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(71) Demandeur/Applicant:
UCL BUSINESS PLC, GB

(72) Inventeurs/Inventors:
KHAW, PENG T., GB;
BROCCHINI, STEPHEN, GB

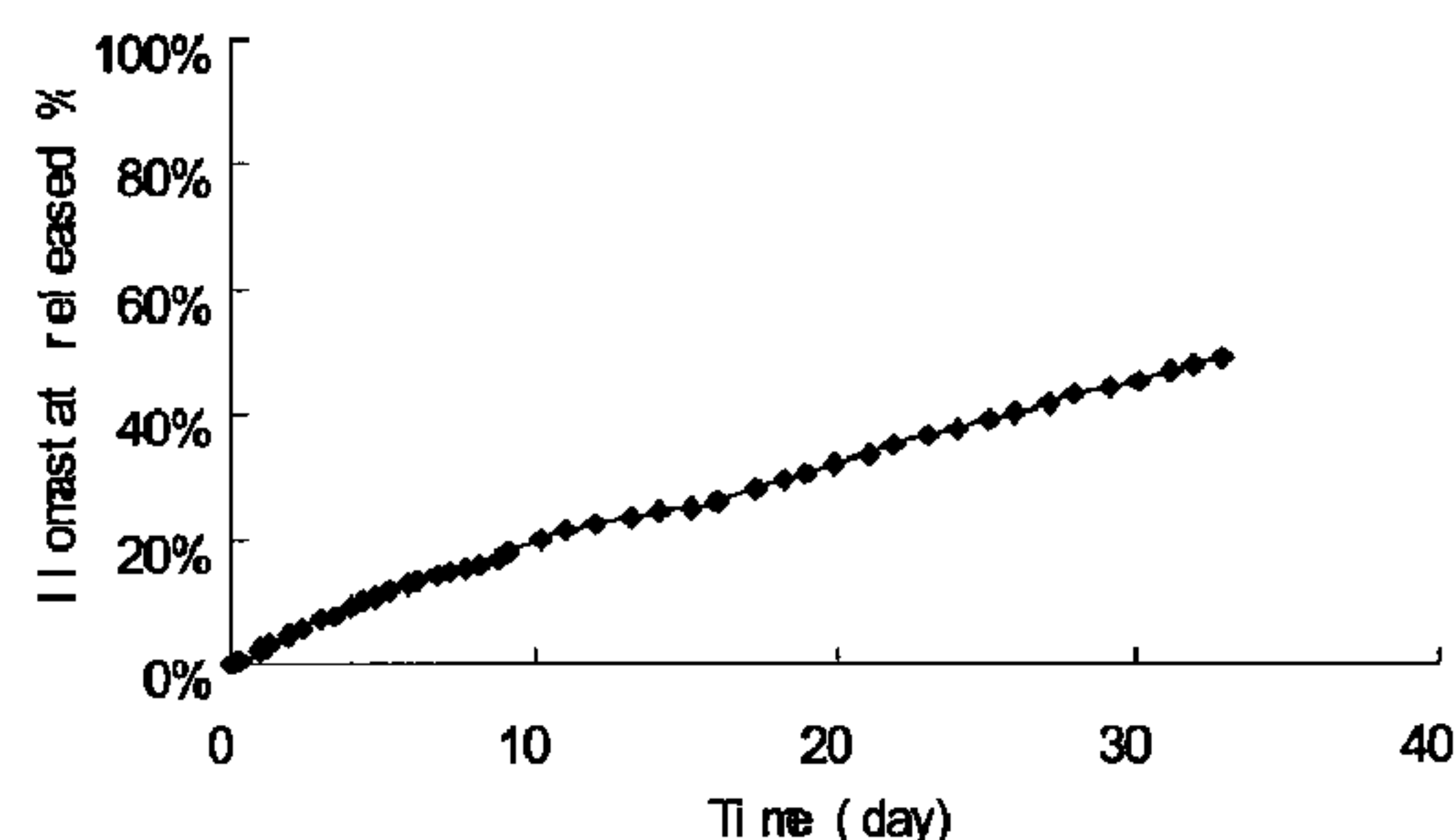
(74) Agent: DIMOCK STRATTON LLP

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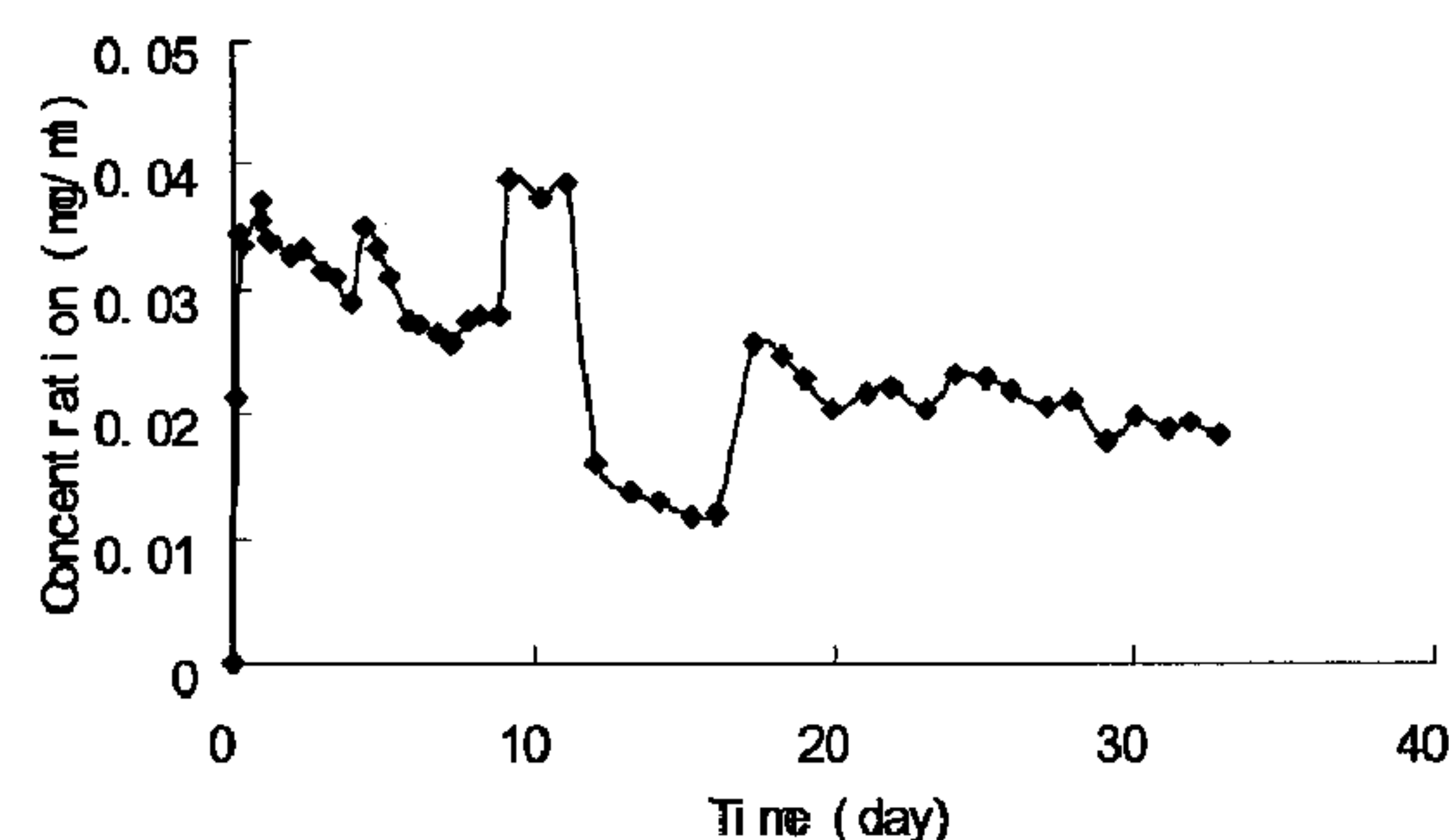
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Figure 13

(a)



(b)



(57) Abrégé/Abstract:

A solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, wherein the one or more excipients, when present, do not lead to a significant delay or

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prolongation of the release of active agent, as compared to an equivalent dosage form containing no excipients when tested in vitro.

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(74) Agents: TOMBLING, Adrian, George et al.; WITHERS & ROGERS LLP, Goldings House, 2 Hays Lane, London SE1 2HW (GB).

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(71) Applicant (*for all designated States except US*): UCL BUSINESS PLC [GB/GB]; The Network Building, 97 Tottenham Court Road, London W1T 4TP (GB).

(72) Inventors; and

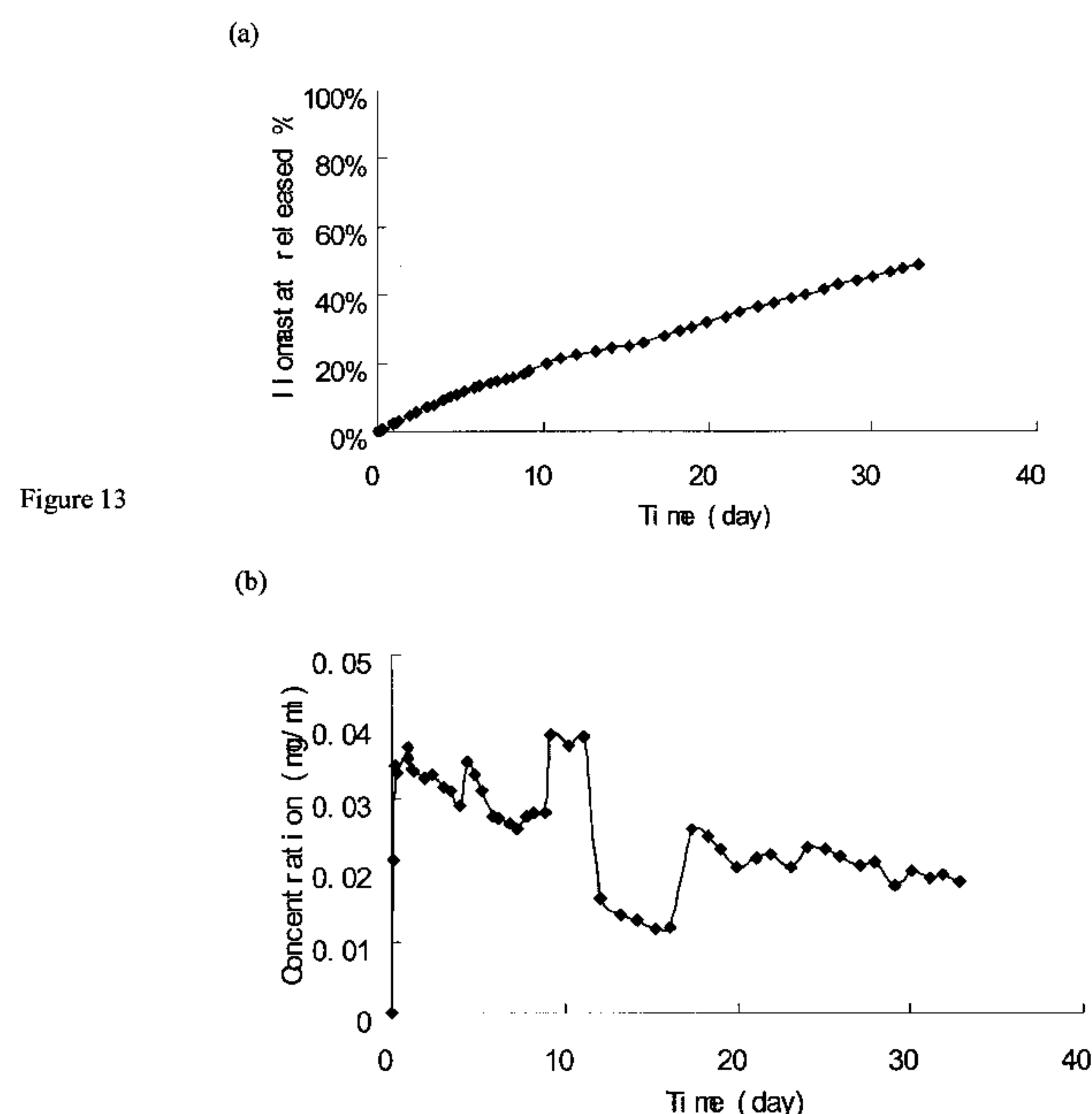
(75) Inventors/Applicants (*for US only*): KHAW, Peng, T. [GB/GB]; National Institute for Health Research Centre, Moorfields Eye Hospital and UCL, Institute of Ophthalmology, City Road, London EC1V 2PD (GB). BROCCINI, Stephen [US/GB]; The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX (GB).

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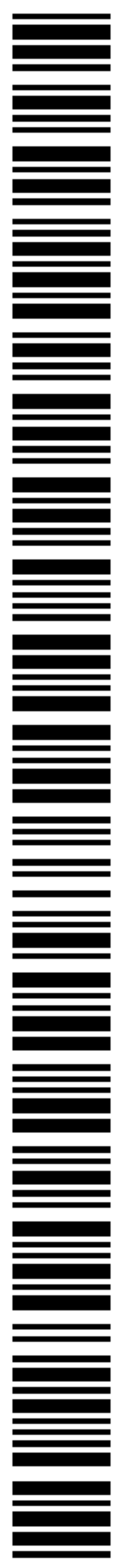
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(57) Abstract: A solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, wherein the one or more excipients, when present, do not lead to a significant delay or prolongation of the release of active agent, as compared to an equivalent dosage form containing no excipients when tested *in vitro*.



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SOLID COMPOSITIONS

The present invention relates to solid pharmaceutical compositions and, in particular, the use of substantially water insoluble therapeutically active agents for local delivery for preventing or treating disease. The present invention more specifically relates to solid matrix metalloproteinase (MMP) inhibitor compositions and their use in preventing scarring. The present invention also relates to specific MMP inhibitor solid dosage forms.

Therapeutic agents that are substantially water insoluble are generally delivered to the human or animal body in a suitable solvent, such as DMSO, etc. However, by delivering the therapeutic agent in a solution, the agent is usually administered systemically. If such a solution is administered locally, it generally only remains at the site of administration for a short period of time (i.e., a few minutes to a few hours). It is desirable to deliver therapeutic agents locally so that only the relevant part of the body is exposed to the agent. It is also important that any therapeutically active agent delivered to the body has a suitable dissolution profile enabling a therapeutically effective concentration of the active agent to be achieved for a sufficiently prolonged period of time to allow treatment. Numerous multicomponent and complicated drug formulations have been developed in an effort to resolve these issues; however, such formulations can be expensive, physically and chemically sensitive and labile, and specific to the therapeutically active agent being delivered.

One preferred aspect of the present invention concerns preventing or treating tissue scarring. The processes involved in scarring can play a part in treatment failure in a variety of situations. Furthermore, scarring appears to play a part in treatment failure in virtually every blinding disease in the world today. A very good example of the importance of healing and scarring in the eye is what happens after glaucoma surgery to create a fistula to reduce the pressure in the eye. The final eye pressure determines the success of the operation and is dependent on the healing and scarring process. The wound healing process that occurs in the eye after trabeculectomy starts after the initial conjunctival incision. Plasma proteins and blood cells are released in the wound area and a fibrin clot is formed. Neutrophils and macrophages are recruited at the wound area and degrade the clot by expressing several enzymes and MMPs such as MMP-8 and -9 among them.

Activation and migration of fibroblasts to the wound site also takes place. The fibroblasts in

normal unwounded tissues are quiescent undifferentiated mesenchymal cells known as fibrocytes. They exist in low numbers in the subconjunctival connective tissue-Tenon's capsule (Wong et al. 2002). After their activation, these fibroblasts produce large amounts of extracellular matrix (ECM) molecules such as collagens, glucosaminoglycans and elastin.

5 They also produce MMPs that facilitate cleavage of the ECM.

Many research groups have investigated the role of MMPs in wound healing after glaucoma filtration surgery (GFS) (Kawashima et al. 1998). With the use of monoclonal antibodies they observed staining for MMP-1, MMP-2, TIMP-1 and TIMP-2 in the cytoplasm of fibroblasts isolated from human subconjunctival connective tissue. Moreover, comparison between
10 normal and healing conjunctiva has shown that the MMP-1 and TIMP-1 were located only in the healing subconjunctival tissue. Neither molecule was found in normal subconjunctival tissue nor in the conjunctival epithelium. Based on these results, a possible role for MMPs in post-operative subconjunctival scarring has been proposed.

Since these early studies the expression of other MMP molecules has been detected in
15 cultured human Tenon's fibroblasts (HTF) (Mietz et al. 2003). MMP-1, -2, -3, -9, -14 and TIMP-1 and -2 are expressed from *in vitro* cultured HTF. During the fibroblast migration over the fibronectin interface, traction forces are generated in the underlying substrate leading to wound contraction (Harris, Stopak, & Wild 1981). Gradually the fibrovascular granulation tissue is formed and a part of the fibroblast population differentiates in the wound site to
20 myofibroblasts due to mechanical stress and growth factor stimulation (mainly TGF- β and PDGF). After continuous remodeling of the granulation tissue and apoptosis of myofibroblasts, dense collagenous subconjunctival scar tissue is formed. Extended subconjunctival fibrosis and the contraction of the tissue is the end result. This causes loss of function of the bleb with subsequent increase of intraocular pressure (IOP).

25 Solutions of antimetabolites such as mitomycin C (MMC) and 5-fluorouracil (5-FU) have been shown to be effective in reducing the scarring after trabeculectomy (Dahlmann et al. 2005; Skuta et al. 1992). Many studies have been published by the inventors that describe the increase of the functioning period of the outflow channel in the bleb. Results indicate that a single five minute application of a 5-FU or mitomycin C solution during surgery reduces the
30 healing response and decreases scar formation. It is thought this is mainly due to suppression of fibroblast proliferation, prolonging the bleb survival (Doyle et al. 1993; Khaw et al. 1994;

Khaw et al. 1992). Unfortunately, severe complications often occur after treatments with these metabolites. The bleb often leaks and there other side effects including hypotony, endophthalmitis and excessive ocular cell apoptosis that can cause irreversible vision loss. Despite this, MMC and 5-FU are still used. Hence safer and more effective agents are
5 needed to reduce scarring and to control healing after GFS.

Since MMPs take part in several pathological conditions, it is important to identify selective inhibitors that can be used therapeutically to control MMP activity in defined ways. The use of the natural TIMP inhibitors has significant disadvantages such as their high molecular weight and their poor oral bioavailability, which prevent their clinical use (Glasspool &
10 Twelves 2001b).

To overcome these difficulties, synthetic compounds to block MMP activities (MMP inhibitors) have been designed. Some of the most well-known MMP inhibitors are Batimastat (BB-94), Marimastat (BB-2516), Prinomastat (AG3340), Tanomastat (BAY12-9566) (Glasspool & Twelves 2001a) and Ilomastat (GM6001) (Galardy et al. 1994d). These are
15 hydroxamic acid derivatives that bind reversibly to the zinc in the active site of MMPs. Most of the potent inhibitors designed to date are right-side binders, as left-side binding is much weaker possibly due to its natural ability to prevent the carboxylate product of substrate cleavage from becoming a potent inhibitor of the enzyme (Skiles, Gonnella, & Jeng 2001).

MMPs play a significant role in wound contraction (Daniels et al. 2003; Porter et al. 1998).
20 In particular, inhibition of MMPs reduced wound contraction in *in vitro* experiments using collagen I lattices as the wound contraction model (Scott, Wood, & Karran 1998). Both *in vitro* and *in vivo* studies have been performed in order to test the effect of MMP inhibitors in contraction models. Daniels et al., 2003, tested the effect of three MMP inhibitors – Ilomastat, BB-94 and BMS-275291 (Cell Tech) in HTF populated collagen gels.
25 Observations revealed inhibition of the contraction of the gels with the application of all the three MMP inhibitors in a dose-dependent manner and Ilomastat was observed to be the most effective.

The tested MMP inhibitors were also found to have a non toxic and reversible effect and zymography results indicated significant reduction of the proteolytic activity of the detected
30 MMP bands after the application of the MMP inhibitors. It was also shown that Ilomastat

inhibited collagen production from fibroblasts in a dose-dependent manner. This was an important finding, as excessive collagen production and deposition at the incision area is mainly responsible for the bleb failure (Cordeiro et al. 2000; Daniels et al. 1998).

Administration of 17 injections of dissolved Ilomastat in DMSO in an *in vivo* 30 days rabbit contraction model after trabeculectomy was found to prolong significantly the bleb survival in comparison to the DMSO only control group as well as to have a lowering IOP effect throughout the experiment (Wong, Mead, & Khaw 2003). Histological findings showed that reduction of scar tissue formation in the Ilomastat treatment group occurred with decreased cellularity compared to the control group. There was also decreased cell apoptosis (that is known from other studies to be associated to MMC), decreased myofibroblasts in the wound area (possibly because of an inhibitory effect of Ilomastat in fibroblast migration) and a large bleb area compared to control group.

The necessity of comparison of the antiscarring effects of Ilomastat with MMC led to the design of a new comparative *in vivo* study (Wong, Mead, & Khaw 2005). The Ilomastat treated group had similar prolonged bleb survival and IOP lowering results as the MMC treated group. Importantly, this study showed that the morphology of the subconjunctival tissue was normal in the Ilomastat group but hypocellular in the MMC group. It is worth mentioning that in none of the inventors' *in vivo* experiments Ilomastat damaged conjunctiva, as can happen in the case of MMC.

The clinical use of Ilomastat for post surgical wound management may have advantages over the currently used cytotoxic antimetabolites. Ilomastat displays specific MMP inhibition and blocks the activation of fibroblasts. No reports of toxicity have been published, so it is possible that Ilomastat will be better tolerated for post-operative GFS treatment than the antimetabolites. There are several other challenges however that have to be addressed to increase the benefit of post-trabeculectomy treatment in order to reduce scarring (Wong, Mead, & Khaw 2005).

The use of MMP inhibitors in preventing tissue contraction is described in International Patent Application WO 95/24921.

Currently, a single administration of MMC is used during trabeculectomy beneath the scleral flap. Multiple, repetitive injections of an antimetabolite is not a viable choice due to toxicity

associated with the drug, and to the discomfort and risk of infection to the patient caused by multiple injections. Furthermore, maintaining a constant local concentration of active agent in the bleb, the capacity of which is approximately 200 μ l, is not possible by bolus injection. The reason is that there is aqueous outflow of 2 μ l/min from the anterior chamber to the bleb, which means that the concentration of the injected agent would be quickly reduced. It is also not possible to continuously infuse the agent.

There is a need to develop a continuous prolonged drug release system that can be placed in the subconjunctival space after trabeculectomy.

The inventors' initial work was on developing a delivery system with Ilomastat. Ilomastat is known to inhibit *in vitro* contraction in collagen I gels in a dose dependent manner in concentrations ranging from 10-100 nM (Daniels et al. 2003 and International Patent Application WO 95/24921). Increased efficacy has been observed during *in vivo* studies with the administration of multiple injections of Ilomastat at a concentration of 100 nM (Wong, Mead, & Khaw 2005; Wong, Mead, & Khaw 2003). While this preliminary work established the favourable pharmacological effects of Ilomastat, the therapeutic concentration could only be achieved with injections that had been prepared from aqueous-DMSO solutions. DMSO has not been approved for ocular human use.

There is a need for a method of localised delivery of a substantially water insoluble therapeutically active agent for treating or preventing a disease. There is also a particular need for an agent that has suitable anti-scarring activity, low toxicity when implanted in the human or animal body, the active agent has low toxicity both locally and systemically, and an optimal dissolution profile for providing long term anti-scarring activity.

The present invention overcomes at least some of the problems associated with the prior art methods.

In accordance with a first aspect of the invention, there is provided a solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, wherein the one or more excipients, when present, do not lead to a significant delay or prolongation of the release of active agent, as compared to an equivalent dosage form containing no excipients when tested *in vitro*.

The dosage form of the first aspect is based on the surprising finding that it is possible to implant relatively simple solid dosage forms at selected sites *in vivo* and these dosage forms provide a steady release of active agent, without the need for complex sustained release formulations in which the release profile is controlled primarily by the excipients. The comparison in dissolution rates between excipient-containing and excipient-free dosage forms may be conducted using any suitable dissolution apparatus providing a flow of media which mimics the flow of *in vivo* media following tissue implantation, such as the flow-through rig described herein. The dissolution should be conducted at around 37 degC, and in media of pH around 7.4.

10 The dosage form is preferably suitable for the localised prevention or treatment of a disease. It is possible that the dosage form of the first aspect may be implanted for the systemic delivery of an active agent. However, it is preferred that the dosage form is prepared with an amount of an appropriate therapeutic agent which makes it suitable for release and/or efficacy only in the locality of the implantation site.

15 In a preferred embodiment, the dosage form is suitable for ocular, periocular or intraocular implantation. For example, the dosage form may be suitable for implantation in the subconjunctival space.

In preferred embodiments, the dosage form is sterilised. Such treatment enables the dosage form to be safely implanted in a wider range of sites *in vivo*. The term 'sterilised' as used
20 herein covers both dosage forms prepared by sterile manufacture, and those prepared by non-sterile manufacture which are subjected to a post-manufacturing sterilisation process, such as by gamma irradiation.

