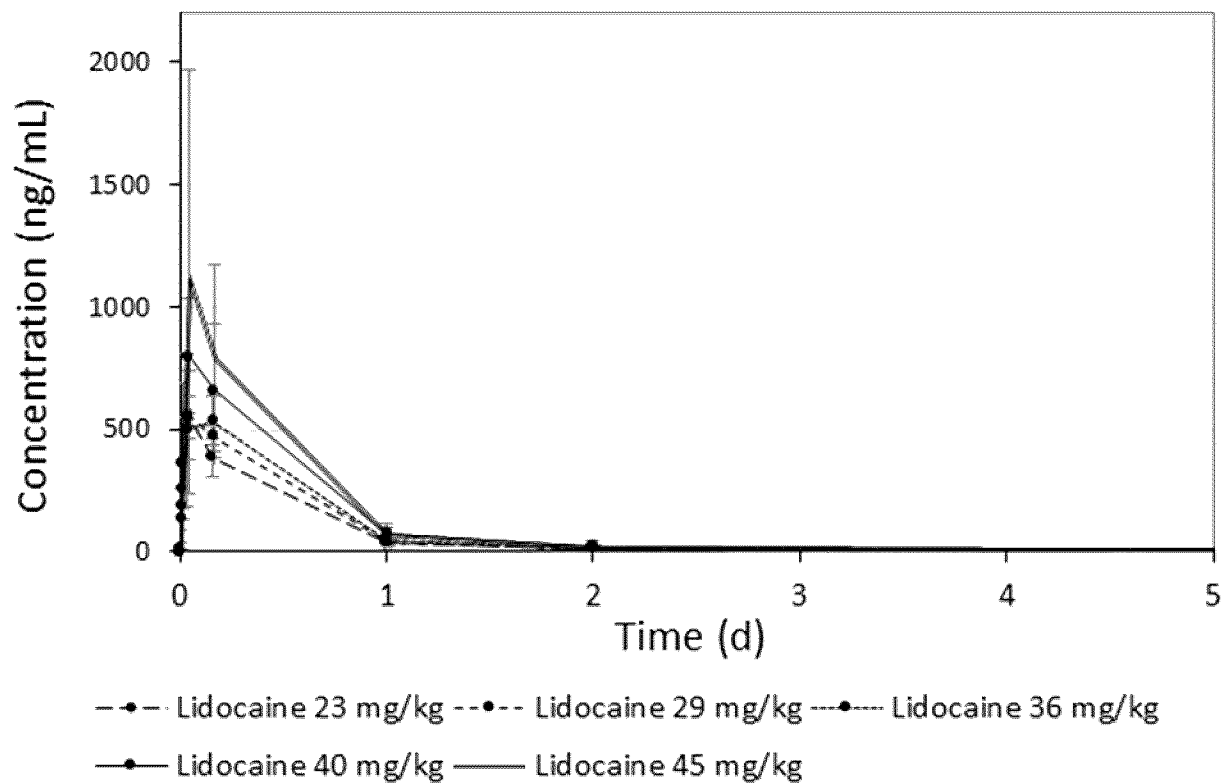


FIGURE 22B

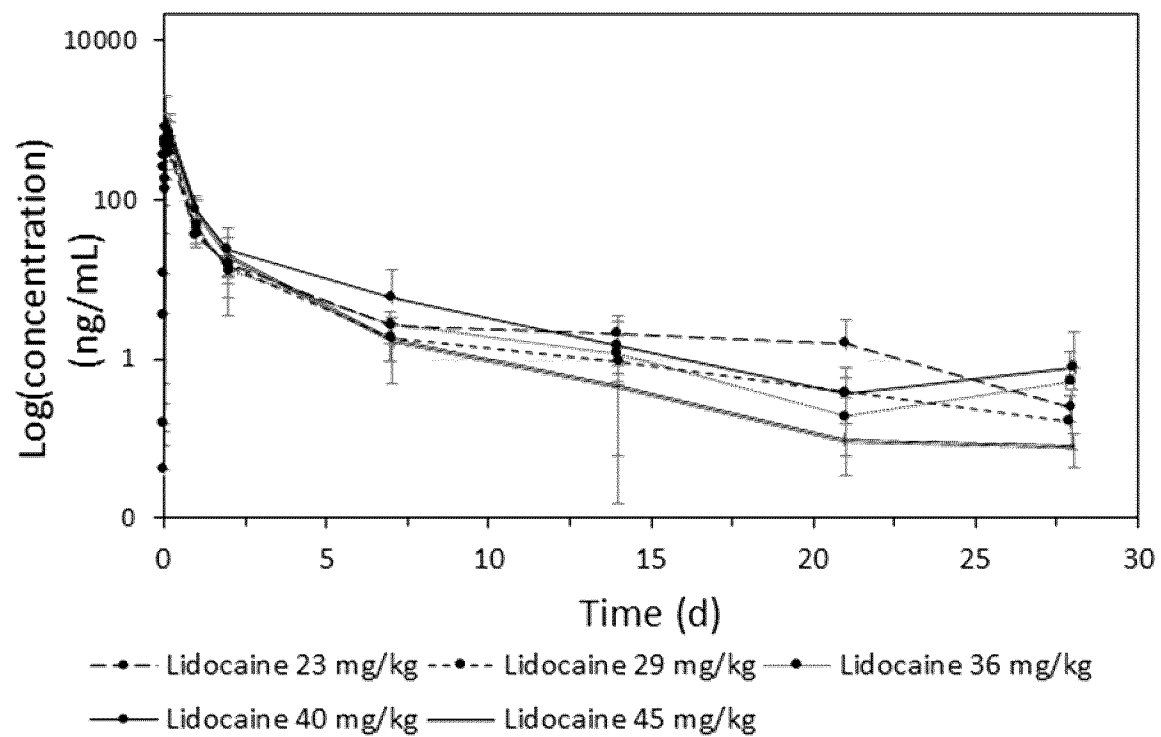