When the dosage form contains one or more excipients, it is preferred that these are biodegradable and/or bioresorbable following *in vivo* implantation. This has the advantage
25 that the dosage form can be implanted and left to dissolve and/or biodegrade, without the need for a subsequent step of removal of any components of the dosage form after complete or partial release of the active agent. It is also an important consideration, for many active agents, that the excipients, when present, are not highly soluble or dispersible at the site of implantation; this avoids dose dumping and/or increased dissolution due to the dispersal of
30 the active. The invention exploits the 'non-sink' conditions of the tissue into which

implantation is made (for many actives, especially matrix metalloproteinase inhibitors). Depending on the solubility of the active agent concerned, and the flow of aqueous biological media through the tissue into which implantation is to be made (both of which may readily be determined), non-sink conditions can generally be achieved. Because the tissue is non-sink,
5 it does not matter, as far as drug release is concerned, if the dosage form has excipient or not. Without excipient, the dosage form is more simple because only the active needs to dissolve. There is no need for consideration of other components dissolving and/or causing problems *in vivo* (e.g. inflammation). Indeed, in many instances, the only reason to use an excipient is to ensure the dosage forms are compliant with manufacturing specifications; in general,
10 excipient use is primarily for processing considerations in fabricating the dosage form. In the vast majority of active agents of usefulness according to the invention, excipient use is not required to aid dissolution or release characteristics.

In certain embodiments, the dosage form is prepared by compression. In particular instances, the dosage form is a tablet.

15 Surprisingly, it has been found that a number of active agents, hitherto known to be formulated in solid dosage forms in which the majority of the dosage form comprises a variety of excipients, can be formulated as implantable tablets with little or no excipient content. This allows the dosage forms to be efficiently prepared using existing tableting apparatus, and also provides advantageous results in terms of dissolution profile of the
20 dosage forms so prepared.

In some embodiments, the dosage form has a volume of between 0.1 mm^3 and 1.5 cm^3 , and/or has a maximum dimension of 5 mm or less, and/or has a weight of 10 mg or less. Such limits allow the dosage form to be implanted in a wider variety of sites *in vivo*.

In particular embodiments, the dosage form is substantially free of excipients. It is a
25 surprising finding that a variety of active agents can be formed into solid unit dosage forms, such as compressed dosage forms (e.g. tablets), and yet still provide a steady release of active agent following implantation *in vivo*.

In preferred embodiments, the active agent is substantially water insoluble. Such insolubility enhances the sustained release of active agent in the dosage forms of the invention. The term
30 'substantially water insoluble', as used herein, is intended to mean sparingly water-soluble

(i.e., requires at least 30 parts water to dissolve one part of the therapeutic agent or, in other words, around 35 mg/ml or less), preferably slightly soluble (i.e., requires at least 100 parts water to dissolve one part of the therapeutic agent or, in other words, around 10 mg/ml or less), more preferably very slightly water-soluble (i.e., requires at least 1000 parts water to dissolve one part of the therapeutic agent or, in other words, around 1 mg/ml or less), and most preferably practically water-insoluble (i.e., requires at least 10,000 parts water to dissolve one part of the therapeutic agent or, in other words, around 0.1 mg/ml or less). The solubility is measured at room temperature (about 20°C) using water that has a physiologically acceptable pH (i.e., between about 5.0 and 8.0).

10 In particular embodiments, the active agent is a matrix metalloproteinase (MMP) inhibitor, which may be a hydroxamic acid derivative that binds reversibly to zinc in the active site of matrix metalloproteinases, and/or which may be a right side binder.

In general, the therapeutically active agent can be any suitable agent that is a solid at ambient temperature and which can be formulated into a solid unit dosage form. Such a limitation
15 can readily be assessed by the skilled formulator. The therapeutically active agent may be a naturally occurring agent or a synthetic agent. In many instances, the active agent will be at least partially crystalline. Preferably the therapeutically active agent is a synthetic chemical compound. For MMP inhibitors (and other receptor antagonists or enzyme inhibitors), agents with low K_i values, i.e., high pK_i values are generally preferred. For example,
20 ilomastat has a K_i of 0.4nM against collagenase.

An advantage of the present invention is that relatively low solubility compounds can be successfully delivered by means of the described dosage form. Traditionally, such compounds (which are frequently encountered), have had to be formulated using high drug contents and/or complex mixtures of excipients to improve solubility and/or provide
25 sustained release. Equally, in traditional formulation approaches to solid active agents, solubility and tissue permeability characteristics of the active are key considerations. In the implantable dosage forms of the present invention, and the related methods and uses, the need for permeation through a mucosal membrane (e.g. from the gut) is not required. This allows the invention to have a very wide applicability.

30 Preferred agents include MMP inhibitors and other anti-scarring agents, steroids, antibiotics,

anticancer agents, antibody molecules and anti-inflammatory agents. Anti-scarring agents include MMP inhibitors, which are defined below, antimetabolites such as MMC and 5-FU, and TGF beta. Suitable steroids include corticosteroids, such as dexamethasone, hydrocortisone, prednisolone, triamcinolone and methylprednisolone. Suitable antibiotics include any of the generally used antibiotics, including beta-lactam antibiotics, e.g., penicillins, macrolide antibiotics, e.g., erythromycin, and doxycycline. Suitable anti-cancer agents include 5FU, paclitaxel and chlorambucil.

Any antibody molecule may be used. The term "antibody molecule" encompasses polyclonal antibodies, monoclonal antibodies or antigen binding fragments thereof, such as Fv, Fab, F(ab')₂ fragments and single chain Fv fragments. Preferably the antibody molecules are lyophilised antibody molecules. The target antigen of the antibody determines the therapeutic activity of the antibody. Numerous therapeutic antibodies are known to those skilled in the art.

Suitable anti-inflammatory agents include steroidal and non-steroidal anti-inflammatory agents. Preferably the anti-inflammatory agents are non-steroidal agents such as naproxen, ibuprofen, diclofenac and ketorolac.

The therapeutically active agent is preferably an agent that is for administration locally to the site of the disease. For example, when the agent is an anticancer agent, it would be desirable to deliver the agent to the site of a tumour. Alternatively, when the therapeutically active agent is an anti-scarring agent or an anti-inflammatory agent it is for implantation at the site of surgery, trauma or inflammation to prevent or treat inflammation or tissue scarring.

The therapeutically active agent is for treating or preventing a disease. The disease to be prevented depends on the therapeutically active agent. For example, when the agent is an anti-inflammatory, the agent is used to treat or prevent inflammation. Inflammation may be associated with a variety of diseases, including asthma, arthritis, localised infections, tissue damage caused by surgery or trauma, etc. When the agent is an anti-cancer agent, the agent is used to treat or prevent cancer. The anti-cancer agent is preferably used to treat tumours. When the agent is an antibiotic, the agent is preferably used to treat infections. When the agent is an anti-scarring agent it is used to prevent or reduce tissue scarring caused by infection, surgery, trauma, etc. As will be apparent to those skilled in the art, active agents

can have more than one therapeutic use. For example, 5-FU is both an anti-scarring agent and an anti-cancer agent.

In preferred embodiments of the first aspect, the active agent is an MMP inhibitor selected from the group consisting of ilomastat batimastat, marimastat, prinomastat, tanomastat, 5 Trocade (cipemastat), AG 3340, CGs227023A, BAY 12-9566, and BMS-275291, or any functional derivatives thereof.

Notwithstanding the above preference, the matrix metalloproteinase (MMP) inhibitor can be any MMP inhibitor that can be formulated into a solid unit dosage form. The MMP inhibitor may be a natural or a synthetic MMP inhibitor. Naturally-occurring MMP inhibitors include 10 α 2-macroglobulin, which is the major collagenase inhibitor found in human blood. Numerous synthetic MMP inhibitors have been developed and are described in the literature. For example, US Patent Specifications Nos. 5,183,900, 5,189,178 and 5,114,953 describe the synthesis of Ilomastat (N [2(R)-2- (hydroxamidocarbonylmethyl)-4-methylpentanoyl-Ltryptophan methylamide), also known as GM6001 or Galardin, and other MMP inhibitors. 15 Other MMP inhibitors based on hydroxamic acid are disclosed in International Patent Applications WO 90/05716, WO 90/05719 and WO 92/13831. Further synthetic MMP inhibitors include those described in European patent applications EP-A-126,974 and EP-A-159,396 and in US Patents 4,599,361 and 4,743,587. Yet another inhibitor is BB-94, also known as Batimastat (British Bio-technology Ltd.), see for example, 20 European patent application EP-A-276436. International Patent Application W090/05719 also discloses MMP inhibitors 4-(N-hydroxyamino)-2R-isobutyl-3S-(thio-phenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide and 4-(N-hydroxyamino)-2R-isobutyl-3S-(thiomethyl)succinyl]-L-phenylalanine-N-methyl-amide. International Patent Application W090/05716 discloses MMP inhibitors 4-(N-hydroxyamino)-2R-isobutylsuccinyl- 25 Lphenylalanine-N-(3-aminomethylpyridine) amide and [4-Nhydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-Lphenylalanine-N-4-(2-aminoethyl)-morpholino amide.

The properties of natural and synthetic collagen inhibitors may vary. Individual inhibitors often have different specificities and potencies. Some inhibitors are reversible, others are irreversible. In general the more potent an inhibitor's inhibitory effects the better. Generally a 30 broad spectrum MMP inhibitor, for example, Ilomastat, is preferred.

The MMP inhibitor may be an anti-MMP polyclonal or monoclonal antibody molecule. Antibodies which are specific for a particular MMP may be made and the use of such specific inhibitors may be preferred under certain circumstances. For example, an antibody to MMP1, MMP2 or MMP3 (collagenase, 72kD gelatinase or stromelysin respectively) or a mixture of
5 two or more thereof may be used. Methods for generating such anti-MMP antibodies are well known to those skilled in the art.

Preferably the MMP inhibitor is any one of the synthetic inhibitors mentioned above. Preferred inhibitors include peptide hydroxamic acids or pharmaceutically acceptable derivatives thereof. Especially preferred are those compounds that are described and claimed
10 in US Patents 5,189,178; 5,183,900 and 5,114,953. Those with low K_i values, i.e., high pK_i values are also generally preferred. Preferably, the MMP inhibitor is a hydroxamic acid derivative that binds reversibly to zinc in the active site of the MMPs, and more preferably a right side binder.

As mentioned above, in a particularly preferred embodiment, the MMP inhibitor is selected
15 from the group consisting of Batimastat, Marimastat, Prinomastat, Tanomastat, Trocade, AG 3340, CGs227023A, BAY 12-9566, BMS-275291, and Ilomastat, or any functional derivatives thereof. More preferably, the MMP inhibitor is Ilomastat, or any functional derivatives thereof. Functional derivatives of the various MMP inhibitors are well known to those skilled in the art. For example, functional derivatives of Ilomastat are disclosed in US patent
20 5,183,900. Ilomastat is especially preferred because it is one of the most potent collagenase inhibitors known at present. However, for certain applications it may be preferable to use a less potent (weaker) inhibitor.

Studies by the inventors have demonstrated that Ilomastat can inhibit MMPs during subconjunctival wound healing without toxic effect. For these reasons the inventors initially
25 focused on Ilomastat for use for scarring inhibition.

As indicated above, Ilomastat (molecular formula $C_{20}H_{28}N_4O_4$, 388.47 g/mol) is a peptide analogue with the formal chemical name of N-[(2R)-2-(hydroxamidocarbonylmethyl)-4-methylpentanoyl]-L tryptophan methylamide. It is a broad spectrum hydroxamate MMP inhibitor (Galaray et al. 1994a). The reported K_i values are as follows: Human MMP-1
30 (Fibroblast collagenase): 0.4 nM, Human MMP-3 (Stromelysin): 27 nM, Human MMP-2 (72

kDa gelatinase): 0.5 nM, Human MMP-8 (Neutrophil collagenase): 0.1 nM, Human MMP-9 (92 kDa gelatinase): 0.2 nM (Galaray et al. 1994c).

The solid dosage form of the present invention may comprise more than one therapeutically active agent, e.g., more than one MMP inhibitor or two or more different classes of therapeutically active agents. However, it is preferred that the solid form only comprises one therapeutically active agent, e.g., an MMP inhibitor.

In accordance with a second aspect of the invention, there is provided a dosage form according to the first aspect, for use in therapy.

In particular, when the dosage form contains an MMP inhibitor, it is preferably for use in preventing or reducing tissue scarring. In certain embodiments, the scarring is ocular, periocular or intraocular. In particular embodiments, the dosage form is implanted following glaucoma filtration surgery. The dosage form may, in instances such as those described, be implanted in the subconjunctival space.

It has been found that by providing the MMP inhibitor in a solid dosage form that a slow dissolution rate is achieved enabling the required *in situ* concentration of the MMP inhibitor to be achieved for at least 30 days. Such a slow dissolution rate results in the prevention or a substantial reduction of scarring leading to a better outcome for the patient being treated. With the previous methods of injecting solutions of the MMP inhibitor, clearance of the MMP inhibitor occurs within minutes. Even when slow release gels are used to provide the MMP inhibitor, clearance occurs within about 3-6 hours. By providing the MMP inhibitor in a solid dosage form, clearance does not occur for over 30 days. A further advantage of appropriate dosage forms of the invention is that the solid dosage form does not need to be removed as it completely dissolves and/or biodegrades *in situ*.

The present invention avoids the inconvenient and dangerous practice of giving multiple injections of an anti-scarring agent to the eye. Furthermore, by reducing the individual's exposure to the anti-scarring agent the risk of systemic complications (such as arthritis) are avoided.

The invention also provides the use of a dosage form according to the first aspect, in the preparation of a medicament for implantation for the localised prevention or treatment of a

disease. In particular embodiments, particularly when the active agent is an MMP inhibitor, the medicament may be for implantation for the localised treatment or prevention of scarring in the tissue.

In a related manner, the invention also provides a method of locally preventing or treating a disease in a patient in need thereof, the method comprising administering a solid dosage form according to the first aspect to said patient, by implantation, in an amount sufficient to prevent or treat the disease. In preferred embodiments, the active agent is an MMP inhibitor, and the dosage form is administered for locally treating or preventing scarring in said patient. In such an instance, the dosage form may be administered by ocular, periocular or intraocular implantation, for example, by being implanted in the subconjunctival space. The scarring to be prevented or treated may be that following glaucoma filtration surgery.

In a third aspect, the present invention also provides the use of an MMP inhibitor in the manufacture of a solid, implantable medicament for preventing or reducing tissue scarring, by local implantation. Similarly, the invention provides an MMP inhibitor, for use in the prevention or reduction of tissue scarring, wherein the MMP inhibitor is formulated as a solid, implantable medicament, optionally containing one or more pharmaceutically acceptable excipients, for local implantation. A method of locally preventing or treating tissue scarring in a patient in need thereof, the method comprising administering a solid, implantable dosage form comprising a matrix metalloproteinase inhibitor, optionally with one or more pharmaceutically acceptable excipients, by local implantation.

In accordance with a fourth aspect of the invention, there is provided a solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, for use in therapy by ocular, periocular or intraocular implantation. Similarly, the invention provides the use of a solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the localised prevention or treatment of a disease by ocular, periocular or intraocular implantation. Also provided is a method of locally preventing or treating a disease in a patient in need thereof, the method comprising administering a solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, by ocular, periocular or intraocular implantation.

The fourth aspect is based on the surprising finding that a solid unit dosage form, containing an active agent in solid form, may be implanted at an appropriate ocular, intraocular or periocular site for the release of the active agent in the locality thereof. The active agent is preferably substantially water insoluble (as defined above). Such a characteristic provides for a longer and more steady release of active agent from the dosage form. In preferred embodiments of the third aspect, the active agent is a matrix metalloproteinase inhibitor. The MMP inhibitor may be as defined above in relation to the first aspect.

In a fifth aspect, the present invention provides a solid, implantable dosage form comprising a matrix metalloproteinase inhibitor, optionally with one or more pharmaceutically acceptable excipients, which is sterilised. The sterilisation of such a dosage form allows it to be implanted in sterile sites *in vivo*.

The invention also provides the use of a matrix metalloproteinase inhibitor in the manufacture of a solid dosage form as described above.

Also provided is a method of manufacturing a dosage form according to the fifth aspect, the method comprising:

- i. forming a compressed dosage form, such as a tablet, containing the matrix metalloproteinase inhibitor and the excipients, when present, and

- ii. sterilising the compressed dosage form by irradiating it with gamma radiation.

Furthermore, the invention provides a kit comprising a dosage form as described above and containing an MMP inhibitor, together with surgical equipment necessary for performing glaucoma filtration surgery.

The present invention also provides a method of preventing or reducing tissue scarring in a patient in need thereof comprising administering a matrix metalloproteinase inhibitor in a solid dosage form to said patient in an amount sufficient to prevent or reduce tissue scarring.

The solid dosage form of the present invention can, unless otherwise specified, be any solid dosage form, such as a tablet, that has the desired dissolution rate. The desired dissolution

rate is one that allows a therapeutically effective concentration of the therapeutic agent to be released into the surrounding media for a substantial period of time. For example, at least one hour, more preferably at least one day, even more preferably for at least 5 days, more preferably at least 20 days, more preferably at least 30 days and, in some instances, up to 60 days. A variable dosing regimen may also be employed. For example, it may be possible, e.g. following surgery on a site, to implant a series of, say, 5 tablets, each of which provides 5 day release. These tablets may contain various doses. This will enable around 25 days of ongoing treatment using the active agent (e.g. MMP inhibitor), potentially using different concentrations thereof.

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It has been found that when the therapeutically active agent is Ilomastat, an MMP inhibitory concentration of 10 μ M is maintained for at least 30 days using a solid dosage form having a weight of about 2 to 5 mg. The concentration of the active agent that is maintained *in situ* will vary depending on the solubility of the agent and on the particular flow rate of fluid within the tissue wherein the solid dosage form is implanted.

15

Preferably the solid dosage form is suitable for implantation into a tissue, wherein on implantation it is slowly dissolved. Preferably the solid dosage form dissolves over a period of at least one day, preferably at least 5 days, more preferably at least 10 days, more preferably at least 20 days and most preferably at least 30 days and, in some instances, up to 60 days.

20

The shape of the solid dosage form can affect the dissolution rate by changing the surface area of the solid dosage form. The solid dosage form may be coated with a polymer that affects the dissolution rate. Such polymers are well known to those skilled in the art. Preferably, however, the solid dosage form is not coated with a polymer. The use of such polymers is generally not preferred as on clearance from the tissue a local inflammatory response may be induced, especially in the case of degradable polymers where degradation products could display toxicity. Another advantage with using an excipient and/or coating free tablet is that a proteinacious capsule does not form around the dosage form *in vivo*. Most implantables cause a foreign body response leading to capsule formation, and it is anticipated that most coatings will result in capsule formation when left in tissue - this being a form of inflammatory response.

30

The concentration of the therapeutically active agent to be delivered in order to prevent or treat the disease can be determined using standard techniques; however, when the active agent is an MMP inhibitor, generally, the concentration required to prevent or reduce tissue scarring is about 1 μM to about 1000 μM , more preferably about 10 μM to about 500 μM .

5

The shape of the solid dosage form will vary depending on the intended use. For example, if the solid dosage form is to be used to prevent tissue scarring after GFS, it is preferably of a shape and size enabling it to be delivered to the subconjunctival space. For example, it is preferred that the solid dosage form is a tablet having a diameter of 5 mm or less and a thickness of 2 mm or less. Preferably the tablet has a diameter of between 0.1 and 4mm with a thickness of between 0.1 and 1mm. The shape of the solid dosage form will vary depending on the disease to be prevented or treated. The solid dosage form may be sized to enable it to be injected into the tissue to be treated, e.g., a tumour tissue, the vitreous humor, etc.

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The present invention provides a substantially water insoluble therapeutically active agent in a solid dosage form for localised prevention or treatment of a disease.

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It has been found that by providing a substantially water insoluble therapeutically active agent in a solid dosage form that a slow dissolution rate is achieved enabling the required *in situ* concentration of the agent to be achieved for a therapeutically effective time. The slow dissolution rate results in a prolonged exposure of the localised area of the body to the agent resulting in more effective localised treatment. A further advantage is that the solid dosage form does not need to be removed as it dissolves *in situ*. The present invention avoids the inconvenient practice of giving multiple injections of a therapeutically effective agent to an individual patient. Furthermore, by reducing the individual's exposure to the agent the risk of systemic complications are avoided.

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The present invention also provides the use of a substantially water insoluble therapeutically active agent in the manufacture of a solid medicament for local delivery for preventing or treating a disease.

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The present invention also provides a method of preventing or treating a disease in a patient in need thereof comprising locally administering a substantially water insoluble

therapeutically active agent in a solid dosage form to said patient in an amount sufficient to prevent or treat the disease. The term “substantially water insoluble” is defined above.

The solid dosage form of the invention preferably has an overall volume of between 0.1mm^3 and 1.5cm^3 , more preferably between 0.5mm^3 and 1cm^3 . The solid dosage form may comprise one or more excipients but preferably is substantially excipient free. The term “substantially excipient free” means that the solid dosage form comprises less than 50% (w/w) excipients, preferably less than 40% (w/w) excipients, more preferably less than 10% (w/w) excipients, and most preferably the solid dosage form comprises at most trace amounts (1-2% (w/w)) of excipients. As described above, dosage forms of the invention may contain excipients, if necessary in levels above these limits, provided that the excipients are preferably bioresorbable and/or biodegradable *in vivo*. It has surprisingly been found that a solid dosage form consisting entirely of an MMP inhibitor, has the correct dissolution rate for preventing or reducing tissue scarring.

Suitable excipients are well known to those skilled in the art and include any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. For example, pharmaceutically acceptable carriers, adjuvants and vehicles that may be used, include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, ethylcellulose, medium or high molecular weight (e.g. number average molecular weight of 600 or higher), polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, solid polyoxyethylene-polyoxypropylene-block copolymers, wool fat, lactose and corn starch. Preferred excipients are biodegradable and/or bioresorbable from the implantation site *in vivo*.

The solid dosage form may comprise one or more additional active agents. Suitable additional active agents include antimetabolites, cytotoxic agents, anti-growth factors (e.g., TGFbeta, VEGF, etc.) or any other agents that may assist in the therapeutic treatment. For example, when the therapeutic agent is a MMP inhibitor, it is preferred that the additional active agent also prevents tissue scarring. However, it is preferred that the only active agent contained within the solid dosage form is the substantially water insoluble therapeutic agent, e.g., a MMP inhibitor.

The weight of the solid dosage form will vary depending on its intended use and on the amount of excipients or additional active agents that may be present. For example, if the solid dosage form is to be used to prevent tissue scarring during GFS, and consists entirely of the substantially water insoluble therapeutic agent, e.g., a MMP inhibitor, it is preferred that the solid dosage form weighs less than 10 mg, more preferably less than 6 mg, most preferably between 1 and 5 mg. The weight of the solid dosage form will vary depending on its intended use. Preferably the solid dosage form comprises between 1 and 5 mg of the substantially water insoluble therapeutic agent, e.g., MMP inhibitor. As the solid dosage form is, in use, positioned at a site within the body where the disease has occurred, or is likely to occur, the solid dosage form is preferably sterilized. The solid dosage form can be sterilized using any standard technique. Preferably, the solid dosage form is sterilized using gamma radiation.

According to the preferred embodiment of the present invention, the substantially water insoluble therapeutic agent is an MMP inhibitor for preventing or reducing tissue scarring. Any type of tissue scarring can be prevented or reduced using the solid dosage form of the MMP inhibitor described herein.

Scarring frequently occurs in the healing of burns. The burns may be chemical, thermal or radiation burns and may be of the eye, the surface of the skin or the skin and the underlying tissues. It may also be the case that there are burns on internal tissues, for example, caused by radiation treatment. Scarring may lead to physical and/or cosmetic problems, for example, loss of movement and/or disfigurement.

Scarring also occurs when producing skin grafts. Skin grafts may be applied for a variety of reasons and scarring may lead to both physical and cosmetic problems. It is a particularly serious problem where many skin grafts are needed as, for example, in a serious burns case.

Specific types of tissue scarring that can be prevented or reduced include ocular tissue scarring following eye surgery. Most forms of eye surgery cause some tissue scarring. For example, glaucoma filtration surgery (GFS) to create new drainage channels often fails due to scarring of tissues. A method of preventing scar tissue forming is therefore invaluable. Scar tissue may also be formed after corneal trauma or corneal surgery, for example laser or surgical treatment for myopia or refractive error. Opacification and cataract extraction can

also cause scarring. Scar tissue may also be formed on/in the vitreous humor or the retina, for example, that which eventually causes blindness in some diabetics and that which is formed after detachment surgery, called proliferative vitreoretinopathy. Other types of scarring that may be prevented or reduced include scarring formed in the orbit or on eye and
5 eyelid muscles after squint, orbital or eyelid surgery, or scarring of the conjunctiva which occurs in thyroid eye disease as may happen after glaucoma surgery or in cicatricial disease, inflammatory disease (e.g., pemphigoid), or infective disease (e.g., trachoma). In addition, the preparation of local ocular environments so as to make them permissive for tissue regeneration could benefit from the dosage forms of the invention.

10 Scarring is also associated with retinopathy of prematurity, macula degeneration, and myopia. Scarring of the optic nerve can also occur in glaucoma.

Another form of scarring is cicatricial contraction, namely contraction due to shrinkage of the fibrous tissue of a scar. In some cases the scar may become a vicious cicatrix, a scar in which the contraction causes serious deformity. A patient's stomach may be effectively separated
15 into two separate chambers in an hour-glass contracture by the contraction of scar tissue formed when a stomach ulcer heals. Obstruction of passages and ducts, cicatricial stenosis, may occur due to the contraction of scar tissue. Contraction of blood vessels may be due to primary obstruction or surgical trauma, for example, after surgery or angioplasty. Stenosis of other hollow visci, for examples, ureters, may also occur. Problems may occur where any
20 form of scarring takes place, whether resulting from accidental wounds or from surgery.

Solid dosage forms of the MMP inhibitors, may be used wherever scar tissue is likely to be formed, is being formed, or has been formed.

Scarring is also involved in conditions of the skin and tendons which involve contraction of collagen-comprising tissues, include posttrauma conditions resulting from surgery or
25 accidents, for example, hand or foot tendon injuries, post-graft conditions and pathological conditions, such as scleroderma, Dupuytren's contracture and epidermolysis bullosa.

The solid dosage form of the MMP inhibitor is preferably used to treat or prevent tissue scarring associated with a chemical burn, a thermal burn or a radiation burn, a skin graft, a post-trauma condition resulting from surgery or an accident, glaucoma surgery, diabetes
30 associated eye disease, scleroderma, Dupytren's contracture, epidermolysis bullosa or a hand

or foot tendon injury. Preferably treatment should take place as early as possible, advantageously as soon as, and most advantageously before, the first signs of scarring. As indicated above, the solid dosage form is preferably for implantation at the site of surgery to prevent or reduce tissue scarring.

- 5 It is particularly preferred that the solid dosage form comprising the MMP inhibitor is for ocular delivery and for preventing scarring of eye tissue. Accordingly, the solid dosage form comprising the MMP inhibitor is preferably used to prevent or reduce ocular tissue scarring following eye surgery, especially following GFS. In particular, it has been found that by placing the solid dosage form within the subconjunctival space following GFS causes the slow
10 release of the MMP inhibitor into the aqueous humor. The presence of the MMP inhibitor prevents the bleb (tissue covering the surgical incision) from scarring and thereby prevents fluid from passing out of the aqueous humor through the incision.

In a preferred embodiment of the present invention, the solid dosage form of the substantially water insoluble therapeutic agent, e.g., MMP inhibitor, consists essentially of the
15 substantially water insoluble therapeutic agent, e.g., MMP inhibitor. The term “consists essentially of” as used herein means that the solid dosage form consists of the substantially water insoluble therapeutic agent, e.g., MMP inhibitor with only trace amounts (up to about 1 to 2% (w/w)) of other components.

The present invention also provides a solid pharmaceutical composition comprising a
20 substantially water insoluble therapeutic agent which is in the form of an implantable tablet. Preferably the tablet is 5 mm or less in diameter and preferably also has a thickness of 2 mm or less. The tablet preferably has an overall volume of between 0.1 mm^3 and 1.5 cm^3 . The therapeutic agent is as defined above. As indicated above, the tablet may comprise excipients and other active agents; however, preferably the tablet is substantially excipient free and
25 consists essentially of the therapeutically active agent.

In a preferred embodiment, the present invention also provides a solid, implantable pharmaceutical composition comprising a matrix metalloproteinase inhibitor which is in the form of a tablet. Preferably the tablet is 5mm or less in diameter and preferably also has a thickness of 2 mm or less. The tablet preferably has an overall volume of between 0.1 mm^3
30 and 1.5 cm^3 .

The MMP inhibitor is as defined above. The tablet is preferably sized to enable it to be inserted into the subconjunctival space in order to prevent tissue scarring following eye surgery, especially GFS. As indicated above, the tablet may comprise excipients and other active agents; however, preferably the tablet is substantially excipient free and consists essentially of the MMP inhibitor.

The present invention also provides a solid pharmaceutical composition comprising a substantially water insoluble therapeutic agent which is in the form of a tablet that weighs less than 10 mg, preferably less than 6 mg.

The therapeutic agent is as defined above. As indicated above, the tablet may comprise excipients and other active agents; however, preferably the tablet is substantially excipient free and consists essentially of the therapeutic agent.

In a preferred embodiment, the present invention also provides a solid pharmaceutical composition comprising a matrix metalloproteinase inhibitor which is in the form of a tablet that weighs less than 10 mg, preferably less than 6 mg.

The MMP inhibitor is as defined above. As indicated above, the tablet may comprise excipients and other active agents; however, preferably the tablet is substantially excipient free and consists essentially of the MMP inhibitor.

The present invention also provides a sterilized solid pharmaceutical composition comprising a substantially water insoluble therapeutic agent. Preferably the substantially water insoluble therapeutic agent is a matrix metalloproteinase inhibitor. The MMP inhibitor is as defined above. Preferably the pharmaceutical composition is in the form of a tablet. As indicated above, the pharmaceutical composition may comprise excipients and other active agents; however, preferably the pharmaceutical composition is substantially excipient free and consists essentially of the substantially water insoluble therapeutic agent as the sole active agent. It is preferred that the solid pharmaceutical composition is sterilized by exposure to gamma radiation.

The present invention also provides a method of manufacturing a sterilized solid pharmaceutical composition comprising a substantially water insoluble therapeutic agent

comprising:

- i. forming a solid tablet of the substantially water insoluble therapeutic agent;
and
- ii. irradiating the tablet with gamma radiation to sterilize the tablet.

5 The method of the present invention enables the manufacture of a sterilized solid pharmaceutical composition for preventing or reducing tissue scarring. The step of forming the solid tablet of the substantially water insoluble therapeutic agent can be performed using any suitable technique. Preferably, the solid tablet is formed by compressing the substantially water insoluble therapeutic agent into a solid tablet using a punch-die or other
10 suitable technique. The step of irradiating the tablet with gamma radiation preferably comprises subjecting the tablet to a 25 KGy dose to ensure sterilization, although lower doses may be sufficient. The therapeutic agent is as defined above, and is preferably a MMP inhibitor. As indicated above, the tablet may comprise excipients and other active agents; however, preferably the tablet is substantially excipient free and consists essentially of the
15 substantially water insoluble therapeutic agent.

The present invention also provides a kit comprising a solid dosage form comprising a MMP inhibitor and surgical equipment necessary for performing glaucoma filtration surgery.

The MMP inhibitor is as defined above. It is also preferred that the solid dosage form is as defined above. The kit may comprise a plurality of the solid dosage forms, wherein a number
20 of the solid dosage form may be implanted in the patient depending on the dosage required. The kit may also comprise instructions indicating how to use the solid dosage form.

Due to the small volume and the low aqueous flow characteristics of numerous body tissues, e.g., the subconjunctiva, non-sink conditions will exist. The rate determining step for the dissolution of the solid form of most active agents will be caused by these non-sink
25 conditions. Dissolution in conditions where flow characteristics are thought to be within a consistent range will be primarily linear. This will prevent dose dumping and burst release kinetics and allow for a constant, sustained concentration of the active agent. Surprisingly there is no local contact tissue toxicity observed when using a tablet dosage form that is devoid of excipients. Also surprising is that small tablets can be fabricated that do not

crumble or fall apart. Without being bound to any particular theory for this, it is presumed that this is due to trace residual water and the poorly soluble characteristics of the biologically active substance. The lack of excipients avoids the need to ensure the active is miscible and compatible with its excipients. This is typically required to ensure that phase
5 separation of the active does not occur in the final dosage form.

Using a substantially water insoluble therapeutic agent, such as an MMP inhibitor, without excipients is surprising because it is stable in this form and maintains its activity. This is surprising because generally it would be expected that excipients would be needed to maintain a stable dispersion of the active and to prevent aggregation phenomena. So it is
10 surprising that in a solid form designed for implantation that is predominantly devoid of excipients, that efficacy is observed without the need for repeat administrations of the active substance.

Since the dosage form is designed for use in the non-sink conditions inherent in the subconjunctiva, and in tissue generally, then use of a solid tablet form that is fabricated
15 predominantly from the active substance will be optimal for maintaining a prolonged and consistent local concentration of the biologically active substance.

In accordance with a sixth aspect of the present invention, there is provided a pharmaceutical composition in solid unit dose form comprising an antibody, in solid form, optionally together with one or more pharmaceutically acceptable excipients.

20 The term 'antibody', which is synonymous with 'antibody molecule', has the same meaning as used in relation to the first aspect of the invention.

Hitherto, therapeutic or diagnostic antibodies have generally been formulated and administered as aqueous solutions. In certain cases, the antibody is presented as a freeze dried solid, but this solid must be reconstituted before use and a suitable dose extracted from
25 the solution resulting therefrom. The inventors have surprisingly found that it is possible to formulate an antibody as a solid unit dosage form, with retention of antigen binding, and with suitable release characteristics for *in vivo* use. Furthermore, by formulating the antibody as a solid unit dose, it is possible to achieve a sustained release of the antibody following implantation *in vivo*; such release is not achievable with an aqueous injectable formulation.
30 Such results are also achievable with other protein-based therapeutic or diagnostic agents.

In certain embodiments, the antibody is a monoclonal antibody. In particular, the antibody may be indicated for the treatment or prevention of a neoplastic disease, and may, for example, be an anti-VEGF antibody. An example of an anti-VEGF antibody is bevacizumab (Avastin).

- 5 The composition of this aspect of the invention is preferably sterilised.

When one or more excipients are present, these are preferably biodegradable and/or bioresorbable following *in vivo* implantation. In certain embodiments, the composition is substantially free of excipients (as defined above). In some embodiments, certain excipients, such as stabilising saccharides (e.g. trehalose), buffer salts, surfactants and/or similar,
10 relatively soluble excipients which would typically be included in an aqueous injectable formulation of antibody, may be present, in some cases in significant amounts, without significantly affecting the advantageous properties of the composition of the invention. Indeed, in some instances, the incorporation of excipients can be used to improve and/or control the release of antibody from the composition. Thus, it has been found that
15 hydrophilic polymers, such as hyaluronic acid, can be included in antibody tablet compositions of the invention, and can lead to an enhancement of antibody release when present in an appropriate amount. In greater amounts, hydrophilic polymers such as hyaluronic acid may be capable of producing a more sustained release of the antibody.

The composition of this aspect may be prepared by compression. A preferred composition of
20 this type is a tablet. In any event, each solid unit dosage form preferably has a volume of between 0.1 mm^3 and 1.5 cm^3 , and/or has a maximum dimension of 5 mm or less, and/or has a weight of 10mg or less.

The composition of this aspect may contain one or more additional therapeutically active ingredients, which may or may not be an antibody, and which may or may not be in solid
25 form.

The invention also provides a composition according to the sixth aspect, for use in therapy. In addition, the invention provides a composition according to the sixth aspect, for use in the treatment or prevention of a neoplastic disease. Similarly, the invention provides a method of treating or preventing a neoplastic disease in a patient in need thereof, the method comprising

administering to said patient a pharmaceutical composition according to the sixth aspect.

In accordance with a seventh aspect of the invention, there is provided a solid, implantable, dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, wherein the one or more excipients, when
5 present, do not control the release of the active agent by means of the chemical or biochemical degradation of one or more of the excipients. The dosage form is preferably sterilised.

In accordance with an eighth aspect of the invention, there is provided a solid, implantable, dosage form comprising a therapeutically active agent in solid form, optionally with one or
10 more pharmaceutically acceptable excipients, wherein the dosage form is prepared by compression. The dosage form is preferably sterilised.

In accordance with a ninth aspect of the present invention, there is provided a pharmaceutical composition in solid unit dose form comprising a protein therapeutic or diagnostic agent, such as an antibody, in solid form, optionally together with one or more pharmaceutically
15 acceptable excipients, wherein the dosage form is prepared by compression. The dosage form of this aspect is preferably in the form of a tablet. The dosage form of this aspect is preferably substantially excipient-free. The dosage form is also preferably sterilised. The dosage form is preferably implantable, and preferably has one or more of the additional features described above regarding suitability for implantation.

20 In accordance with a tenth aspect, the invention also provides a method of delivering a therapeutically active agent to an *in vivo* site for local prevention or treatment of a condition affecting that site, the method comprising implanting at the site a solid dosage form comprising the therapeutically active agent in solid form, optionally together with one or more pharmaceutically acceptable excipients. In certain embodiments, the dosage form is
25 substantially excipient free. In certain embodiments, the excipients are non-polymeric.

The present invention is now described by way of example only with reference to the following Figures.

Figure 1 shows a calibration curve of solubility for Ilomastat in pH 7.6 aqueous solution.

Figure 2 shows the release profile from Ilomastat tablet 1.

Figure 3 shows the concentration of Ilomastat in the samples collected from the rig with tablet 1.

Figure 4 shows the release profile from Ilomastat tablet 2.

- 5 Figure 5 shows the concentration of Ilomastat in the samples collected from the rig with tablet 2.

Figure 6 shows a calibration curve of solubility for 5-FU.

Figure 7 shows the release profile from the 5-FU tablets.

Figure 8 shows the concentration of 5-FU in the samples collected from the rig.

- 10 Figure 9 shows the cumulative release (a) and the concentration (b) of 5-FU released from excipient-free tablets under various conditions. The release profiles show ♦ Tablets in 50 µl chamber, ■ Tablets at the centre of 200 µl chamber, ▲ Tablets placed in 200 µl chamber closed to the in-going tube, ○ Tablets placed in 200µl chamber closed to the out going tube, and * Tablets at the side of 200 µl chamber.
- 15 Figure 10 shows the cumulative release (a) and the concentration (b) of triamcinolone released from excipient free tablets.

Figure 11 shows the cumulative release (a) and the concentration (b) of dexamethasone released from excipient free tablets.

- Figure 12 shows the cumulative release (a) and the concentration (b) of naproxen released
20 from excipient free tablets.

Figure 13 shows the cumulative release (a) and the concentration (b) of ilomastat released from excipient free tablets in a 200 µl flow dissolution rig.

Figure 14 shows the release profile and retention of activity of bevacizumab from

substantially excipient-free tablets.

Figure 15 shows the 'active protein' data of Figure 14 with actual data points plotted.

Figure 16 shows the size exclusion chromatography trace of bevacizumab from excipient free tablets, compared to that obtained from the commercial injectable product Avastin.

- 5 Figure 17 shows the release profile of bevacizumab from tablets according to the invention and containing hyaluronic acid as an excipient.

EXAMPLES

Solubility experiments suggested the possibility that a therapeutic dose of Ilomastat and other MMP inhibitors can be achieved by slow dissolution of a solid tablet form of Ilomastat or
10 other MMP inhibitors. It was established that compared to simple injections where clearance occurs in less than 5 minutes in an *in vitro* flow cell, prolonged release could be achieved with Ilomastat in the tablet form. A clinically validated *in vivo* model of GFS was then used to examine the effects of prolonged release at the site of surgery over different time points up to a period of 30 days. For GFS, Ilomastat has not been found to be toxic; however, the
15 teaching is applicable to a variety of MMP inhibitors and other substantially water insoluble therapeutic agents.

MATERIALS AND METHODS

FLOW SYSTEM

To obtain some indication of release kinetics, flow rigs of 50-200 μ l capacity were used to
20 model the bleb. An Ilomastat tablet (one tablet per rig) was placed into the flow chamber. Two tubes are connected to each rig: one was connected to a peristaltic pump to introduce an aqueous solution and the other tube allowed the removal of the solution out of the rig. Flow rates were used to model the flow of the aqueous solution into and out from the subconjunctival space to the scleral veins. Samples were collected as the solution flowed
25 from the rig to determine the concentration of Ilomastat in this slow release system.

A range of flow rates was used in the rig experiments; however, in most of the experiments a

flow rate of 2 µl/min was used to simulate the aqueous flow rate in the bleb. To further simulate the actual conditions in the eye, the aqueous solution used was maintained at pH 7.4-7.6 (as this is the pH of normal human aqueous humor) and the temperature was maintained at 37°C. The aqueous solution that was prepared using Oxoid® Phosphate Buffered Saline Tablets (one tablet for every 100 ml of de-ionized water). The PBS tablets were dissolved in de-ionized water and the pH was adjusted to 7.6. The aqueous solution was kept at 37°C.

TABLET FABRICATION

A tablet punch and die was used and solid Ilomastat was placed in the die and the punch was fitted. The solid Ilomastat was accurately weighed prior to the placement in the die. The fitted punch-die was then placed into a tablet compressor and pressed to a pressure of 5 bars for about ten seconds.

HPLC METHOD

Several reverse phase columns and mobile phases were evaluated to determine the optimal conditions required for HPLC separation of Ilomastat. It was found that a C-18 column (SIGMA) and a 25% acetonitrile aqueous mobile phase gave good base line resolution. The mobile phase was prepared as follows. To make 1000 ml of buffer 1.54 gm of ammonium acetate (Fluka), 6 ml of triethylamine 99.5% (Sigma Aldrich), ~950 ml de-ionized water were mixed and then approximately 10 ml of acetic acid 100% (Analar BDH) was added to adjust the pH of the buffer to 5.0 ± 0.1 . When the pH was adjusted, de-ionized water was added to make the buffer volume of 1000 ml. Aliquots of each sample (0.1 ml) were transferred to HPLC vials that were then placed in the HPLC auto-sampler. The mobile phase eluted at 1 ml/min and the UV detector was set to 280 nm to determine the concentration of an Ilomastat solutions (Galaridy et al. 1994b). Three injections (10 µl each) for each time point were evaluated. A computer was connected with the UV detector and with the use of the programme Chrom+, the peak area was analyzed to determine the amount of Ilomastat. The surface of the peak represents the concentration of Ilomastat in the tested solution. The average of the three measurements was used to determine the amount of Ilomastat.

STERILIZATION OF THE TABLET WITH GAMMA RADIATION

Following the regulations of European and American Pharmacopoeia, it is necessary the final dosage forms of the administered drugs to be sterile. Since tablet fabrication was not conducted in aseptic conditions and since sterile Ilomastat is not commercially available it was necessary to sterilise the Ilomastat tablets using gamma radiation. Gamma radiation is widely used as it has significant advantages including better assurance of product sterilization than aseptic processing and filtration, is penetrating into final fabricated objects, is a low temperature process and has a simple validation process. Also there are no residues which must be removed as for example with ethylene oxide sterilisation. One potential disadvantage is that gamma radiation can initiate chemical reactions that can result in the modification of chemical structure within the sample. Generally, a 25 kGy dose is needed to achieve the minimum sterility assurance level of $SAL=10^{-6}$ (the probability is one in a million the item to be non-sterile after the process). Lower doses may be validated using appropriate sterility tests. Under the regulations of European and American Pharmacopoeia, a 25 KGy dose of radiation ensures sterilization (2000a; 2000b). In co-operation with Cranfield University in the UK a Cobalt 60 gamma radiation source was utilized. This is considered suitable to sterilise drugs and biomaterials by irradiation. Ilomastat was thus irradiated as an unprocessed powder and as a fabricated tablet. As the Cobalt 60 gamma source applies about 4500 KGy radiation per hour, the samples were left in the Cobalt 60 panoramic chamber for about 5 hours and 35 minutes in order to obtain the 25 kGys exposure.

20 *IN VITRO EXPERIMENTS*

1. Human Tenon's Fibroblasts (HTF)

Human Tenon's fibroblasts (HTF) were used for *in vitro* cultures. These cells are involved in subconjunctival scarring. The process of HTF isolation and proliferation was performed by using 0.5 cm³ tissue explants from donor eyes obtained from Moorfields Hospital Eye Bank under the Tenets of the Declaration of Helsinki (1989). Explants of 0.5 cm³ were kept for two hours in the bottom of 25 cm³ flasks, with a coverslip placed over them. Each flask contained 5 ml of normal culture medium consisting of Dulbecco's modified Eagle's Medium (DMEM) with 10% fetal calf serum, 2 mM L-glutamine, 100 U/ml penicillin, 50 mg/ml gentamicin, 100 µg/ml streptomycin and 0.25 µg/ml amphotericin. The flasks were placed in incubators at 37°C and 5% humidified CO₂ in air. The culture medium was changed every 3 days and when they became confluent, usually within one month, they were passaged into new flasks

for direct experimental use or were stored in liquid nitrogen.

2. Passaging and maintenance of cell cultures

After the HTFs reached confluence, the culture medium was aspirated and the monolayer was washed with 1 ml of trypsin 1x (Gibco) and the trypsin was quickly aspirated for about 15 seconds. Next, 2 ml of trypsin 1x (Gibco) were added to each flask and HTFs were detached from the flasks by incubation for 2 minutes at 37°C and 5% humidified CO₂ in air. After confirming by phase contrast microscopy using a Leica microscope with x10 magnification that the cells had been detached from the bottom of the flask and that they had obtained a round shape, 2 ml of cell culture medium were added to neutralise the trypsinisation. The cell suspension was transferred to a 15 ml centrifuge tube (STARLAB GMBH) and was centrifuged at 1600 rpm for 5 minutes. The cell pellet was then resuspended in 10 ml of cell culture medium and was divided into 4 different 75cm³ flasks (1:4 expansion). In each flask 7.5 ml of cell culture medium were added. Flasks were placed in incubators at 37°C and 5% humidified CO₂ in air and the culture media was changed every three days. The time that was required from passage to passage in order to reach confluence was 1 week on average.

3. Preparation of the collagen gels (*in vitro* contraction model)

With a Neubauer plate, 6.2×10^4 HTF were counted and then were resuspended in 170 µl FBS in a 50 ml universal tube. Concentrated medium (160 µl) was added (stock solution consisting of 3.5 ml DMEM (x10 stock), 0.35 ml glutamine (2 mM stock) and 0.9 ml sodium bicarbonate (7.5% stock). 830 µl of First Link type I collagen solution collagen (stock 2.2mg/ml in 0.6% acetic acid) were then added and the solution was mixed by swirling to avoid air bubbles. Sterile 1M NaOH (75-80 µl) was rapidly added to change the acidic pH of the solution. This caused the solution to turn a pink colour without reverting back to yellow. Quickly 150 µl collagen gel solution was cast into the wells of Mattek dishes making sure to cast the gel to the edges of the central groove using the pipette tip. Creation of air bubbles when ejecting the gel from the tip should be avoided. If air bubbles were formed, they were aspirated out. Usually, from a 1.2 ml gel suspension, 6 gels can easily be cast. Following this process, the wells of Makket dishes with the gels were placed in incubator to set for at least 10-15 min (up to 30 mins). Gels were detached from the edges of the central groove using yellow tips and excess unpolymerised solution was aspirated off. Two milliliters of cell

culture medium were added and the dishes were placed in incubators at 37°C and 5% humidified CO₂ in air; the medium was replaced every 3 days.

4. Preparation of media with Ilomastat

Generally solid Ilomastat is diluted into DMSO before being added into the media, however
5 in this experiment Ilomastat could be directly dissolved in the normal media without DMSO. Media and solid Ilomastat that had been sterilised, and media and solid non-irradiated Ilomastat were placed in different 50 ml universal tubes and stirred for about 5-6 hours. The concentration of both samples was then confirmed by HPLC.

5. *In vitro* evaluation of Ilomastat activity

10 The inhibitory effect of non-irradiated Ilomastat on HTF contraction of collagen I gels is known. To compare with irradiated Ilomastat, experiments were conducted with three different treatment groups of collagen gels. Each treatment group had 3 collagen I gels with HTFs. The gels of the first group were treated with media without Ilomastat (negative control), the gels of the second group were treated with media with non-irradiated Ilomastat
15 (positive control) and the gels of the third group were treated with media with irradiated Ilomastat.

In a second *in vitro* experiment the inhibitory effect of the irradiated Ilomastat tablet dissolved directly in normal media was compared with the non-irradiated Ilomastat powder dissolved initially in DMSO and then in normal media. This experiment was conducted to
20 determine if the tablet fabrication process results in solid state changes such as crystallisation which could lead to reduced effectiveness of Ilomastat.

The inhibitory effect of Ilomastat was determined by measuring the contraction of the collagen gels. Photographs of the gels were obtained daily. The % contraction was determined using the software called Image J. The media of the treated gels then stored at -
25 70°C for future zymographic analysis in order to test the levels of active MMPs.

IN VIVO EXPERIMENT

1. Experimental Design

A random, one block study design was performed, with 4 rabbits undergoing glaucoma drainage surgery to the left eye. Animals were observed for a period of 30 days. The experiment was performed as a randomised, blind, controlled study with masked observers. One observer was used to assess clinical data.

5 2. Animals

Four Female New Zealand White Rabbits (Harlan UK Ltd; c. 2-2.2 kg, 12 - 14 weeks old) were used. Animals were housed in the BRU Unit of Ophthalmology and were allowed an acclimatisation period of 7 days, as is normally required.

3. Treatment Regimen

- 10 Animals were randomly assigned to either of two groups, as shown in Table 1. Animals in Group A received the Ilomastat excipient free tablet (also referred to as a pellet) and Group B received the ethylcellulose tablet which was used as the control. Ethylcellulose is an excipient that does not dissolve in aqueous solution and does not have any known inhibitory activity against MMP's. The size of the ethylcellulose tablet remained unchanged during the
- 15 30 day period of the *in vivo* experiment. The control pellet was the same size as the Ilomastat pellet in order to determine if the biological activity of Ilomastat itself maintained the bleb and its functionality rather than the simple placement of an inert ethylcellulose tablet.