FIGURE 23

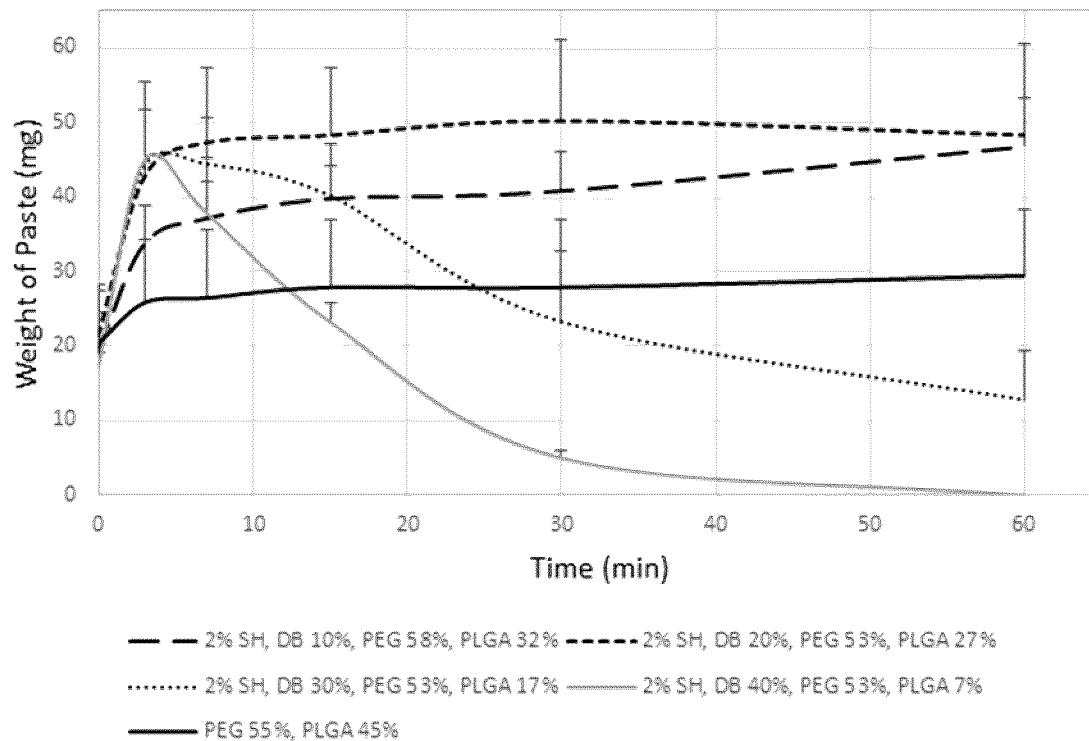