Group #	Treatment	Tablet characteristics	Schedule	Control eye (right)	Study End
A (3 rabbits)	Ilomastat tablet	Weight: 2.1-2.3 mg Diameter: 3mm Thickness: 0.4 mm	Placement of one pellet in the left eye during GFS	No treatment	Day 30 – all rabbit eyes to histology
B (1 rabbits)	Ethylcellulose tablet	Weight: 1.5 mg Diameter: 3mm Thickness: 0.4 mm	Placement of one pellet in the left eye during GFS	No treatment	Day 30 – all rabbit eyes to histology

TABLE 1: TREATMENT GROUPS

20

Either an Ilomastat or an ethylcellulose tablet was placed subconjunctivally into the left eye just before conjunctival closure at the end of GFS.

4. Glaucoma Filtering Operation- Model of Glaucoma Filtration Surgery

Surgery is carried out using a standard method that has been thoroughly described in the literature. The consistency of the surgical procedure and its use in the rabbit allows for approximate comparisons with previous studies. This is particularly important since this model is clinically validated and this surgical procedure is in wide clinical use.

5. Collection of samples

At the end of the experiment on day 30, aqueous humor, vitreous and blood were collected for Ilomastat detection on HPLC.

RESULTS

CALIBRATION CURVE

A calibration curve for Ilomastat at pH 7.6 in aqueous solution without DMSO is shown in Figure 1. The curve was generated by measurement of Ilomastat as it eluted from the HPLC column (C18) using the mobile phase as described above and a UV detector (280 nm) with the software called Chrom+.

The curve was created as follows. Ilomastat (0.3885 mg) (Caldiochem, purity>95%) was dissolved in 7.6 pH aqueous solution (10 ml) to give a stock solution at a concentration of 100 μ M. The stock solution was then diluted in individual containers to give six other solutions with the following concentrations: 80 μ M, 60 μ M, 40 μ M, 20 μ M, 10 μ M and 5 μ M. Each solution was then evaluated three times by HPLC and the absorbance was determined. The Ilomastat peak was detected at approximately 6-8 min after the injection. The average calibration curve obtained is shown in the Figure 1.

ILOMASTAT TABLET RELEASE

The overall aim was to determine if placing a small tablet made of compressed pure Ilomastat in the subconjunctival space after glaucoma filtration surgery could result in slow release of Ilomastat in the aqueous humor. As Ilomastat is a very expensive compound, experience was obtained in small tablet fabrication using other compounds such as 5-FU prior to the formation of the Ilomastat tablets. Three excipient free Ilomastat tablets were fabricated using 6.5 mg, 5.6 mg and 3.2 mg of solid Ilomastat. A standard tablet punch and die and a press with an applied a pressure of five bars were used. The first tablet had a diameter of 3 mm, a

thickness of 0.87 mm and a weight of 4.8 mg. The second tablet had the same diameter, a thickness of 0.62 mm and a weight of 4.1 mg. The third tablet had diameter of 3 mm, a thickness of 0.4 mm and a weight of 2.3 mg. Small amounts of Ilomastat remained on the surface of the punch and die. The quantity of the Ilomastat that was used for the first tablet fabrication was based on the hypothesis that in every time point during the period of thirty days, Ilomastat would maintain the theoretical maximum dissolution in the aqueous solution (about 100 μ M).

After the placement of each tablet into the rig, 7.6 pH aqueous solution was pumped into the rig. The flow rate was set in 2 μ l/min, similar to the flow rate of aqueous humour through the trabecular meshwork. Liquid samples were collected after exiting the rig. The samples after filtration were then analysed by HPLC and the concentration of Ilomastat was determined using the calibration curve.

The data from tablets A and B were used to graphically show the release profiles for each tablet (Figures 2, 3, 4 and 5)

FABRICATION OF THE ILOMASTAT TABLET TO BE USED IN THE IN VIVO EXPERIMENTS

As the two tablets tested were found not to dissolve completely after 30 days in the flow rig, the inventors attempted to create a softer tablet using 2.3 mg of Ilomastat. We placed this tablet in a flow rig of 200 μ l capacity, the system was set in flow rate 2 μ l/min and the release profile of this tablet is shown in the Table 4.

Table 2: Ilomastat tablet 1

Galardin Tablet A without excipient (W=4.8mg) started on 14-12-2006 HPLC results									
Collect point	No.	time point	Peak Area		AVR PA	Volumn (ml)	Concentration (µM)	Released Amount (mg)	Release %
19.00 14-12-06	0	0					0	0	0.00%
23.40 14-12-06	1	280	157.488	155.957	156.809	1.2001	114.7491472	0.05350051	1.11%
9.30 15-12-06	N1	870	137.229	135.642	136.502	2.592	99.91459552	0.100613198	3.21%
11.40 15-12-06	2	1000	134.968	132.079	133.747	0.629	97.82419591	0.023904956	3.71%
13.30 15-12-06	3	1110	129.648	130.721	130.331	0.5332	95.36464425	0.019754614	4.12%
15.30 15-12-06	4	1230	129.561	128.325	129.147	0.5724	94.47112573	0.021008243	4.56%
19.30 15-12-06	5	1470	131.138	132.783	129.365	0.9864	95.99476121	0.036786767	5.32%
9.35 16-12-06	6	2315	112.444	113.384	113.338	4.1481	82.80762671	0.133447542	8.10%
19.30 16-12-06	7	2910	97.03	97.095	98.225	2.9284	71.4002193	0.081230844	9.80%
9.45 17-12-06	8	3765	73.847	73.202	72.517	4.7233	53.66532651	0.098475984	11.85%
19.30 17-12-06	9	4350	69.816	67.342	69.007	2.6526	50.39997563	0.051938944	12.93%
9.30 18-12-06	10	5190	59.512	59.458	58.878	3.89	43.50012183	0.065740212	14.30%
17.45 18-12-06	11	5685	58.327	60.744	59.668	2.4366	43.7172271	0.041383562	15.16%
17.45 19-12-06	13	6180	55.1	54.563	54.488	2.0125	40.1626462	0.031401416	15.82%
9.40 20-12-06	14	7135	58.549	57.778	58.256	4.264	42.70455653	0.070742831	17.29%
19.10 20-12-06	15	7705	54.922	55.193	54.477	2.7983	40.27010234	0.043779221	18.20%
9.40 21-12-06	16	8575	55.348	55.694	55.868	4.151	40.83491715	0.06585298	19.57%
18.15 21-12-06	17	9090	83.965	83.557	83.618	2.1473	61.3587963	0.051187106	20.64%
10.15 22-12-06	18	10050	103.506	104.524	103.178	4.1123	75.99524854	0.121412179	23.17%
18.15 23-12-06	19	11970	94.154	93.2	91.605	8.7515	68.13730507	0.231663958	28.00%
12.15 26-12-06	20	15930	72.826	73.267	72.786	18.8311	53.49792885	0.391384553	36.15%
11.45 27-12-06	21	17340	69.403	70.947	69.854	6.7603	51.38413743	0.134954094	38.96%
13.30 29-12-06	22	20325	62.785	62.415	63.097	14.4484	46.04617446	0.258466543	44.35%
14.55 31-12-06	23	23290	71.743	71.822	71.599	14.0847	52.59271442	0.287782387	50.34%
14.00 02-01-07	24	26115	68.958	69.033	69.623	13.4965	50.75304581	0.266118026	55.89%
9.55 04-01-07	25	28750	54.295	54.414	53.755	12.9323	39.75158382	0.19971985	60.05%
13.00 06-01-07	26	31815	44.125	44.864	45.289	15.0127	32.8836501	0.191791717	64.04%

18.00	08-01-07	27	34995	43.208	43.358	43.558	43.37466667	15.2311	31.87146686	0.188592468	67.97%
12.15	10-01-07	28	37530	14.723	14	14.022	14.24833333	11.4824	10.58028752	0.047197736	68.95%
10.25	12-01-07	29	40300	10.038	10.702	10.739	10.493	12.6964	7.835160819	0.038647333	69.76%
10.00	15-01-07	30	44595	12.813	13.096	13.132	13.01366667	20.0826	9.677753411	0.075506704	71.33%
14.40	16-01-07	31	46315	12.744	12.918	13.31	12.99066667	8.0509	9.660940546	0.030217245	71.96%

Galardin Tablet B without excipient (W=4.1mg) started on 17-1-2006 HPLC results										
Collection point	No.	time point	Peak Area		AVR PA	Volumn (ml)	Concentration (µM)	Released Amount (mg)	Release %	
17/01/2007 12:10	0	0					0	0	0.00%	
17/01/2007 14:15	1	125	76.724	76.738	77.07866667	0.2353	55.16239618	0.005042618	0.12%	
17/01/2007 16:20	2	250	124.471	124.647	124.70033333	0.2453	88.77689937	0.008460354	0.33%	
17/01/2007 18:40	3	390	121.179	121.461	121.33866667	0.2683	86.40401402	0.009006284	0.55%	
18/01/2007 10:15	4	1325	134.017	134.277	134.414	1.8601	95.63344392	0.069109398	2.23%	
18/01/2007 12:20	5	1450	128.249	128.879	128.75966667	0.241	91.642224371	0.008580326	2.44%	
18/01/2007 14:55	6	1605	122.177	123.375	123.02566667	0.318	87.59480953	0.010821726	2.71%	
18/01/2007 18:10	7	1800	121.623	122.639	122.11333333	0.3767	86.95082469	0.012725075	3.02%	
19/01/2007 10:00	8	2750	118.387	117.594	118.11366667	1.897	84.127597	0.062000735	4.53%	
19/01/2007 19:10	9	3300	118.88	120.321	119.92033333	1.0905	85.40286111	0.036181712	5.41%	
20/01/2007 11:40	10	4286	113.81	114.048	114.13	1.9651	81.31566316	0.06207974	6.93%	
20/01/2007 21:20	11	4866	111.149	111.503	111.45633333	1.1597	79.42841345	0.035785951	7.80%	
21/01/2007 11:45	12	5726	104.638	104.145	104.111	1.7169	74.24359427	0.049521639	9.01%	
21/01/2007 23:05	13	6286	126.784	126.61	126.90433333	1.1772	90.33262747	0.041312923	10.02%	
22/01/2007 09:40	14	6921	119.29	120.395	120.07633333	1.096	85.51297617	0.036411083	10.90%	
22/01/2007 20:05	15	7526	111.619	111.656	111.754	1.0547	79.63852615	0.032631962	11.70%	
23/01/2007 10:30	16	8387	99.59	98.474	99.249	1.5183	70.81167502	0.041768943	12.72%	
23/01/2007 17:30	17	8807	97.844	97.385	97.792	0.7384	69.78322863	0.020018603	13.21%	
24/01/2007 10:25	18	9822	95.043	95.341	95.39666667	1.396	68.09244488	0.036929665	14.11%	
24/01/2007 21:00	19	10454	92.692	92.532	92.68833333	0.8332	66.18072516	0.021422582	14.63%	
25/01/2007 09:29	20	11203	99.118	99.057	99.144	1.0931	70.73755912	0.030040073	15.36%	
25/01/2007 19:05	21	11779	100.226	100.796	100.58066667	0.8713	71.7516529	0.024287938	15.95%	
26/01/2007 10:20	22	12694	101.087	101.081	100.98933333	1.5272	72.0401167	0.04274264	17.00%	
26/01/2007 18:50	23	13204	140.128	140.666	140.67533333	0.8061	100.0531046	0.031333616	17.76%	
27/01/2007 19:10	24	14664	133.228	133.705	134.5716667	2.0833	95.74473542	0.077492155	19.65%	

28/01/2007 15:20	25	15874	139.667	139.716	140.24	139.8743333	1.9183	99.48770617	0.074144163	21.46%
29/01/2007 15:00	26	17294	57.499	57.445	57.715	57.553	2.6583	41.37989694	0.04273507	22.50%
30/01/2007 18:00	27	18914	49.137	49.309	49.563	49.33633333	3.0499	35.58003341	0.042158289	23.53%
31/01/2007 17:30	28	20324	46.969	46.287	45.8	46.352	2.4316	33.47349474	0.031621627	24.30%
01/02/2007 18:45	29	21841	41.858	42.031	41.797	41.89533333	2.7759	30.32768641	0.032706504	25.10%
02/02/2007 14:15	30	23011	42.755	42.323	42.551	42.543	2.2261	30.78485212	0.026623967	25.75%
03/02/2007 21:45	31	24901	93.056	92.924	92.431	92.80366667	3.3564	66.26213501	0.086403266	27.86%
04/02/2007 21:50	32	26346	88.894	88.676	88.447	88.67233333	2.776	63.34596833	0.068317107	29.52%
05/02/2007 15:25	33	27401	82.583	82.637	82.669	82.62966667	1.9655	59.08065693	0.045113798	30.62%
06/02/2007 14:02	34	28758	72.349	72.755	72.87	72.658	2.5736	52.04199901	0.05203386	31.89%
07/02/2007 17:45	35	30421	77.961	77.421	78.448	77.94333333	3.1176	55.77273476	0.067551245	33.54%
08/02/2007 16:25	36	31661	79.964	79.743	79.56	79.75566667	2.4373	57.05199878	0.054022027	34.86%
09/02/2007 20:12	37	33328	73.109	73.59	72.785	73.16133333	2.9739	52.39728477	0.060537735	36.33%
10/02/2007 20:02	38	34758	83.51	82.953	82.943	83.13533333	2.5168	59.4375897	0.058116696	37.75%
11/02/2007 19:39	39	36175	82.228	82.482	82.312	82.34066667	2.4738	58.87666173	0.05658467	39.13%
12/02/2007 15:24	40	37460	78.173	78.153	78.111	78.14566667	2.1196	55.91555493	0.04604448	40.25%
13/02/2007 19:00	41	39110	73.434	73.821	73.954	73.73633333	2.9937	52.80315757	0.061412842	41.75%
14/02/2007 16:18	42	40388	75.344	75.714	75.904	75.654	2.4126	54.15677278	0.050760878	42.99%
15/02/2007 18:15	43	41945	63.16	63.386	63.451	63.33233333	2.9028	45.459333037	0.051266205	44.24%
16/02/2007 17:40	44	43342	71.482	71.508	71.743	71.57766667	2.2821	51.27942872	0.045464129	45.35%
17/02/2007 19:20	45	44882	67.218	67.43	67.623	67.42366667	2.664	48.34726242	0.050037676	46.57%
18/02/2007 14:30	46	46032	68.866	68.951	69.157	68.99133333	2.0982	49.45382462	0.04031232	47.55%
19/02/2007 11:25	47	47347	65.282	65.489	65.722	65.49766667	2.106	46.98776499	0.038444497	48.49%

TABLE 4: RELEASE PARAMETERS OF THE 2.3 mg ILOMASTAT TABLET

Collection point	No.	time point	Peak Area				AVR PA	Volume (ml)	Concentration (μ M)	Released Amount (mg)	Release %
27/05/2007 11:25	0	0							0		0.00%
28/05/2007 13:35	1	1570	118.017	117.66	117.746	117.466	117.72225	3.1243	83.85130938	0.101777927	4.43%
29/05/2007 16:50	2	3205	114.342	114.49	114.053	114.761	114.4115	3.2863	81.51436437	0.104071635	8.95%
30/05/2007 13:15	3	5655	113.414	113.822	113.69	113.546	113.618	2.4501	80.9542599	0.077057434	12.30%
31/05/2007 14:30	4	7170	62.568	62.567	62.588	62.633	62.589	3.302	44.93463683	0.057643365	14.81%
01/06/2007 09:20	5	8300	77.02	77.173	76.899	76.791	76.97075	2.2374	55.0862215	0.047882591	16.89%
02/06/2007 16:55	6	10195	75.027	75.15	75.409	75.137	75.18075	3.6196	53.82272182	0.075686297	20.18%
04/06/2007 08:10	7	12430	79.74	78.995	79.474	78.903	79.278	4.4702	56.71483024	0.098495097	24.46%
05/06/2007 11:25	8	14065	71.271	71.165	71.17	71.141	71.18675	3.3518	51.00349404	0.066415439	27.35%
06/06/2007 17:10	9	15850	71.049	71.059	71.301	71.187	71.149	3.5702	50.9768476	0.070706045	30.42%
07/06/2007 16:15	10	17235	57.555	58.416	58.827	58.799	58.39925	2.7007	41.97723583	0.044043437	32.34%
08/06/2007 19:20	11	18980	72.262	72.248	72.361	72.499	72.3425	3.839	51.81929837	0.07728597	35.70%
09/06/2007 12:45	12	20025	73.139	72.187	72.203	72.141	72.4175	2.0691	51.8722383	0.041697258	37.51%
10/06/2007 13:05	13	21485	55.137	56.024	55.776	55.777	55.6785	2.92	40.05675161	0.04544118	39.49%
11/06/2007 21:40	14	23440	58.535	53.968	54.773	54.357	55.40825	3.9206	39.86599139	0.060722008	42.13%
13/06/2007 07:05	15	25445	54.524	54.362	54.123	54.705	54.4285	4.1503	39.17441943	0.063164503	44.87%
14/06/2007	16	27210	63.931	64.116	64.717	64.678	64.3605	3.5123	46.185078	0.063020858	47.61%

COMPARISON OF IRRADIATED AND NON-IRRADIATED ILOMASTAT WITH HPLC

Implantation of the Ilomastat tablet during glaucoma filtration surgery required that the tablet be sterile. The International Conference on Harmonization (ICH) recommends the
5 use of high-performance liquid chromatography (HPLC), mass spectrometry or gas chromatography to characterize and compare the irradiated product versus the non-irradiated product. Following these guidelines gamma irradiated Ilomastat was dissolved in pH 7.6 aqueous solution and evaluated it by HPLC. The chromatogram for the irradiated
10 Ilomastat was compared with the chromatogram for the non-irradiated Ilomastat. The chromatogram of the irradiated Ilomastat has displayed an extra peak representing compared to total Ilomastat, 0.25% trace products being formed after irradiation. This meets the criteria for both the American and European Pharmacopoeias.

STABILITY OF ILOMASTAT TABLET

15 A solution of Ilomastat in DMSO or water at a concentration of 0.1 mM decomposes 1% per month at 4°C and at 37°C this increases to 1% per day (Caldiochem data). No data have been published that describe the stability of Ilomastat as a solid tablet when left at 37°C in a moist environment for several days. An Ilomastat tablet was evaluated for possible
20 decomposition while in an aqueous environment at 37°C for 30 days. After collecting samples from the second tablet, the inventors removed the remaining solid from the rig and dissolved it in aqueous solution (pH 7.6). The chromatogram of the aqueous solution with the remaining Ilomastat compound on day 30 and the chromatogram of the aqueous solution collected from the rig at the first time point were compared. Both chromatograms were very similar suggesting that no decomposition had occurred during the 30 day period
25 (data not shown).

EXAMPLE 1

*ABILITY OF IRRADIATED ILOMASTAT POWDER AND OF IRRADIATED ILOMASTAT
TABLET DIRECTLY DISSOLVED IN MEDIA WITHOUT DMSO TO
30 INHIBIT CONTRACTION IN VITRO.*

The gels of all the three treatment categories (normal media, non-irradiated and irradiated Ilomastat) did not start contracting immediately. For that reason no significant changes were shown in the three treatment groups up to day 1. From day 2, the gels started to

contract and the inhibitory effect of both the irradiated and non-irradiated Ilomastat was apparent. There was a statistically significant difference in contraction between the negative control group and the Ilomastat group up to day 7 that the experiment was terminated.

5

Table 5: Contraction (%) of HTF collagen I gels over time

	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
NORMAL MEDIA	0	12.23	52.16	66.52	69.47	69.1	69.93	72.03
NON IRRADIATED	0	11.96	27.19	32.97	39.9	41.66	42.03	43.19
IRRADIATED ILOMASTAT	0	12.51	23.65	28.44	30.8	32.23	33.76	36.12

2nd in vitro experiment

10

Table 6: Contraction (%) of HTF collagen I gels over time

	Day 1					
	Group 1	Group 2	Group 3	Group 4	Average	standard error
Normal Media	39.06	42.25	47.43	28.54	39.32	3.565058122
Non-Irradiated Ilomastat with DMSO	13.03	19.45	20.69	24.23	19.35	2.09071577
Irradiated Ilomastat tablet	23.24	24.98	21.44	25.46	23.78	0.817728962
	Day 2					
	Group 1	Group 2	Group 3	Group 4	Average	standard error
Normal Media	55.56	58.93	61.1	54.12	57.4275	1.418302026
Non-Irradiated Ilomastat with DMSO	19.75	22.77	21.37	26.63	22.63	1.314107426
Irradiated Ilomastat tablet	28.57	26.24	23.93	26.99	26.4325	0.863325151
	Day 3					
	Group 1	Group 2	Group 3	Group 4	Average	standard error
Normal Media	69.95	74.05	72.06	59.3	68.84	2.941247917
Non-Irradiated Ilomastat with DMSO	20.44	24.14	21.55	27.17	23.325	1.339744676
Irradiated Ilomastat tablet	30.97	27.16	24.66	27.39	27.545	1.161244442
	Day 4					
	Group 1	Group 2	Group 3	Group 4	Average	standard error
Normal Media	82.26	81.72	82.54	69.95	79.1175	2.73753794
Non-Irradiated Ilomastat with DMSO	21.15	25.19	22.11	28.11	24.14	1.412473469
Irradiated Ilomastat tablet	31.39	30.49	25.87	28.32	29.0175	1.101253257
	Day 5					
	Group 1	Group 2	Group 3	Group 4	Average	standard error
Normal Media	84.8	84.45	85.82	72.12	81.7975	2.897043657

Non-Irradiated Ilomastat with DMSO	23.36	25.33	22.96	29.85	25.375	1.412371982
Irradiated Ilomastat tablet	32.02	31.86	25.99	32.47	30.585	1.374865422
	Day 6					
	Group 1	Group 2	Group 3	Group 4	Average	standard error
Normal Media	85.21	85.89	86.65	78.45	84.05	1.690242695
Non-Irradiated Ilomastat with DMSO	24.42	27.9	24.9	33.35	27.6425	1.835769566
Irradiated Ilomastat tablet	34	32.03	27.76	34.39	32.045	1.358533111
	Day 7					
	Group 1	Group 2	Group 3	Group 4	Average	standard error
Normal Media	85.91	86.9	86.93	80.47	85.0525	1.382621144
Non-Irradiated Ilomastat with DMSO	25.07	29	24.9	34.04	28.2525	1.922235588
Irradiated Ilomastat tablet	35.36	32.99	27.92	36.63	33.225	1.719558018

EXAMPLE 2*THE EFFECTIVENESS OF ILOMASTAT TABLET IN THE IN VIVO EXPERIMENT*

5 1. Clinical observations

The bleb in the rabbit that received the ethylcellulose tablet (control) failed on day 10 after glaucoma filtration surgery. In contrast, the blebs of the three rabbits that received the Ilomastat tablet did not fail. After 30 days the experiment as planned was terminated. In one rabbit the scleral sutures broke on day 7 and the tube fell into the anterior chamber.

10 When this occurs the normal expectation is that the bleb will fail; however, a well structured bleb surprisingly remained present in this rabbit until day 30. No corneal epitheliopathy was observed in the rabbits of the treated and control groups. Additionally, the conjunctiva over the bleb area was normal and not avascular. Avascular blebs have been observed after the use of MMC in glaucoma filtration surgery. Moreover, no soft eyes
15 were observed.

2. Detection of Ilomastat in the fluid samples collected from rabbits on day 30

Using the HPLC method described above, no Ilomastat was detected in the aqueous humor from the anterior chamber, vitreous or blood samples collected from the left (operated) eye of the rabbits on day 30. The retention time of Ilomastat as it was previously mentioned is 6.5-8 minutes and around that time point no peak was detected. These observations indicate that for GFS treatment outflow of the Ilomastat occurred with the result that any potential local toxicity can be avoided.

CONCLUSIONS

The inventors observed a prolonged release of Ilomastat from the tablets tested. These tablets were fabricated without use of any excipients. During the release period (30 days), a therapeutic dose of Ilomastat (10 μ M) was achieved. The use of a solid form of Ilomastat provides a method of preventing tissue scarring that does not require multiple injections. In contrast to previous *in vitro* and *in vivo* experiments, the inventors avoided using DMSO throughout the experiments, as it has not been approved for ocular clinical use.

A very important issue is the need to sterilize the tablet. The effects of irradiation in other metalloproteinase inhibitors, such as Captopril, have been evaluated (Engalytcheff et al. 2004; Engalytcheff, Vanhelleputte, & Tilquin 2004). Degradation of Captopril caused from irradiation was not significant. The inventors have found that the degradation of Ilomastat caused by the 25KGys gamma radiation dose was not significant and is within the acceptable limits as defined by the European and US Pharmacopoeias. Gamma irradiation provides a significant advantage to perform Ilomastat tablet sterilization in their package, as the package can be opened in the operating room without any further process needed to take place between gamma irradiation and the placement of the tablet in the subconjunctival space.

Furthermore, the inventors tested the effectiveness of irradiated Ilomastat to inhibit collagen I gel contraction and observed significant inhibition compared to the negative control and inhibition at about the same levels as the positive control. Although irradiated Ilomastat seems to be slightly more potent in inhibiting gel contraction than the non-irradiated Ilomastat, this difference is not statistically significant. The inventors believe that the main reason for this difference could be the use of slightly higher number of cells in the non-irradiated Ilomastat gels. The number of cells used for each gel is unfortunately a parameter that is not very accurate and this can result in slight differences in contractions being observed.

Finally, in the *in vivo* GFS model, the inventors observed that Ilomastat inhibited scarring after GFS in all the rabbits until day 30 when the experiment was required to be terminated. Another encouraging result was the lack of detection of Ilomastat in the

aqueous humor, vitreous and blood. Thus Ilomastat would be expected not to interfere with other eye structures and other parts of the body.

The use of Ilomastat and other MMP inhibitors in a solid tablet form for implantation at the site of surgery has been shown to have significant beneficial advantages for reducing and preventing tissue scarring.

EXAMPLE 3

IN VITRO EXPERIMENT USING 5-FU

As indicated above, a tablet of solid 5-FU was fabricated using the same technique as described above. The dissolution rate of the tablet was then determined using the same rig as described above.

RESULTS

CALIBRATION CURVE

A calibration curve for 5-FU dissolution at 7.6 pH aqueous solution without DMSO is shown in Figure 6. The curve was generated by measurement of the 5-FU peak in the HPLC reader using the software PC Chrom+.

The calibration curve for 5-FU was created in the same manner as that for Ilomastat.

RELEASE PROFILE

The first tablet (tablet A) had a diameter of 3mm, thickness of 0.71 mm and a weight of 7.1 mg. The second tablet (tablet B) had the same diameter, thickness of 0.88 mm and weight of 8.7 mg. The third tablet (tablet C) had diameter of 3 mm, thickness of 0.76 mm and weight of 7 mg.

Each tablet was placed into the rig as described above and liquid samples analysed by HPLC and concentration of 5-FU was determined using the calibration curve.

The data from tablets A, B and C was averaged and the release profiles shown graphically in Figures 7 and 8.

The data shows a prolonged release of 5-FU. These tablets were fabricated without use of any excipients. During the release period (25 hours), a substantially constant therapeutic dose of 5-FU was achieved. The use of a solid form of 5-FU provides a prolonged release that is of benefit in preventing tissue scarring.

EXAMPLE 4

SUSTAINED RELEASE OF ACTIVE AGENT FROM EXCIPIENT-FREE TABLETS

Figures 9 to 13 show the results obtained with a variety of chemically unrelated active agents, formulated as excipient-free tablets (as described above), using the flow-through dissolution rig. In each case, (a) shows the cumulative release of drug as a percentage of total drug content in the tablet, whereas (b) shows the concentration in the flow-through cell at each point in time.

It will be observed that each of the tablets tested produces essentially zero order (i.e. constant rate) release of drug. This is illustrated by the linear traces in (a) and the (for the most part) essentially flat traces in (b). This confirms that such tablets would be capable of producing essentially constant, therapeutically relevant levels of drug in an implantation site *in vivo*, over a period of many days. Even the dosage form containing the significantly more soluble drug 5-FU (Figure 9) is shown to produce essentially linear release of drug over a period of many hours. These results show that, compared to conventional dosage forms for local administration of drugs to the eye (e.g. eye drops or ocular injectables), the residence time of the dosage forms of the invention would be much greater. This would provide significant clinical advantage since the active agent would be present in the tissue for far longer.

EXAMPLE 5

TABLET COMPOSITION CONTAINING SOLID ANTIBODY

The aqueous injectable formulation of bevacizumab (marketed as Avastin) was used as starting material. To remove excipients (e.g. trehalose), pharmaceutical Avastin (50 µl of 25 mg/ml) was added to a spin column with membrane of cutoff of 10000 daltons

(Vivaspin 10000 from Vivascience). Distilled water (4ml) was added and the column centrifuged for 4 minutes at 4000 rpm. This step was repeated twice. Removal of trehalose was confirmed by thin layer chromatography (TLC; aqueous methanol 90%). Different concentrations of trehalose and intact Avastin were used as control. TLC film was dipped into a mixture of sulfuric acid (10%) and ethanol (90%) and then heated.

The obtained solution of bevacizumab was then freeze dried to isolate the antibody as a powder which was then used to fabricate a 1.25 mg bevacizumab tablet (as described above, and containing essentially only the freeze dried antibody). A release profile is shown in Figure 14 where total protein (BCA assay - upper line in Figure 14) and protein that binds to a VEGF chip (determined using a Biacore biosensor) are compared. These data confirms that the antibody is released from the tablet, potentially over a period of days, and also confirms that a significant portion of the antibody retains its VEGF-binding activity. The data for 'active protein' release is re-plotted in Figure 15 with actual data points shown.

Figure 16 shows the size exclusion chromatography (SEC) results for bevacizumab reconstituted from an excipient-free tablet according to the invention (labeled b), compared to untreated Avastin solution (labeled a), and compared to bevacizumab reconstituted from a tablet according to the invention, but with excipients not removed (unlabeled trace). In brief, the SEC conditions were as follows:

Sample injection volume: 150 μ l

Mobile phase: phosphate buffer (NaH_2PO_4 , 25 mM, pH 6.8 and NaCl 150 mM)

Flow rate: 1 mL/min

Column:(Hiload TM, Superdex TM 200)

UV detector:280 nm

The data of Figure 16 confirm that the molecular weight of the tableted bevacizumab is not changed compared to the Avastin control solution, i.e. the purification and tableting steps do not lead to aggregation of the antibody. As with the results shown in Example 4, the implantation site residence time of a dosage form prepared according to the present example would be significantly greater than that of, e.g. eye drops or ocular injectables. This would provide significant clinical advantage.

Manipulation of the release profile of antibody-containing compositions of the invention, such as tablets, may be achieved by the incorporation of certain excipients. This approach may also lead to improvements in the retention of antibody activity. Figure 17 shows the effect of adding 1.75 mg hyaluronic acid (Healon) per tablet. The concentrations achieved in the first 48 hours or so of release are markedly higher than from an equivalent excipient-free tablet (see Figures 14 and 15). This effect could be due to increased release *per se* of antibody, and/or could be related to an improved retention of antibody binding in the hyaluronic acid-containing tablet. Note that the biphasic release profile shown in Figure 17 is believed to be an artifact of the dissolution rig employed.

When the amount of hyaluronic acid is increased to 3.5 mg per tablet, the antibody release is dramatically reduced. Again, artifacts of the dissolution apparatus could be reflected in this data (small beads of the formulation were observed to stick to the sides of the flow cell), but it is believed that the higher hyaluronic acid content leads to a more sustained and steady release of the antibody. The dissolution profile of the antibody tablets can thus be tailored by an appropriate choice of excipients.

All documents cited herein are incorporated herein by reference.

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Claims

1. A solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, wherein the one or more excipients, when present, do not lead to a significant delay or prolongation of the release of active agent, as compared to an equivalent dosage form containing no excipients when tested *in vitro*.
2. A dosage form according to claim 1, which is suitable for localised prevention or treatment of a disease.
3. A dosage form according to claim 1 or claim 2, which is suitable for ocular, periocular or intraocular implantation.
4. A dosage form according to any preceding claim, which is sterilised.
5. A dosage form according to any preceding claim, wherein the one or more excipients, when present, are biodegradable and/or bioresorbable following *in vivo* implantation.
6. A dosage form according to any preceding claim, which is prepared by compression.
7. A dosage form according to claim 6, which is a tablet.
8. A dosage form according to any preceding claim, having a volume of between 0.1 mm³ and 1.5 cm³, and/or having a maximum dimension of 5 mm or less, and/or having a weight of 10mg or less.
9. A dosage form according to any preceding claim, which is substantially free of excipients.
10. A dosage form according to any preceding claim, wherein the active agent is substantially water insoluble.

11. A dosage form according to any preceding claim, wherein the active agent is a matrix metalloproteinase inhibitor.
12. A dosage form according to claim 11, wherein the matrix metalloproteinase inhibitor is a hydroxamic acid derivative that binds reversibly to zinc in the active site of matrix metalloproteinases.
13. The matrix metalloproteinase inhibitor of claim 12, wherein the matrix metalloproteinase inhibitor is a right side binder.
14. A dosage form according to claim 11, wherein the active agent is selected from the group consisting of ilomastat batimastat, marimastat, prinomastat, tanomastat, Trocade (cipemastat), AG 3340, CGs227023A, BAY 12-9566, and BMS-275291, or any functional derivatives thereof.
15. A dosage form according to any of claims 1 to 10, wherein the active agent is selected from the group consisting of anticancer agents, steroids, antibiotics, antibody molecules, anti-inflammatory agents and anti-scarring agents.
16. A dosage form according to claim 15, wherein the anticancer agent is 5-fluorouracil, the steroid is selected from triamcinolone and dexamethasone, and the anti-inflammatory agent is naproxen.
17. A dosage form according to any preceding claim, for use in therapy.
18. A dosage form according to any of claims 11 to 14, for preventing or reducing tissue scarring.
19. A dosage form according to claim 18, wherein the scarring is ocular, periocular or intraocular.
20. A dosage form according to claim 18 or claim 19, wherein the dosage form is implanted following glaucoma filtration surgery.

21. A dosage form according to claim 19 or claim 20, wherein the dosage form is implanted in the subconjunctival space.
22. A solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, for use in therapy by ocular, periocular or intraocular implantation.
23. A dosage form according to claim 22, wherein the active agent is substantially water insoluble.
24. A dosage form according to claim 22 or claim 23, wherein the active agent is a matrix metalloproteinase inhibitor.
25. Use of a dosage form according to any of claims 1 to 10, or 15, in the preparation of a medicament for implantation for the localised prevention or treatment of a disease.
26. Use of a dosage form according to any of claims 11 to 14, in the preparation of a medicament for implantation for the localised treatment or prevention of tissue scarring.
27. Use of a solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the localised prevention or treatment of a disease by ocular, periocular or intraocular implantation.
28. A method of locally preventing or treating a disease in a patient in need thereof, the method comprising administering a solid dosage form according to any of claims 1 to 10, or 15, to said patient, by implantation, in an amount sufficient to prevent or treat the disease.
29. A method of locally preventing scarring in a patient in need thereof, the method comprising administering a solid dosage form according to any of claims 11 to 14 to said patient, by implantation, in an amount sufficient to ameliorate said scarring.

30. A method according to claim 29, wherein the dosage form is administered by ocular, periocular or intraocular implantation.
31. A method according to claim 30, wherein the dosage form is implanted in the subconjunctival space.
32. A method according to any of claims 29 to 31, wherein the scarring is that following glaucoma filtration surgery.
33. Use of a matrix metalloproteinase inhibitor in the manufacture of a solid dosage form according to any of claims 1 to 15.
34. A method of locally preventing or treating a disease in a patient in need thereof, the method comprising administering a solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, by ocular, periocular or intraocular implantation.
35. A method according to claim 34, wherein the active agent is substantially water insoluble.
36. A method according to claim 34 or claim 35, wherein the active agent is a matrix metalloproteinase inhibitor
37. A method of locally preventing or treating tissue scarring in a patient in need thereof, the method comprising administering a solid, implantable dosage form comprising a matrix metalloproteinase inhibitor, optionally with one or more pharmaceutically acceptable excipients, by local implantation.
38. An MMP inhibitor, for use in the local prevention or reduction of tissue scarring, wherein the MMP inhibitor is formulated as a solid, implantable medicament, optionally containing one or more pharmaceutically acceptable excipients, for local implantation.

39. A solid, implantable dosage form comprising a matrix metalloproteinase inhibitor, optionally with one or more pharmaceutically acceptable excipients, which is sterilised.
40. A method of manufacturing a dosage form according to claim 39, the method comprising:
- i. forming a compressed dosage form, such as a tablet, containing the matrix metalloproteinase inhibitor and the excipients, when present, and
 - ii. sterilising the compressed dosage form by irradiating it with gamma radiation.
41. A kit comprising a dosage form according to any one of claims 11 to 14 and surgical equipment necessary for performing glaucoma filtration surgery.
42. A pharmaceutical composition in solid unit dose form comprising an antibody in solid form, optionally together with one or more pharmaceutically acceptable excipients.
43. A composition according to claim 42, wherein the antibody is a monoclonal antibody.
44. A composition according to claim 42 or 43, wherein the antibody is indicated for the treatment or prevention of a neoplastic disease, such as anti-VEGF antibody.
45. A composition according to any of claims 42 to 44, which is sterilised.
46. A composition according to any claims 42 to 45, wherein the one or more excipients, when present, are biodegradable and/or bioresorbable following *in vivo* implantation.
47. A composition according to any of claims 42 to 45, which is substantially free of excipients.

48. A composition according to any of claims 42 to 47, which is prepared by compression.
49. A composition according to claim 48, which is a tablet.
50. A composition according to any of claims 42 to 49, wherein each solid unit dosage form has a volume of between 0.1 mm^3 and 1.5 cm^3 , and/or has a maximum dimension of 5 mm or less, and/or has a weight of 10mg or less.
51. A composition according to any of claims 42 to 50, containing one or more additional therapeutically active ingredients, which may or may not be an antibody, and which may or may not be in solid form.
52. A composition according to any of claims 42 to 51, for use in therapy.
53. A composition according to claim 44, for use in the treatment or prevention of a neoplastic disease.
54. A method of treating or preventing a neoplastic disease in a patient in need thereof, the method comprising administering to said patient a pharmaceutical composition according to claim 44.
55. A solid, implantable, dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, wherein the one or more excipients, when present, do not control the release of the active agent by means of the chemical or biochemical degradation of one or more of the excipients.
56. A solid, implantable, dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, wherein the dosage form is prepared by compression.
57. A pharmaceutical composition in solid unit dose form comprising a protein therapeutic or diagnostic agent, such as an antibody, in solid form, optionally

together with one or more pharmaceutically acceptable excipients, wherein the dosage form is prepared by compression.

58. A method of delivering a therapeutically active agent to an *in vivo* site for local prevention or treatment of a condition affecting that site, the method comprising implanting at the site a solid dosage form comprising the therapeutically active agent in solid form, optionally together with one or more pharmaceutically acceptable excipients.