FIGURE 24

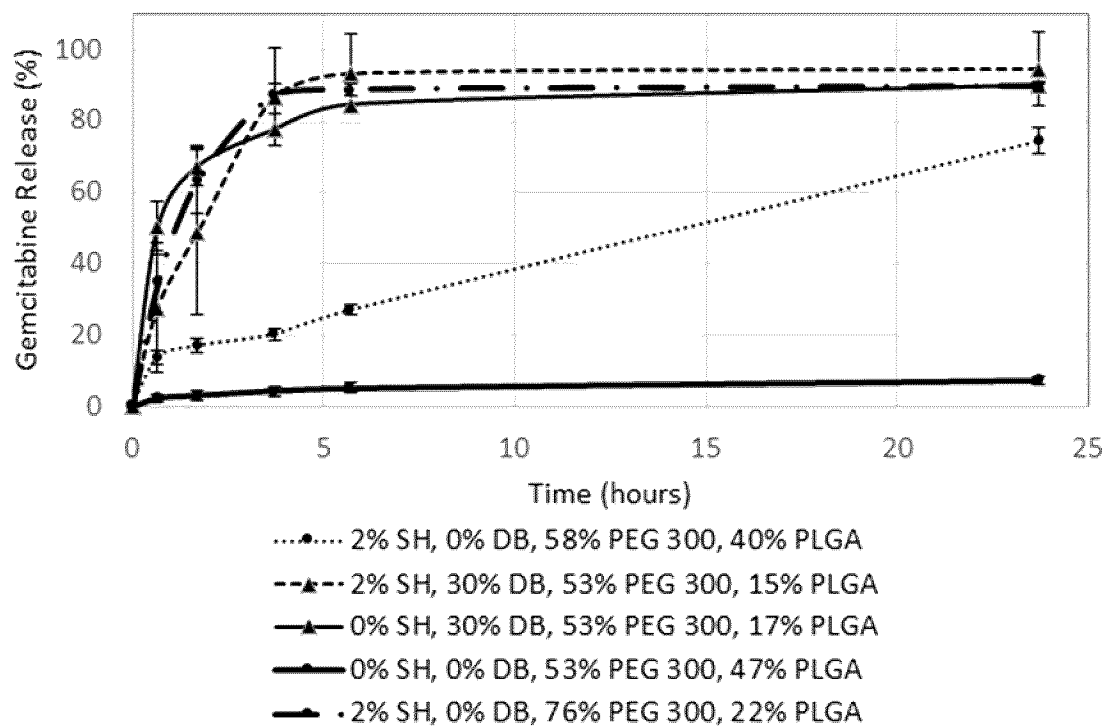


FIGURE 25A