Figure 1

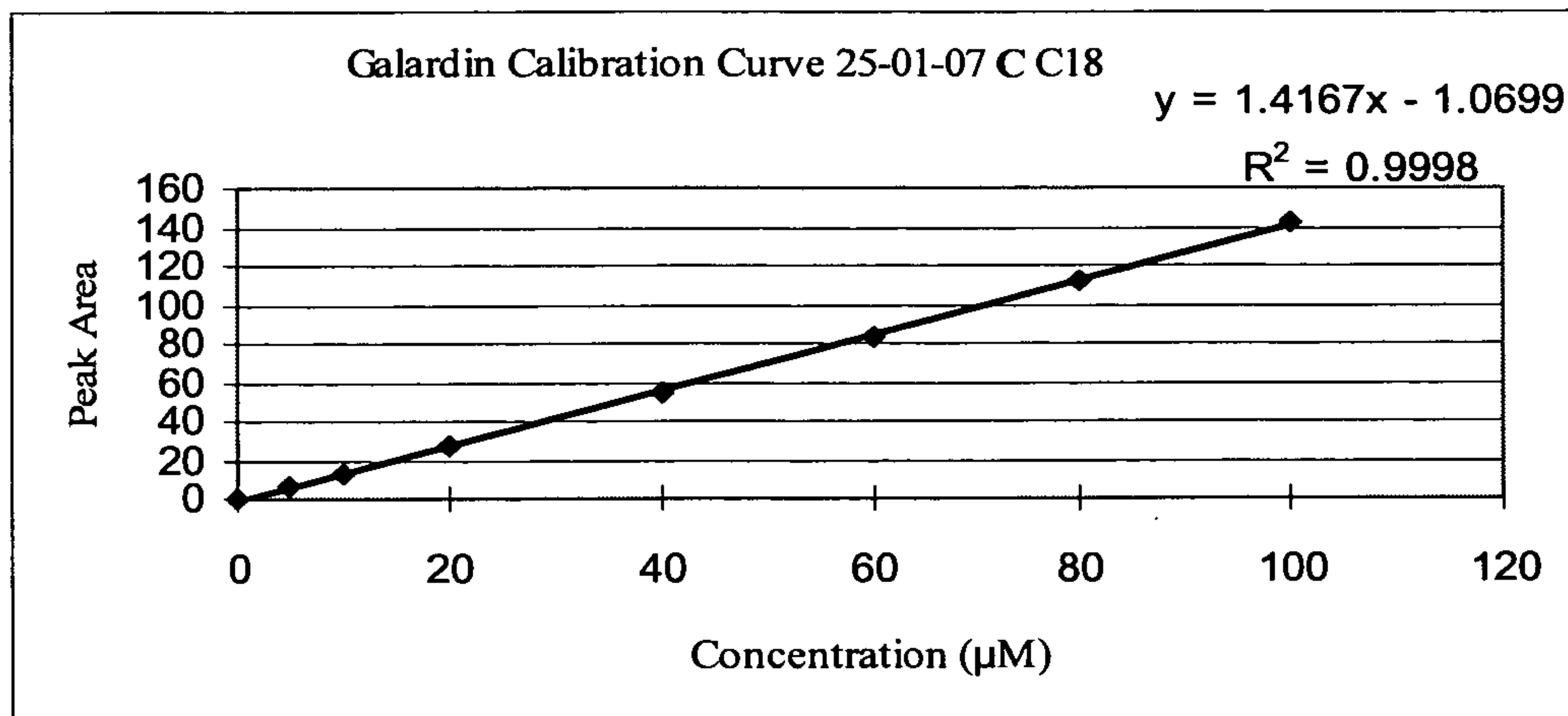


Figure 2

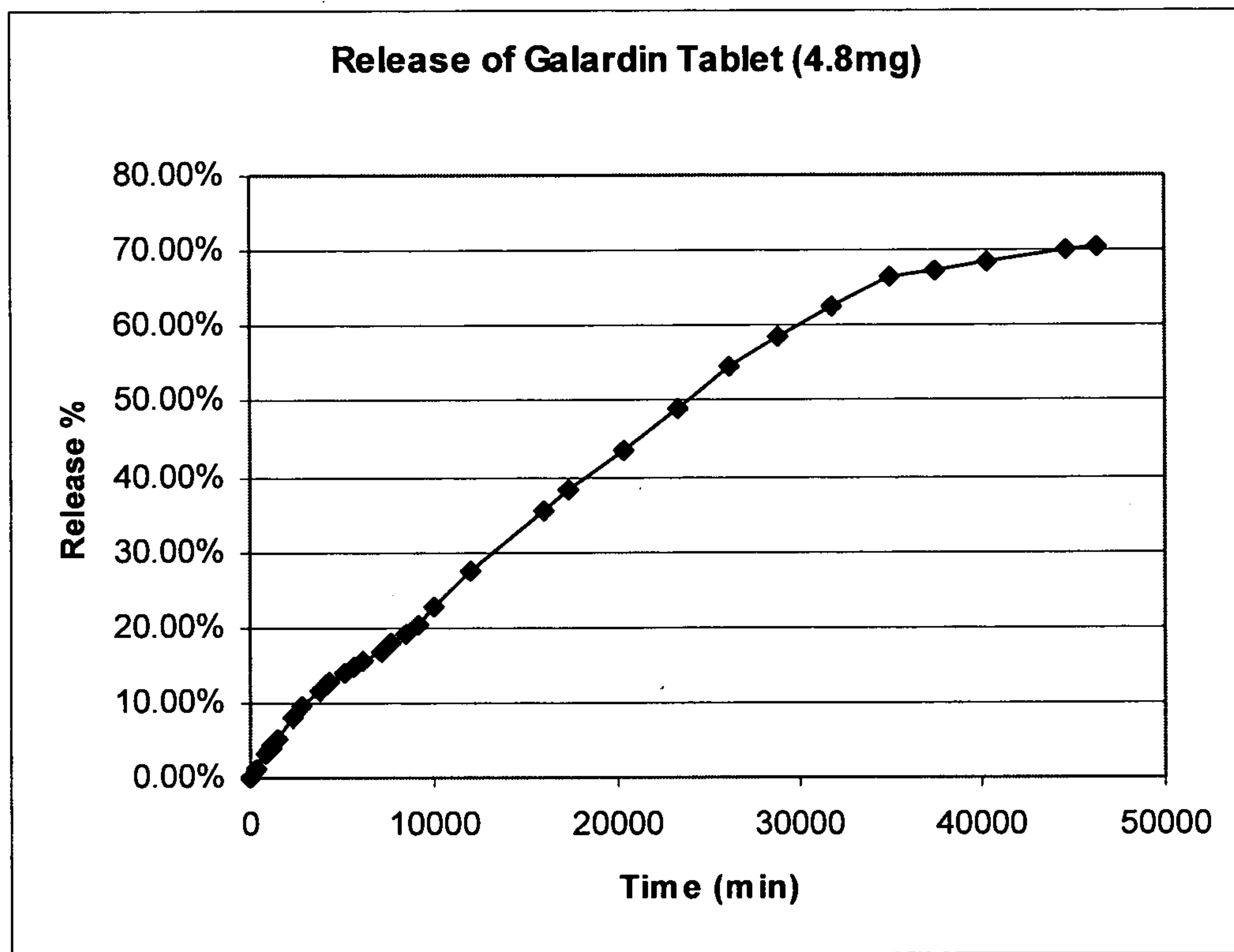


Figure 3

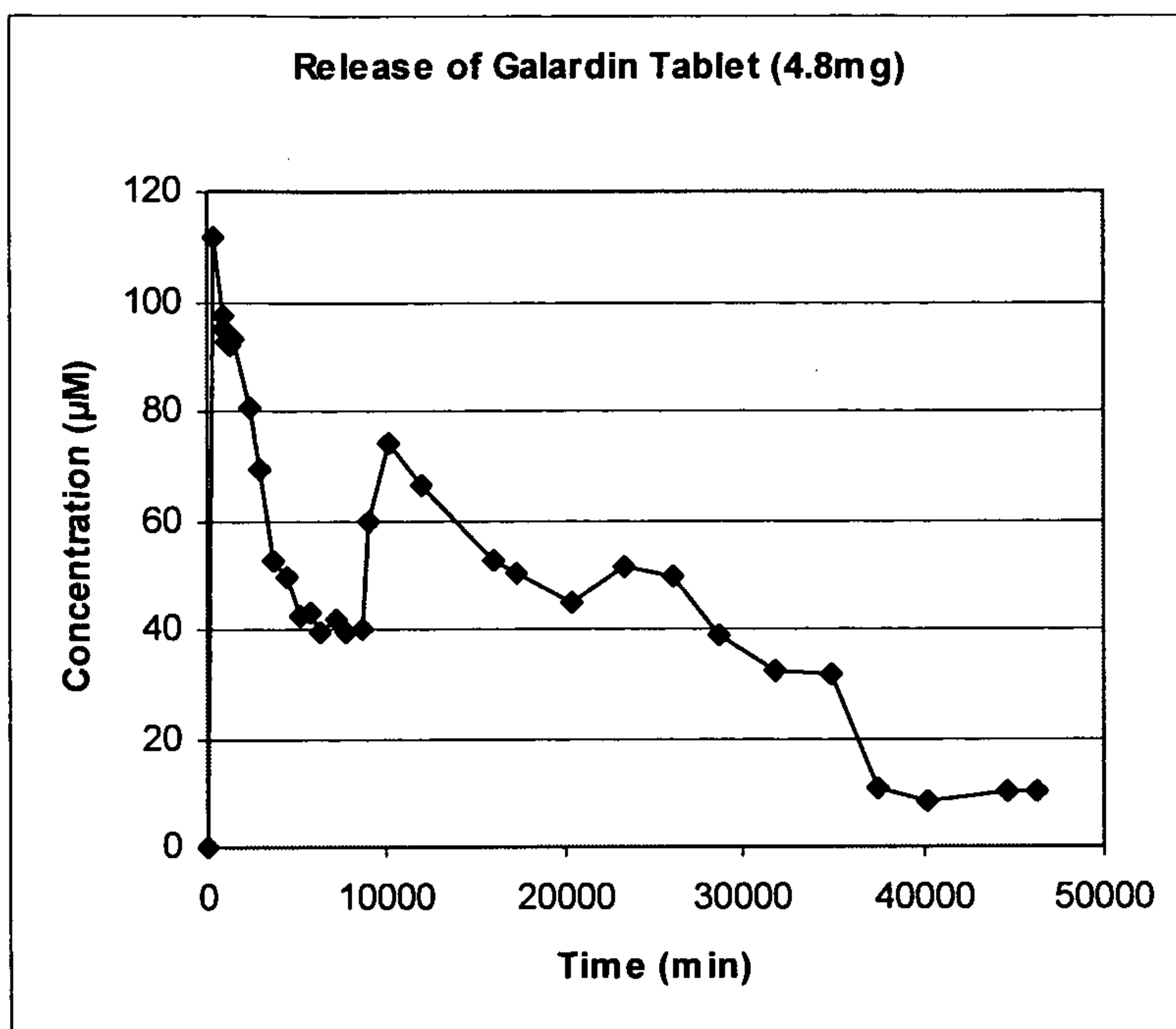


Figure 4

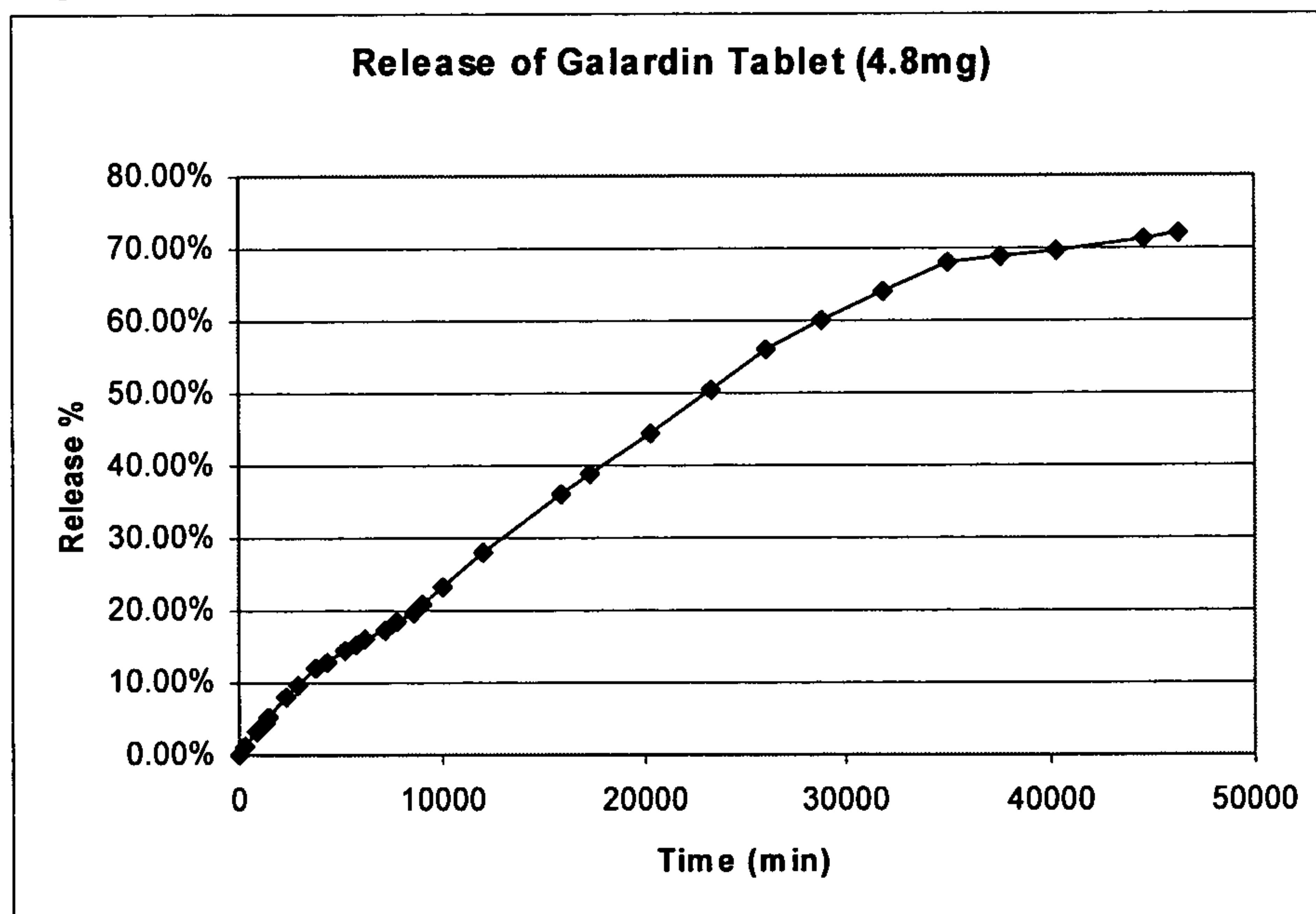


Figure 5

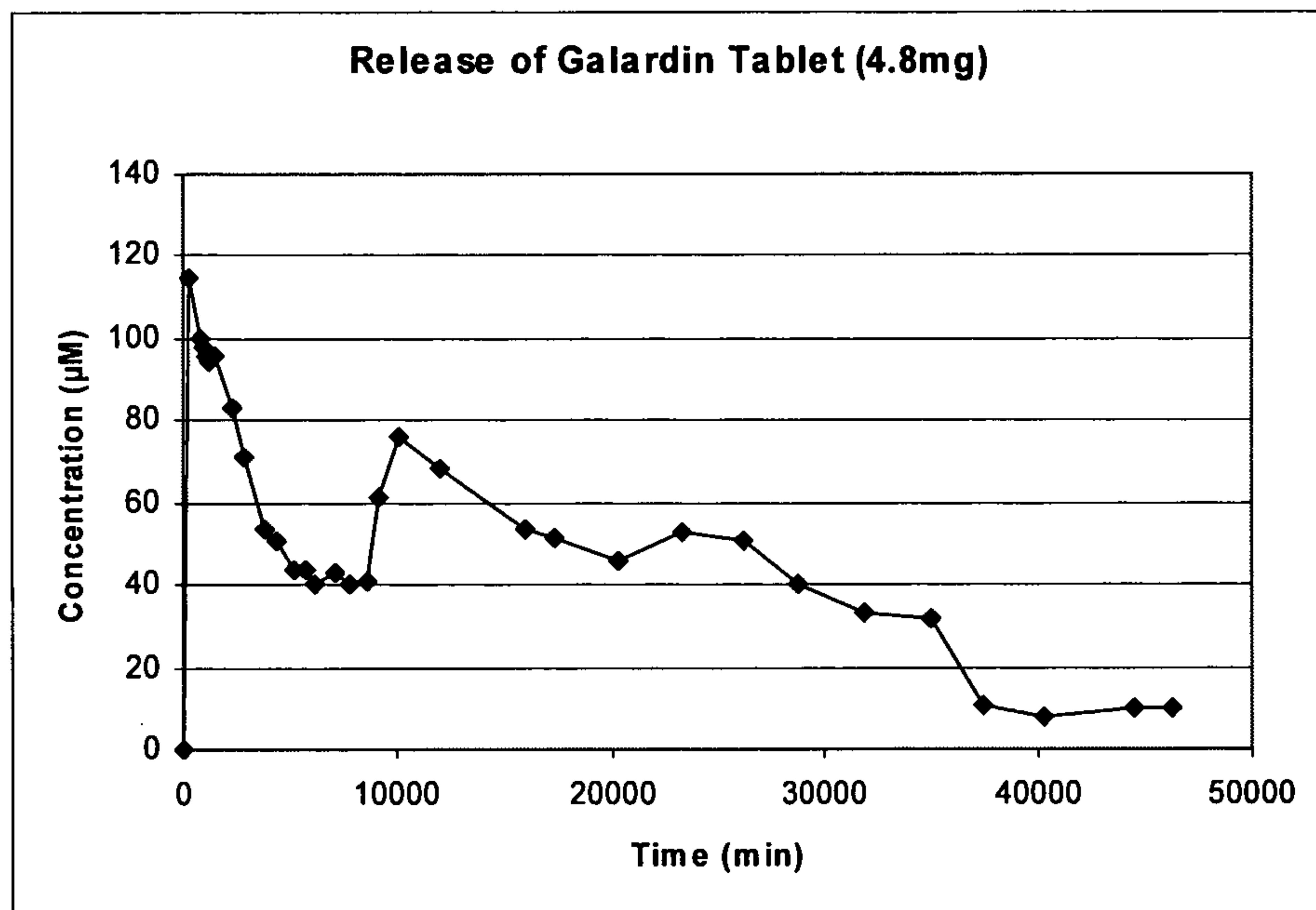


Figure 6

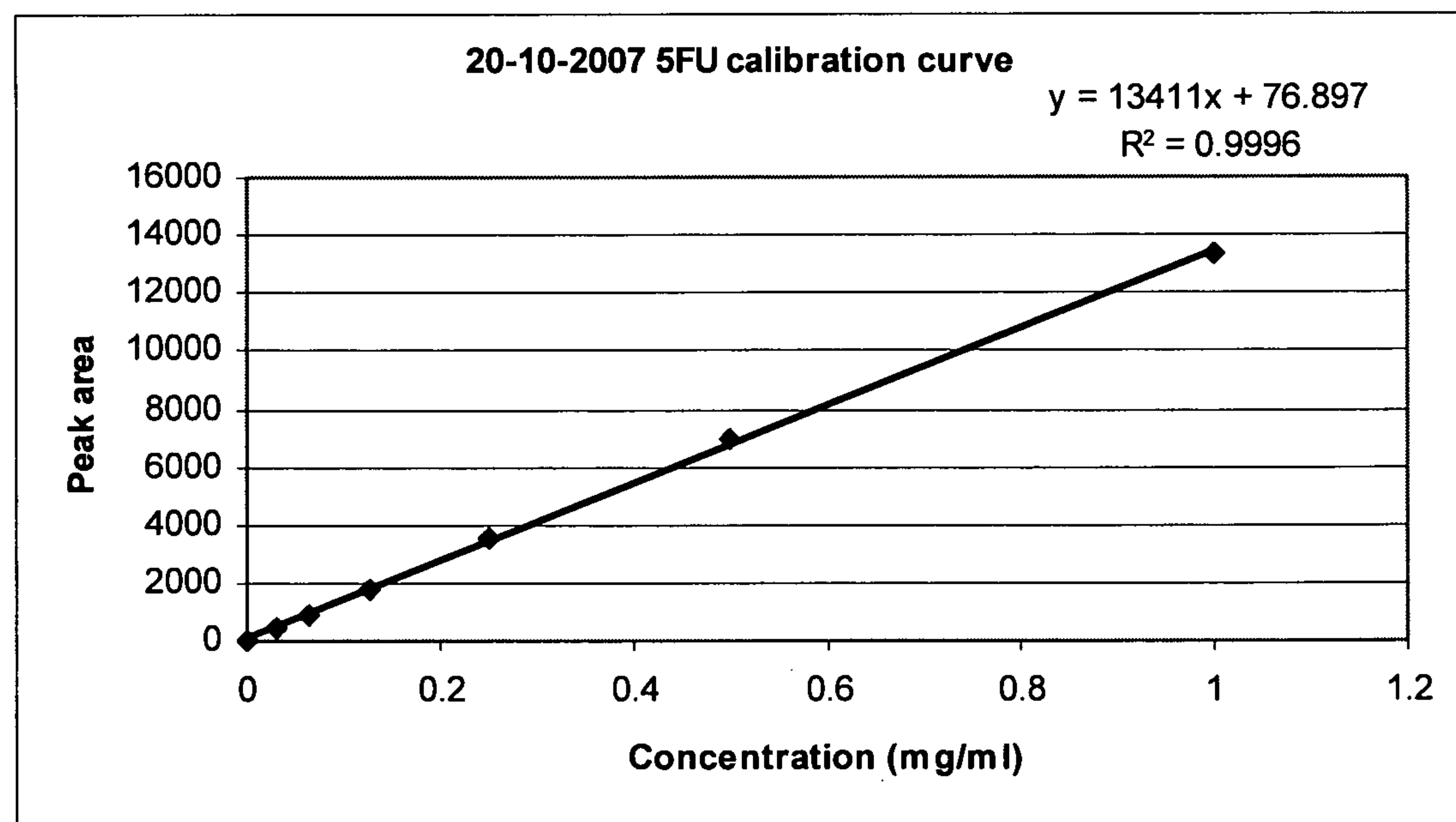


Figure 7

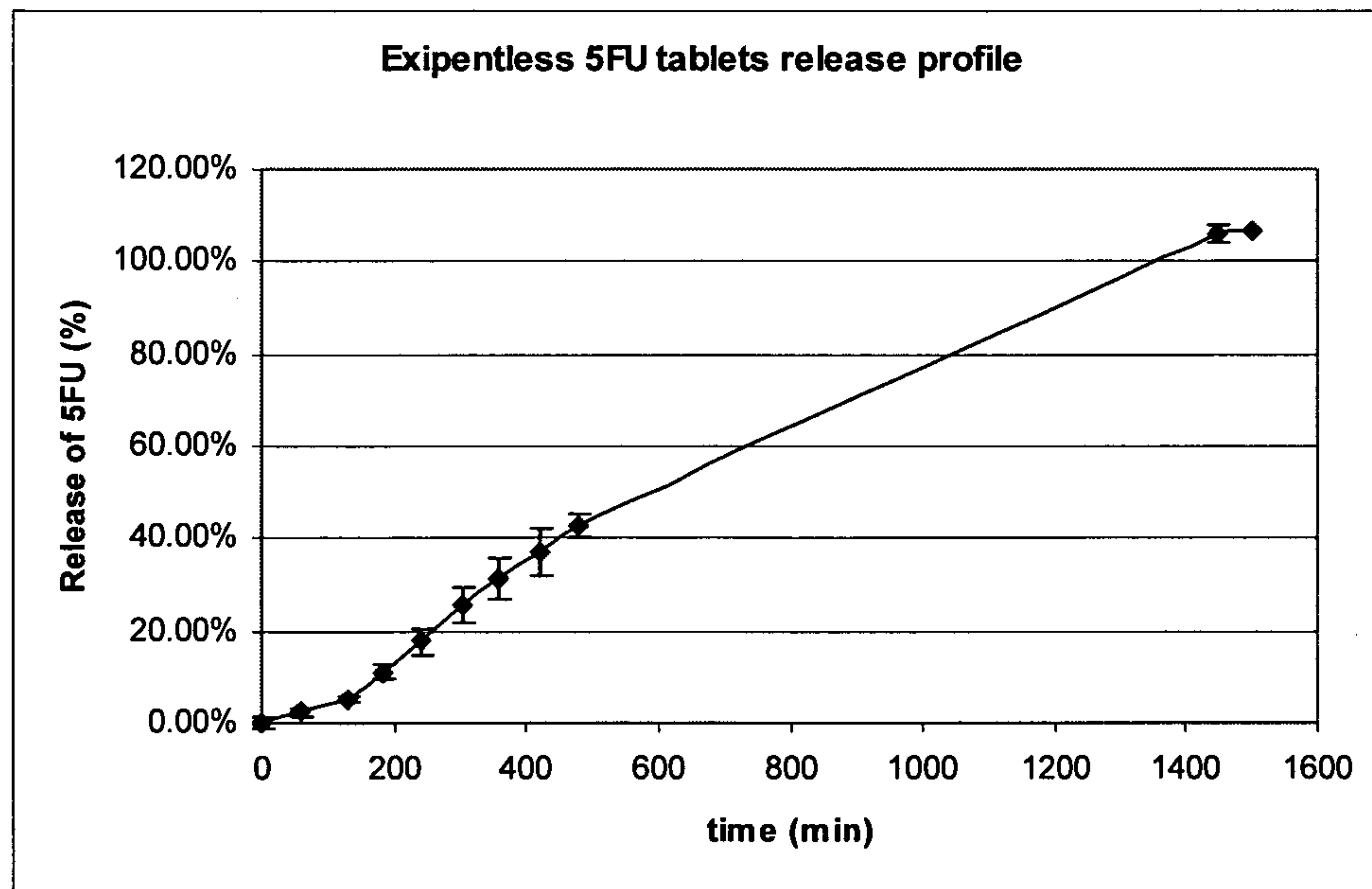


Figure 8

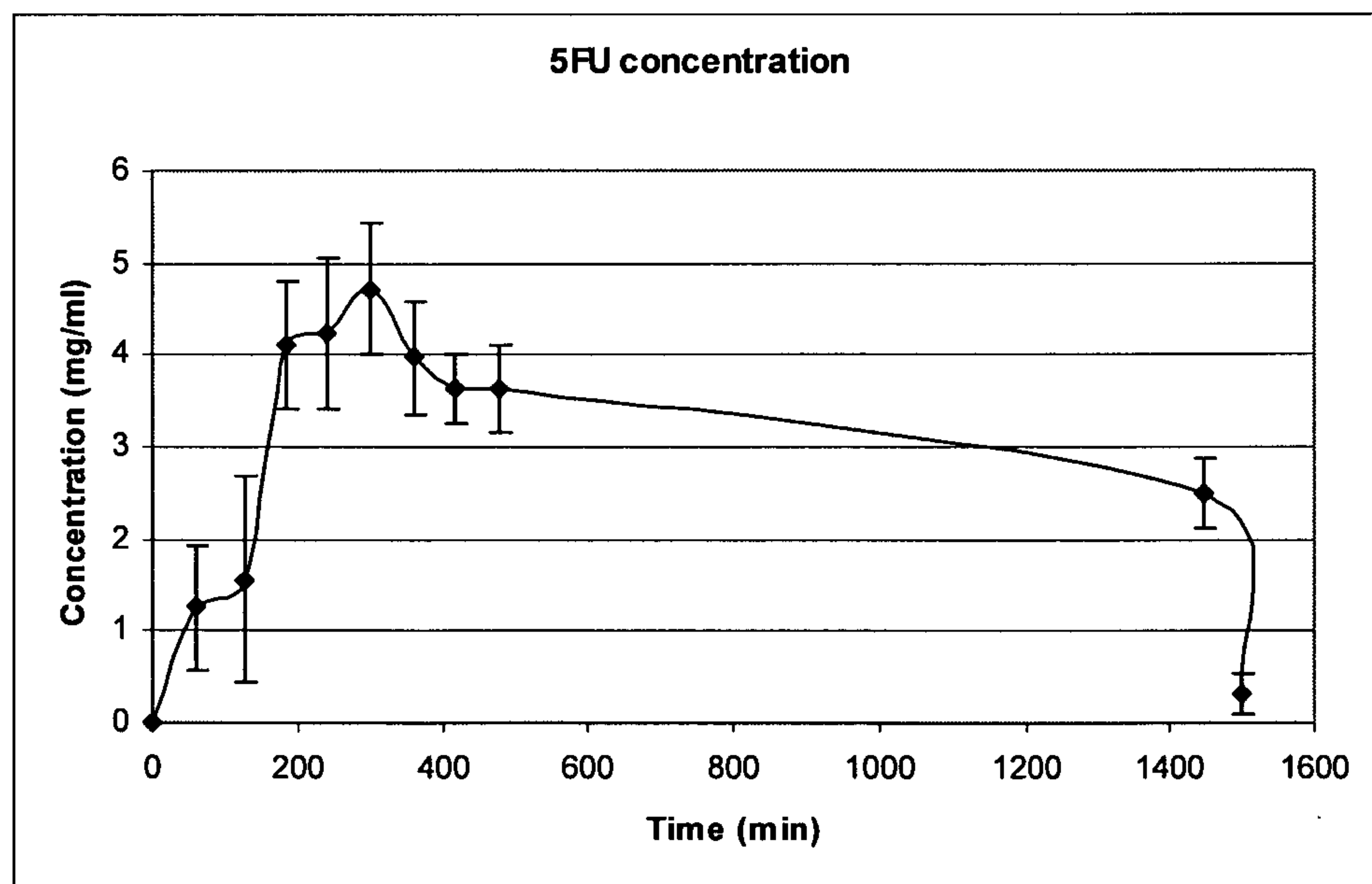
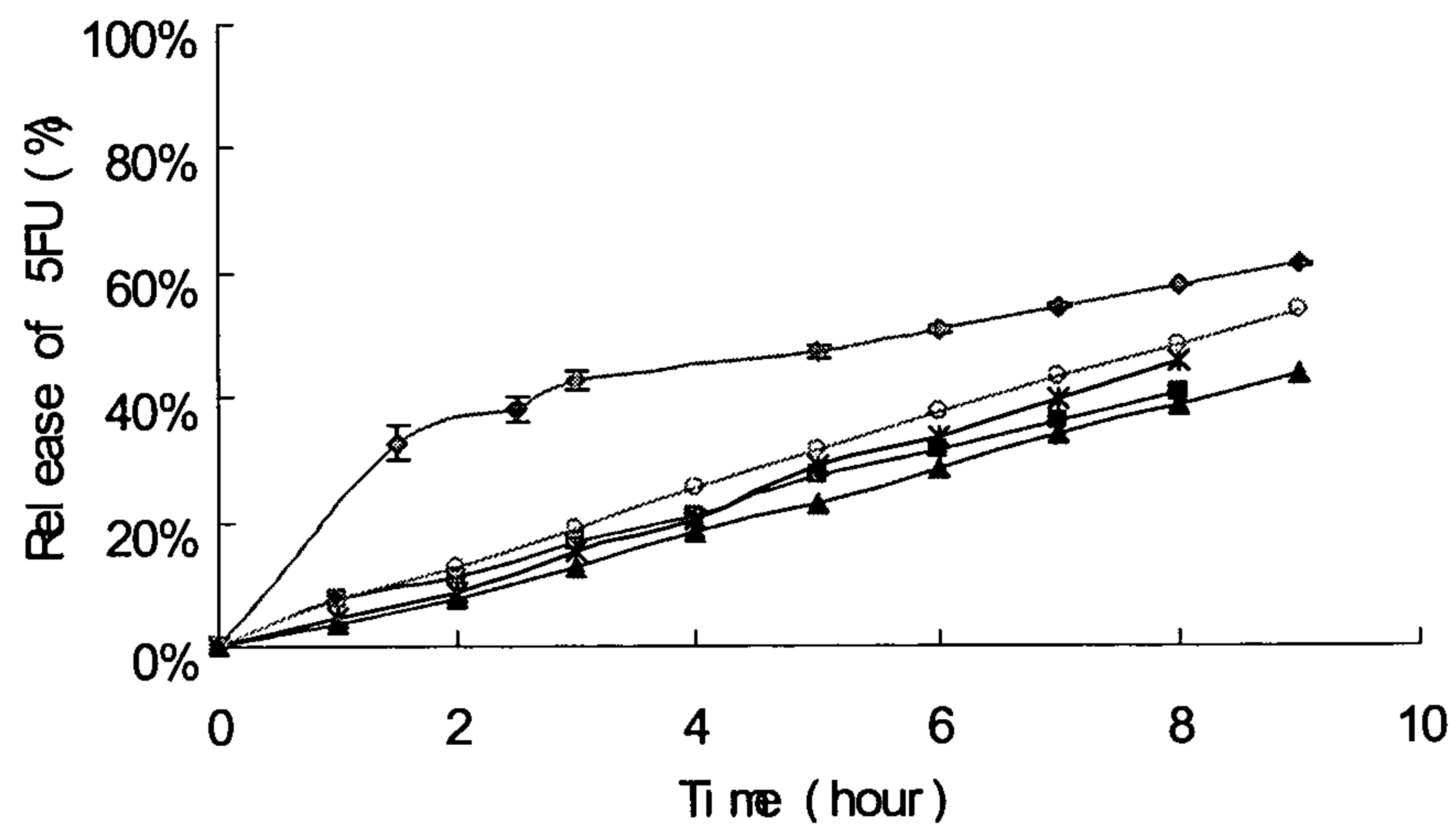


Figure 9

(a)



(b)

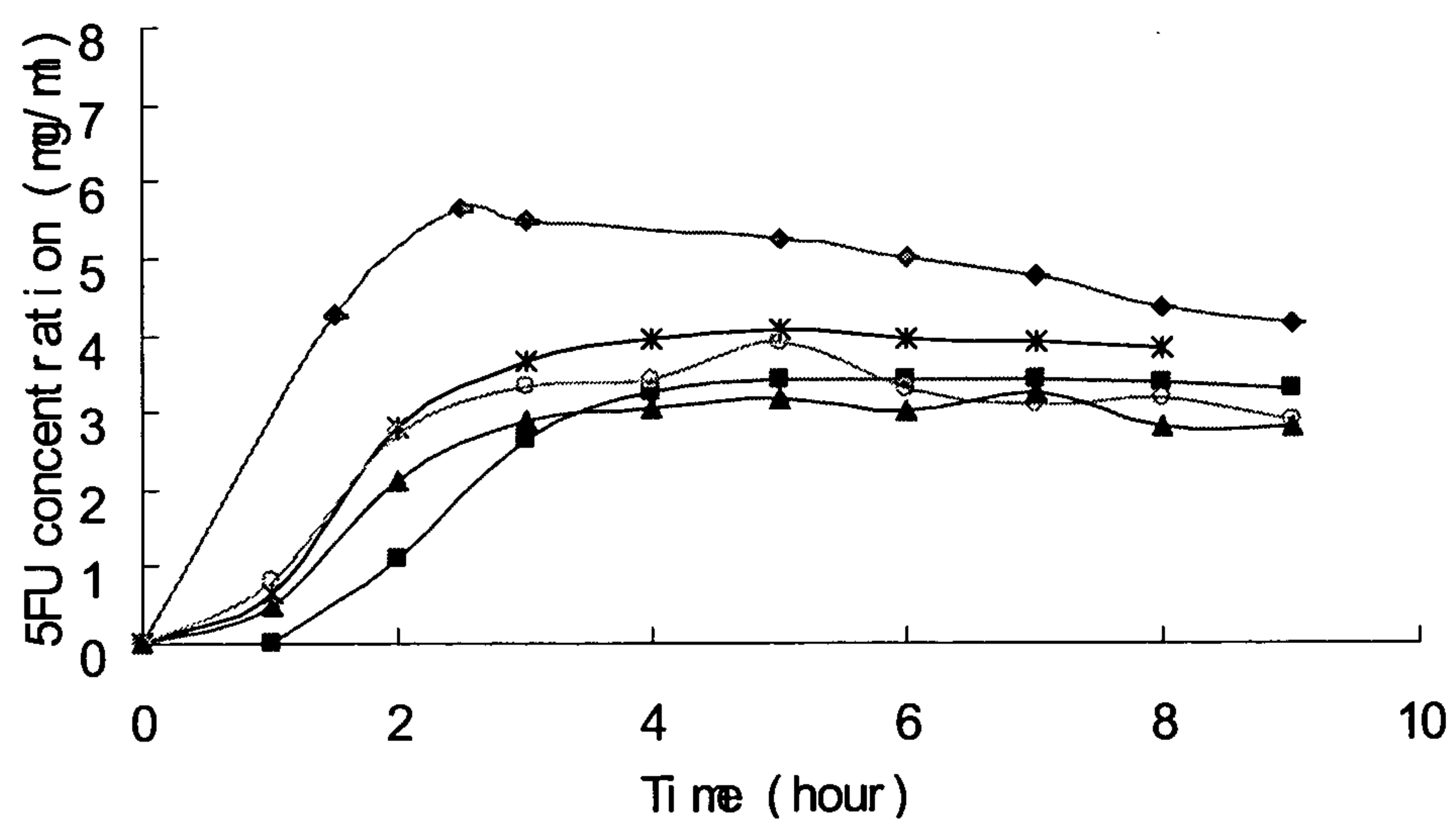
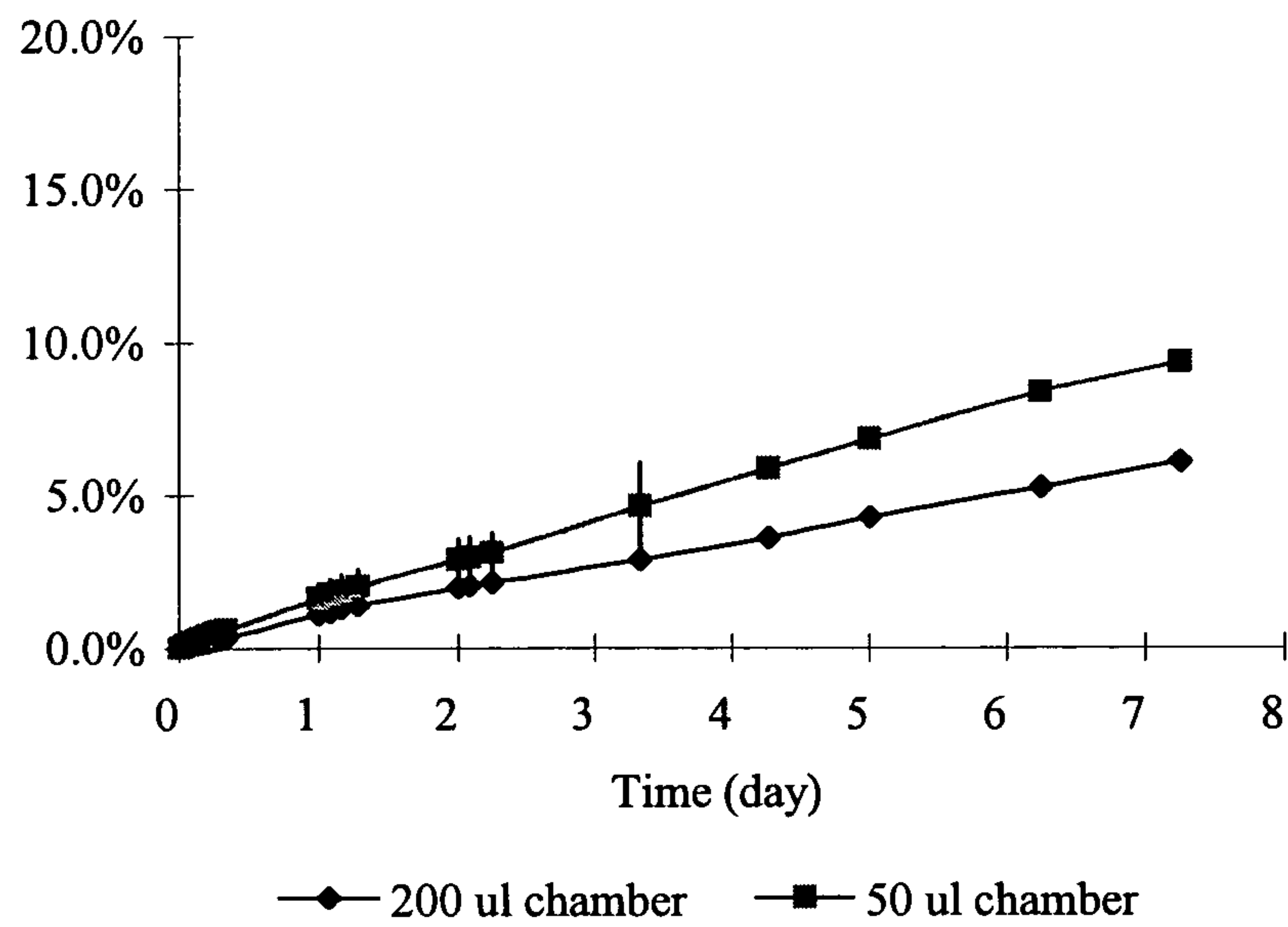


Figure 10

(a)



(b)

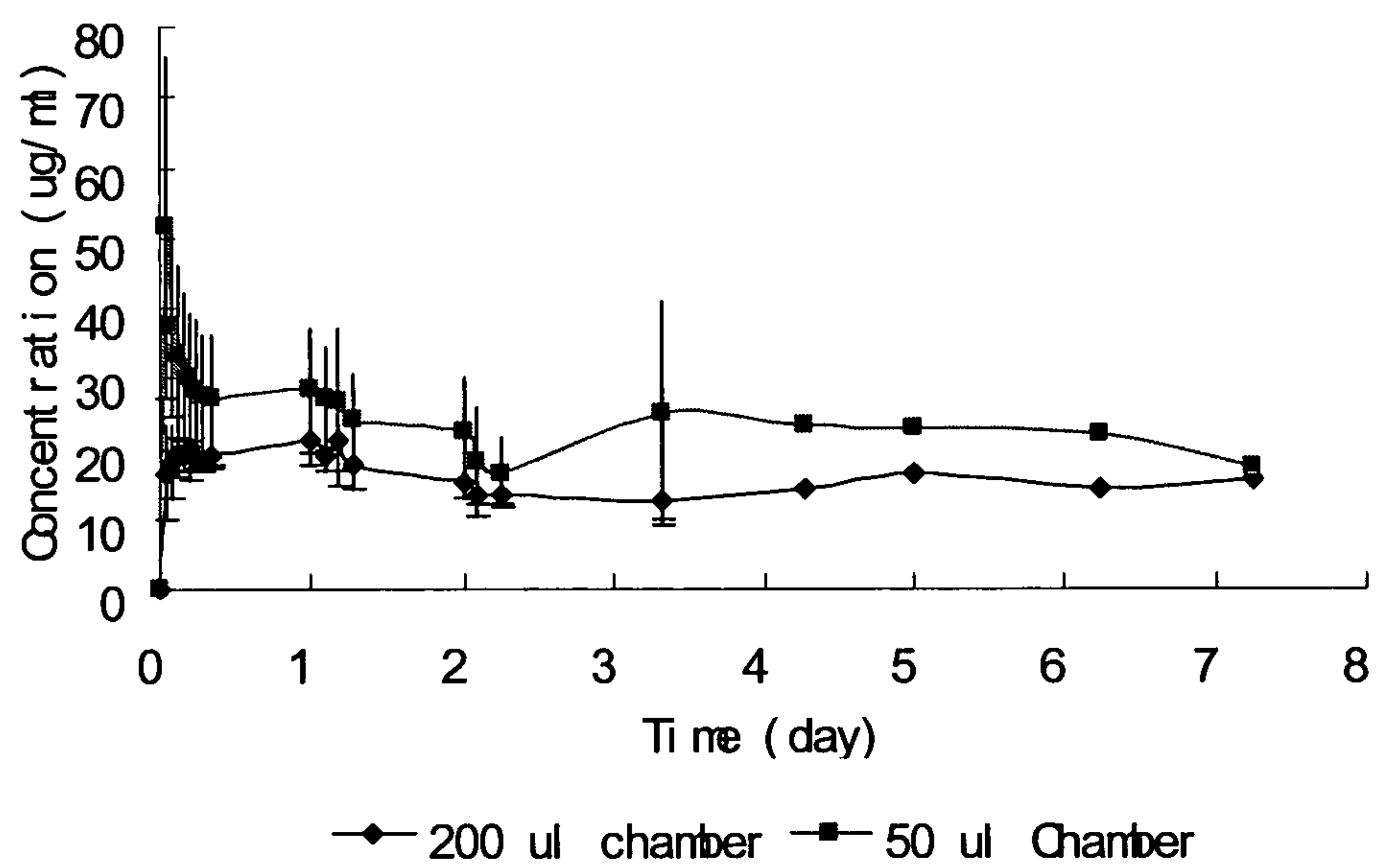
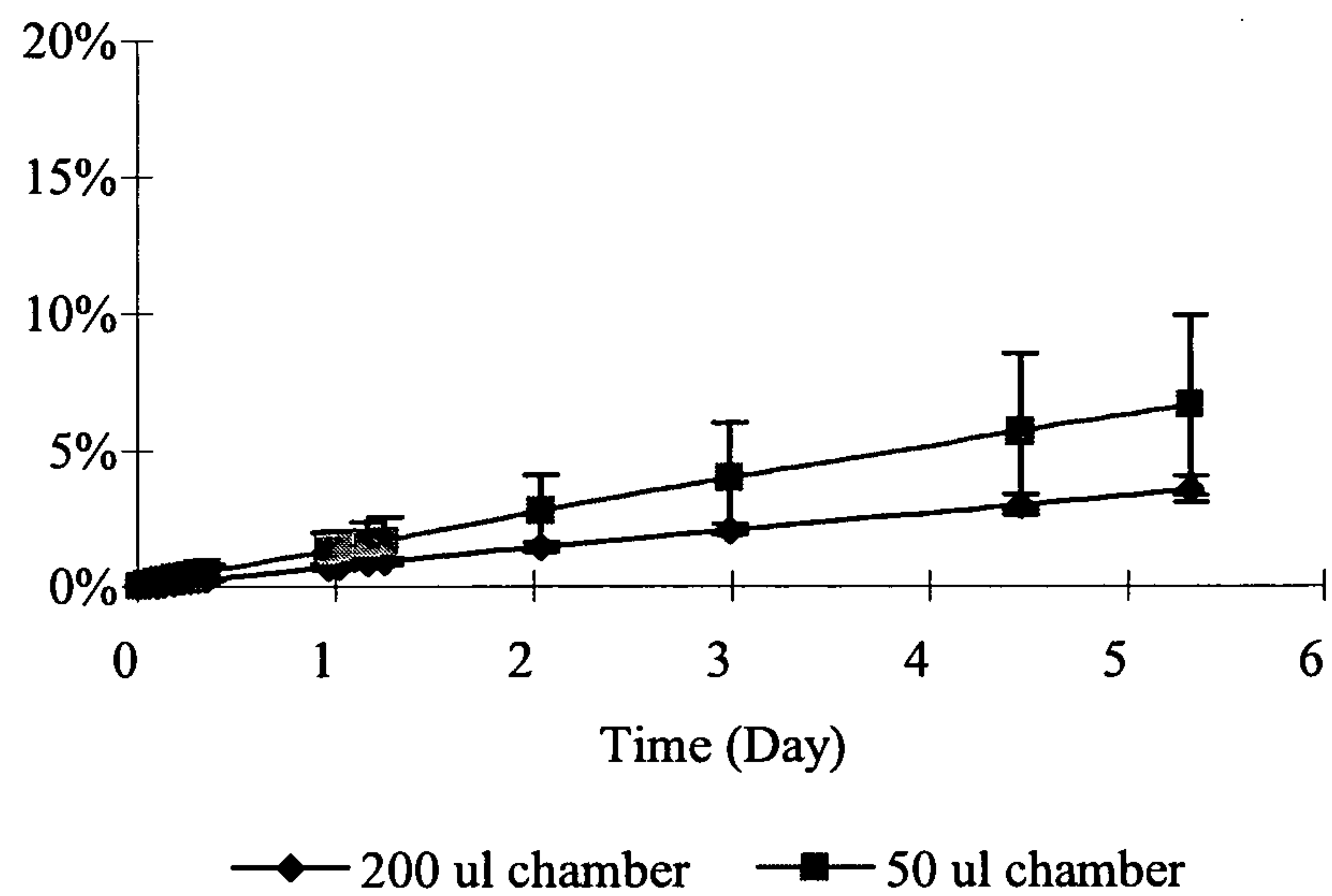


Figure 11

(a)



(b)

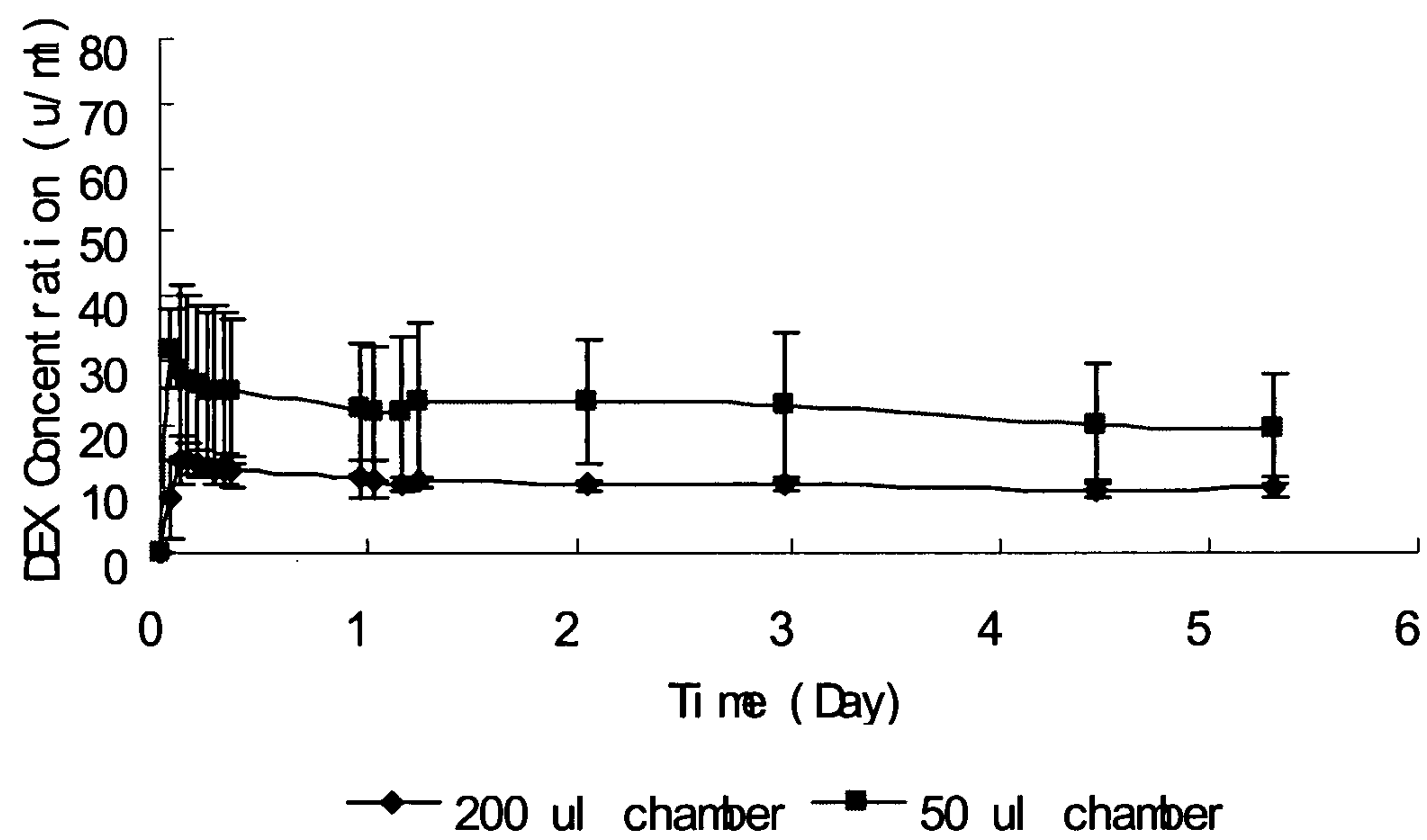
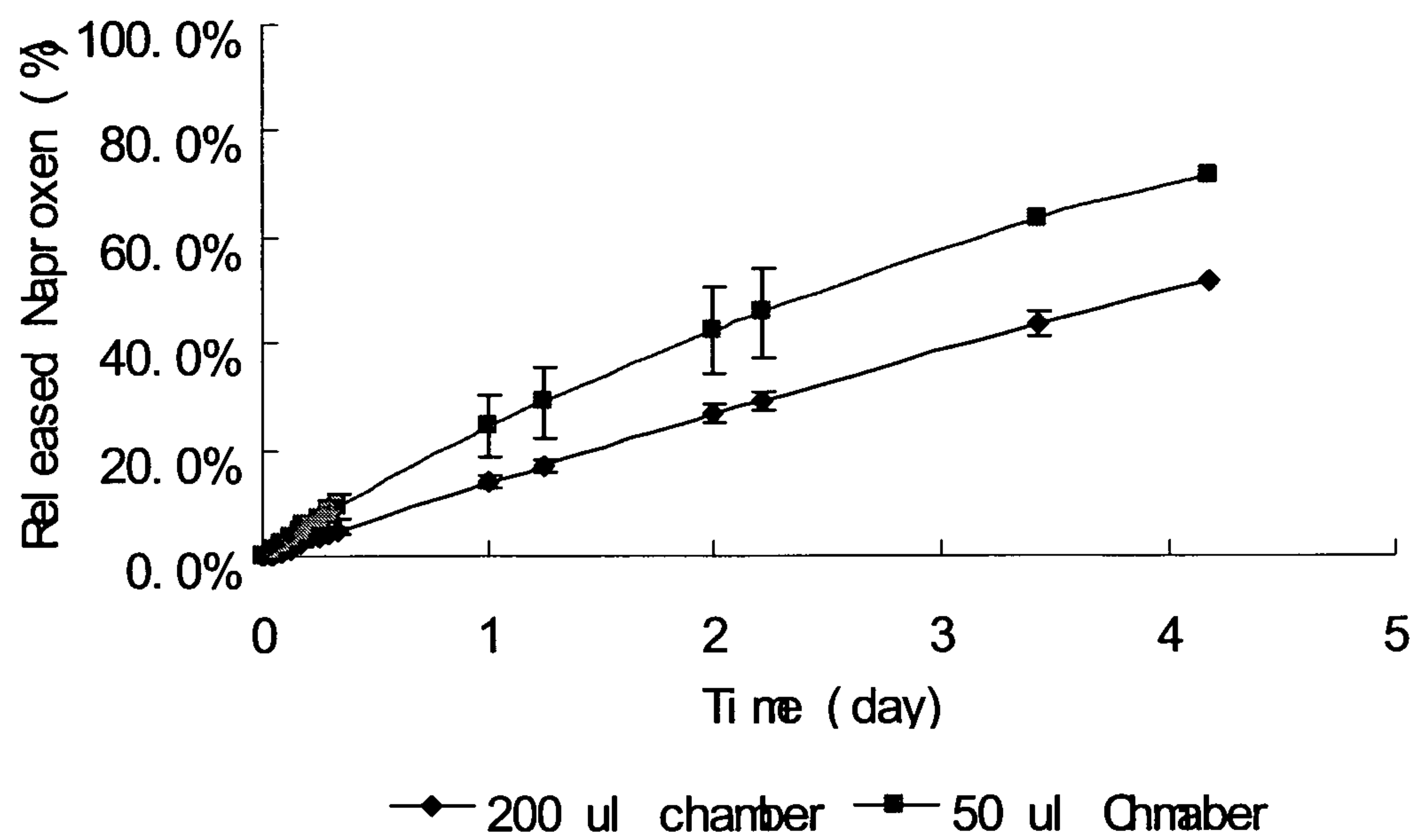


Figure 12

(a)



(b)

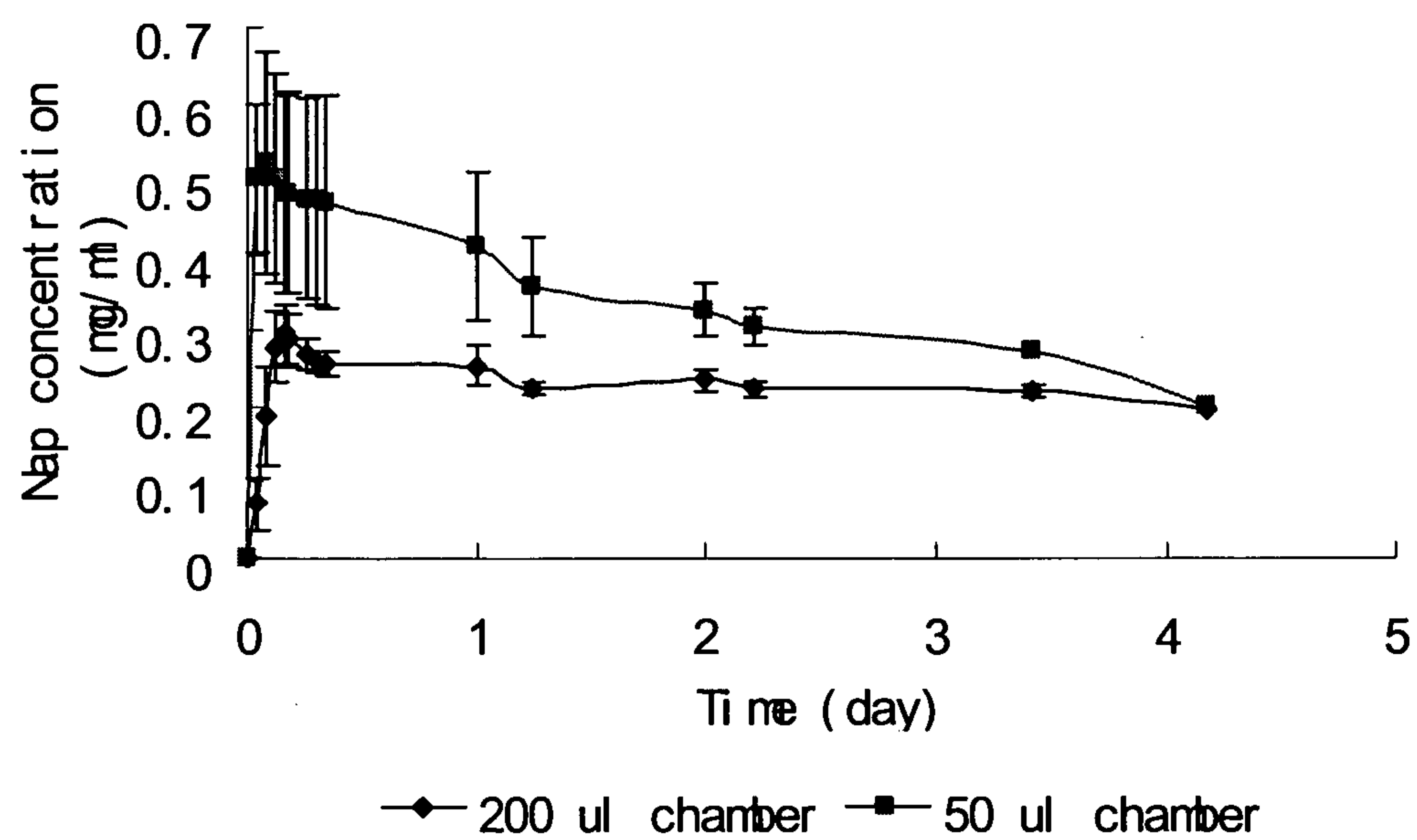
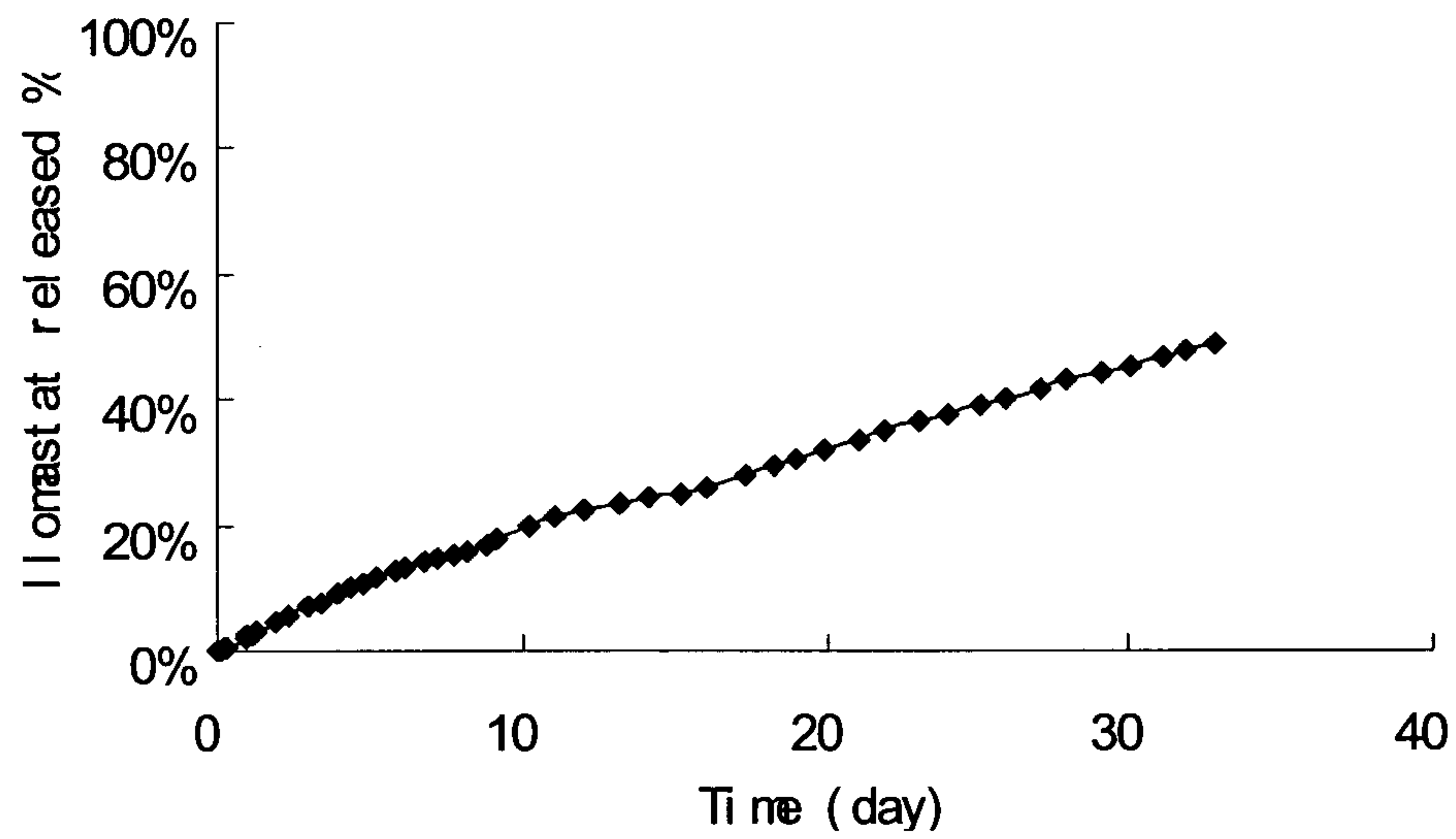