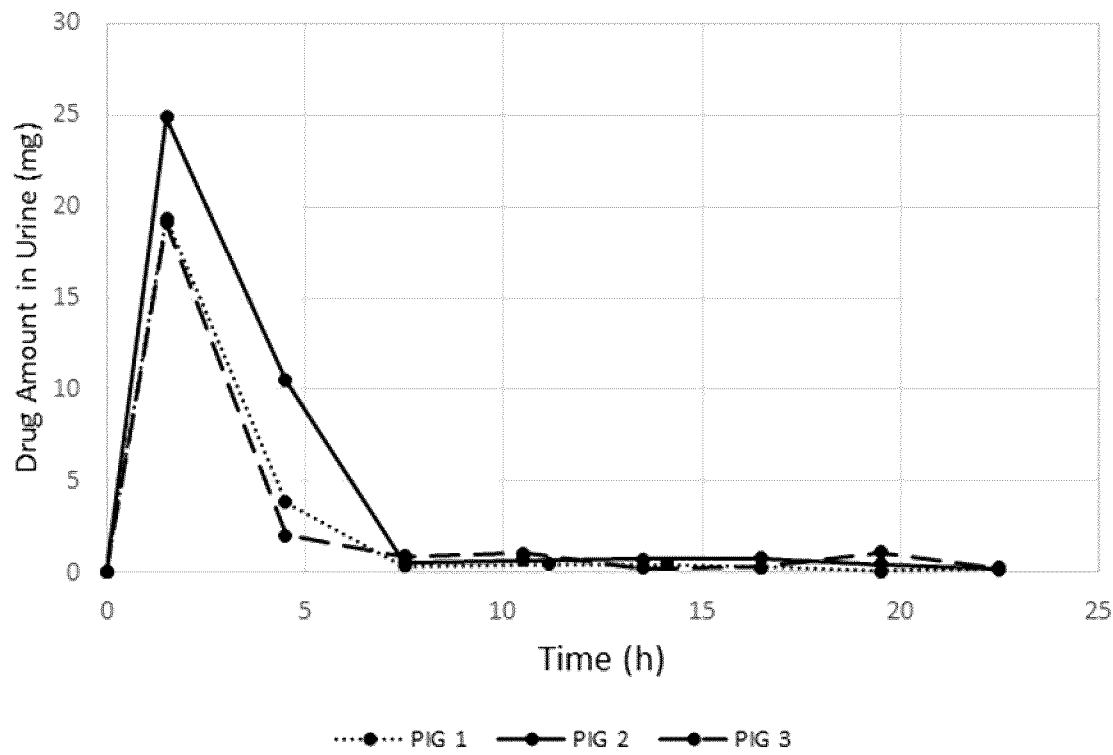
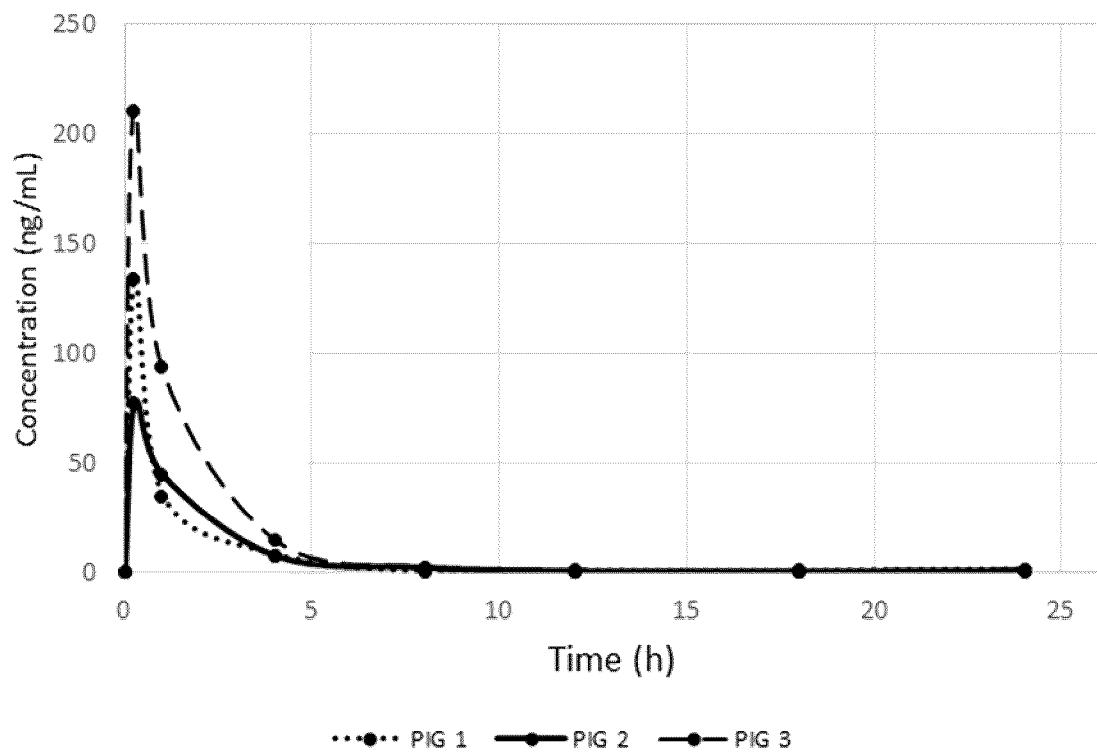