Figure 13

(a)



(b)

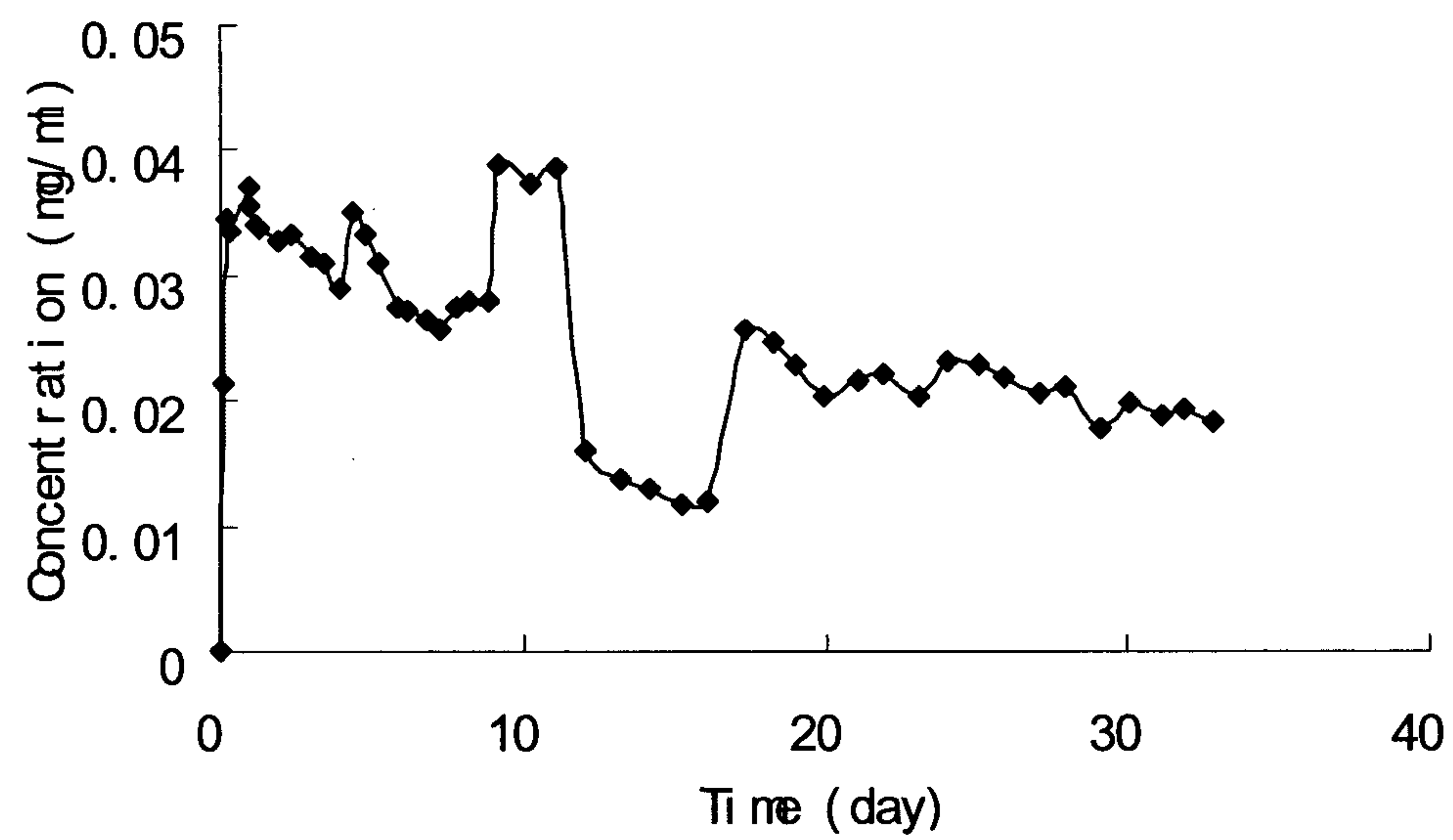


Figure 14

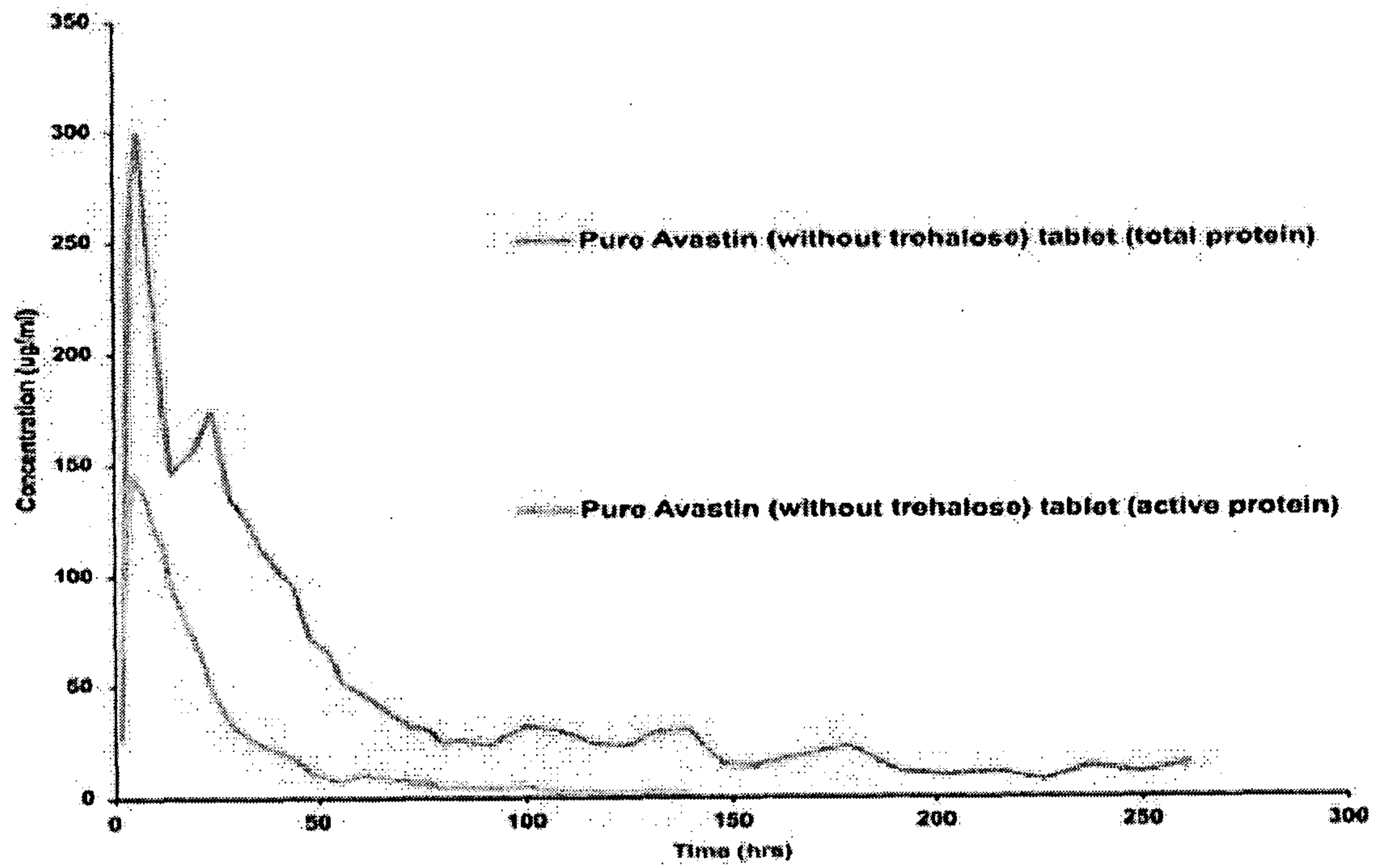


Figure 15

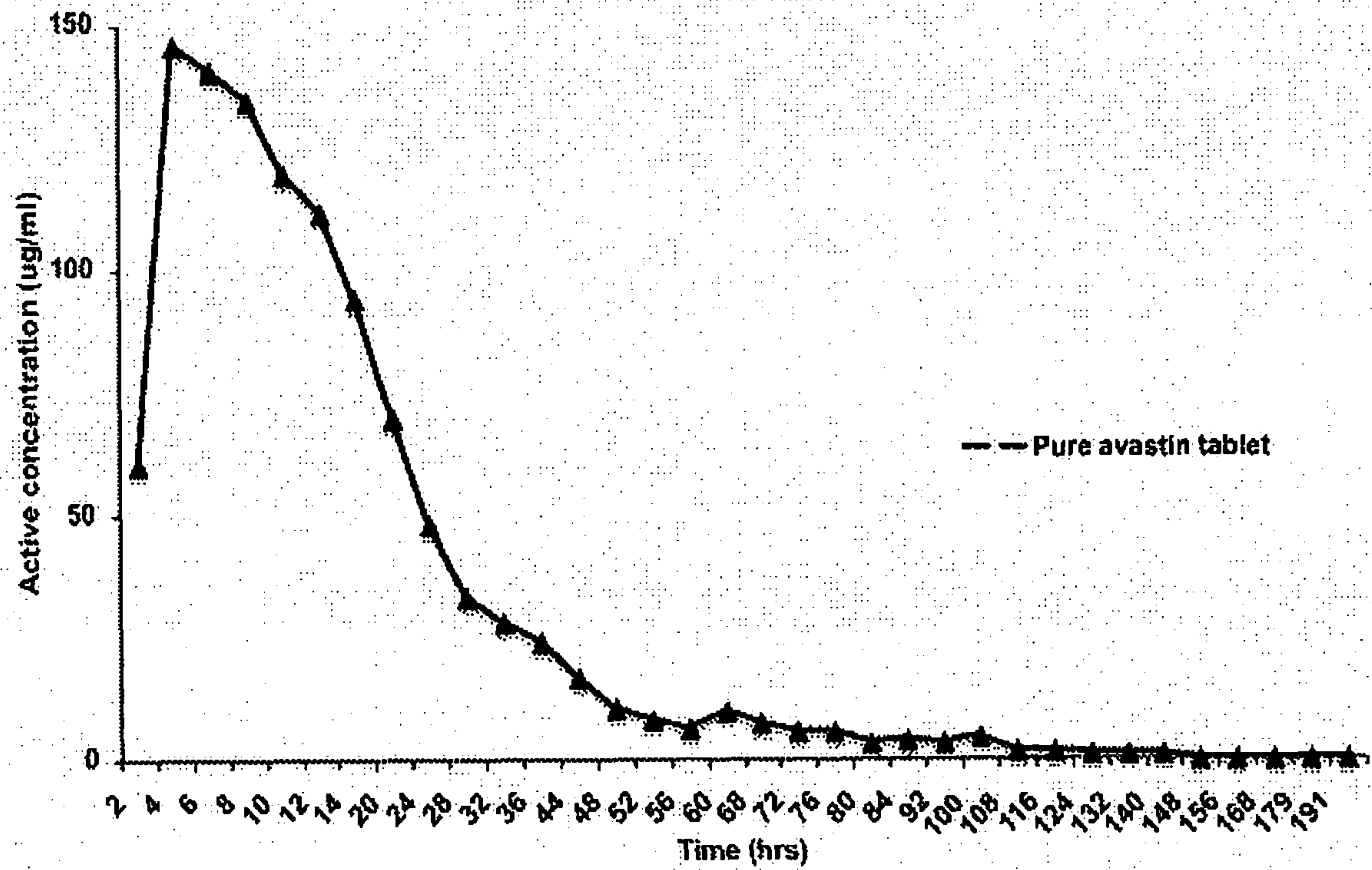


Figure 16

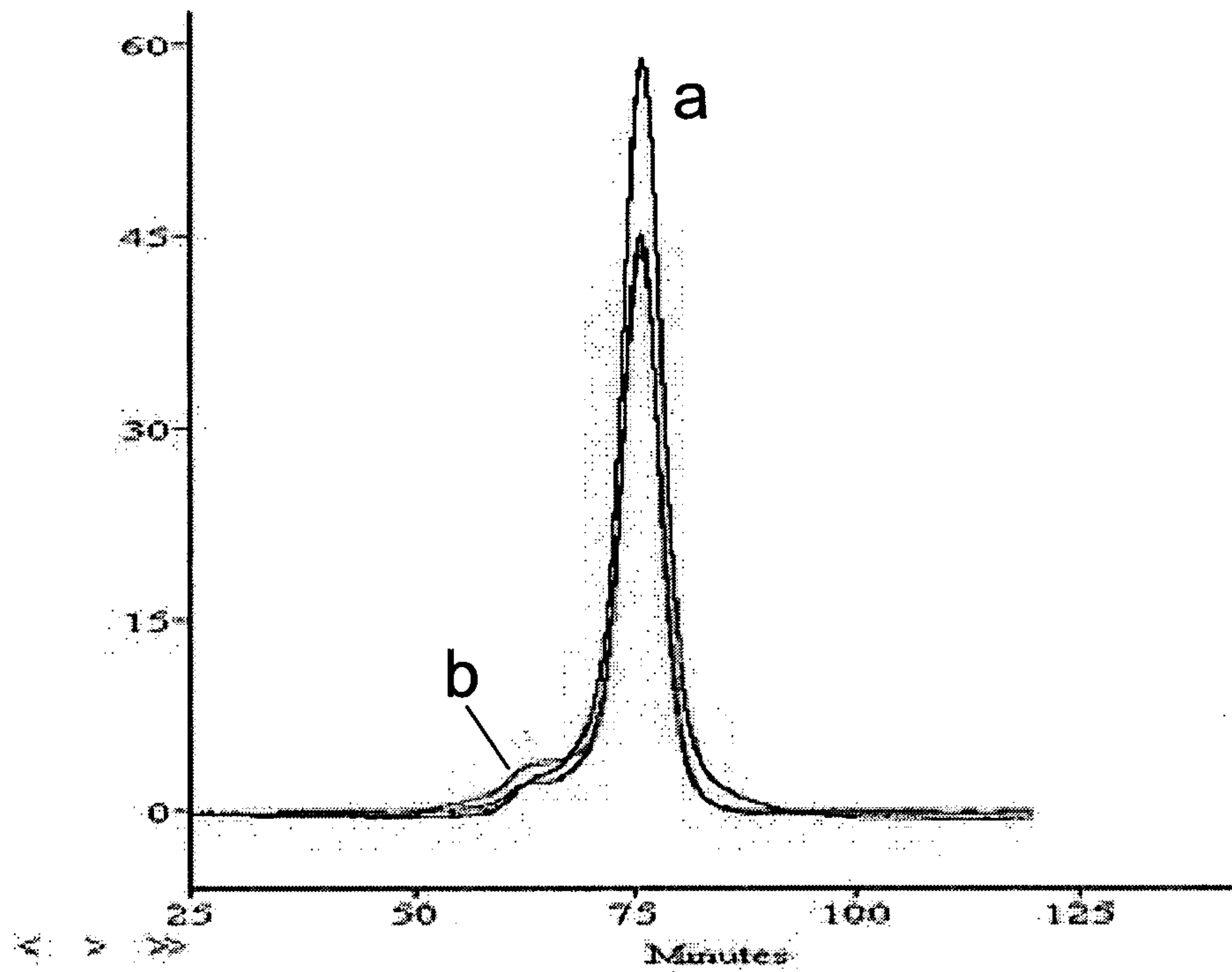


Figure 17

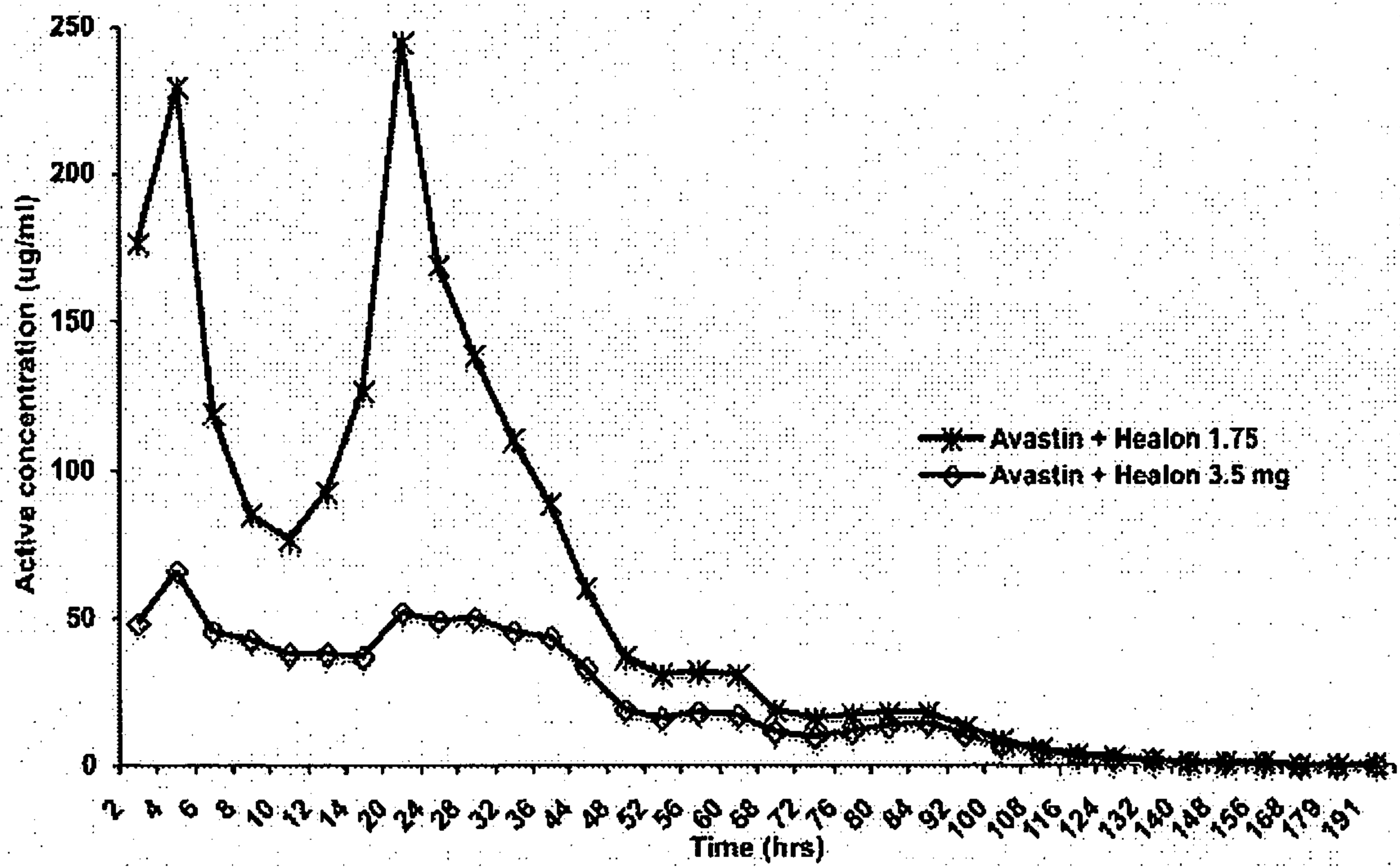
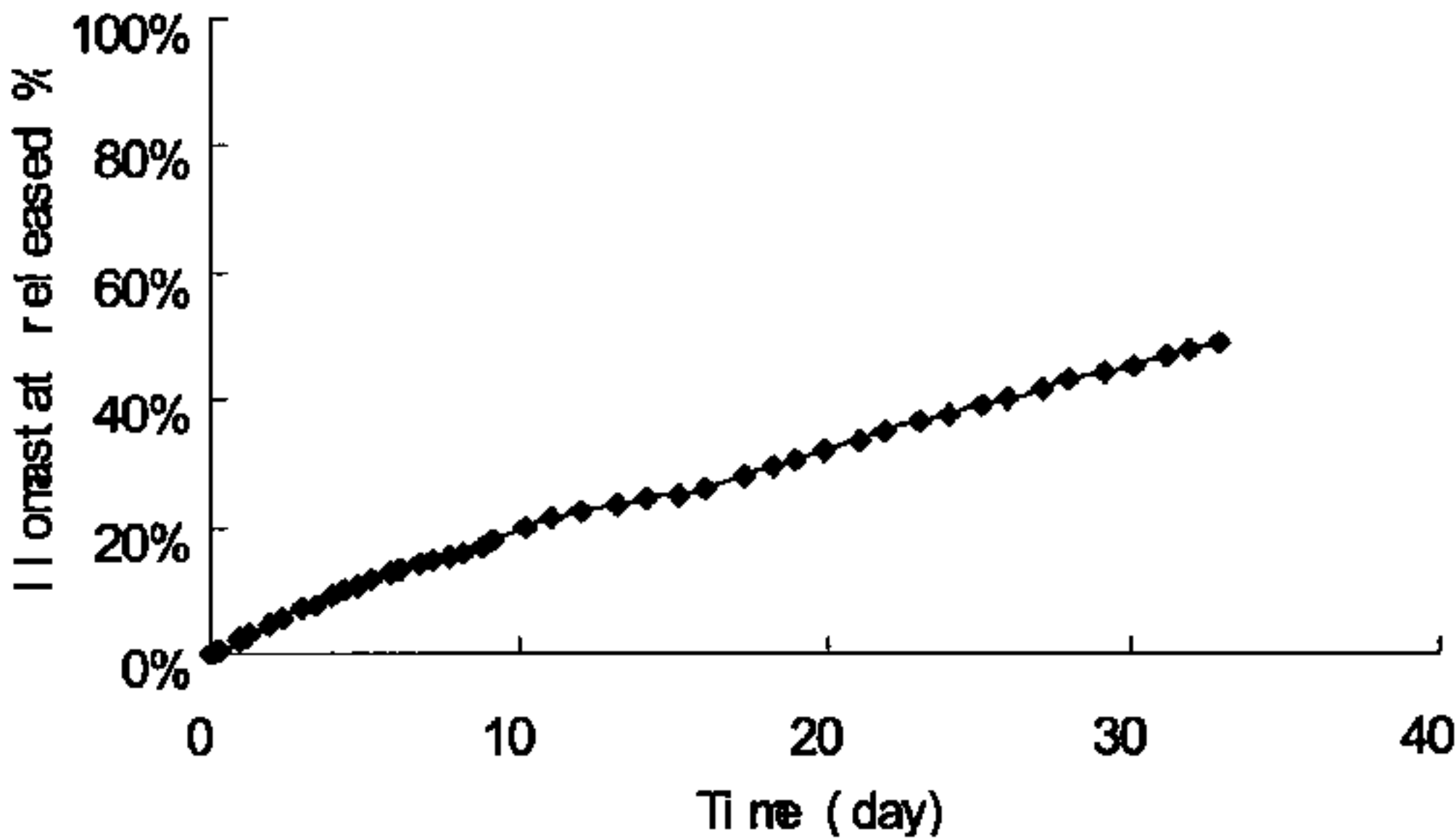


Figure 13

(a)



(b)