FIGURE 25B



INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2018/050714

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **A61K 47/30** (2006.01), **A61K 47/10** (2017.01), **A61K 47/34** (2017.01), **C08G 63/08** (2006.01), **C08G 65/28** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: **A61K 47/30** (2006.01), **A61K 47/10** (2017.01), **A61K 47/34** (2017.01), **C08G 63/08** (2006.01), **C08G 65/28** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
 Questel orbit (Fampat), CIPO Library Discovery Tool (sample search terms: PLGA, PEG, MePEG, PEO, paste, implant, in situ, prostate, DURECT, RESOMER, block copolymer, and injectable)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2005/002625 A2 [ASHTON, P. et al.] 13 January 2005 (13-01-2005) (see page 7, line 9 – page 11, line 25)	1, 3-14 and 20-29 2 and 15-19
X	WO 2005/120595 A2 [HELLERBRAND, K. et al.] 22 December 2005 (22-12-2005) (see page 12, lines 20-23; page 32, line 3 – page 33, line 4 and Example 10)	1, 3-14, 20-22 and 25-29
X	WO 01/45742 A1 [SEO, M.H. et al.] 28 June 2001 (28-06-2001) (see Abstract and Examples)	1, 7-10, 14, 21, 22 and 25-29
Y	WO 97/10849 A1 [KIM, S.C. et al.] 27 March 1997 (27-03-1997) (see Abstract, Table 1)	2 and 15-19
A	RAHMAN, C. V. et al. "Adjuvant Chemotherapy for Brain Tumours Delivered via a Novel Intra-Cavity Moldable Polymer Matrix" <i>PLOS ONE</i> 2013 , 8(10), e77435 (see Materials and Methods)	1-29

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* "A" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier application or patent but published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "&"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
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Date of the actual completion of the international search
24 July 2018 (24-07-2018)

Date of mailing of the international search report
31 July 2018 (31-07-2018)

Name and mailing address of the ISA/CA
 Canadian Intellectual Property Office
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 Owen Terreau (819) 639-9384

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2018/050714

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2005002625A2	13 January 2005 (13-01-2005)	AR028372A1 AT409023T AU5367501A BR0110243A CA2406277A1 CN1438873A CY1108665T1 DE60135907D1 DK1276462T3 EA200201140A1 EP1276462A2 ES2315282T3 HK1053263A1 IL152294A IN4939DEN2012A JP2006514658A KR20030009447A MXPA02010442A MY135804A NO20062362A NZ522002A PT1276462E SH1276462T1 TWI290054B US6375972B1 US2004186116A1 ZA200208415B	07 May 2003 (07-05-2003) 15 October 2008 (15-10-2008) 07 November 2001 (07-11-2001) 07 January 2003 (07-01-2003) 01 November 2001 (01-11-2001) 27 August 2003 (27-08-2003) 09 April 2014 (09-04-2014) 06 November 2008 (06-11-2008) 09 February 2009 (09-02-2009) 27 February 2003 (27-02-2003) 22 January 2003 (22-01-2003) 01 April 2009 (01-04-2009) 29 May 2009 (29-05-2009) 30 April 2013 (30-04-2013) 25 September 2015 (25-09-2015) 11 May 2006 (11-05-2006) 29 January 2003 (29-01-2003) 06 September 2004 (06-09-2004) 31 July 2008 (31-07-2008) 13 August 2006 (13-08-2006) 25 June 2004 (25-06-2004) 08 January 2009 (08-01-2009) 28 February 2009 (28-02-2009) 21 November 2007 (21-11-2007) 23 April 2002 (23-04-2002) 23 September 2004 (23-09-2004) 17 October 2003 (17-10-2003)
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