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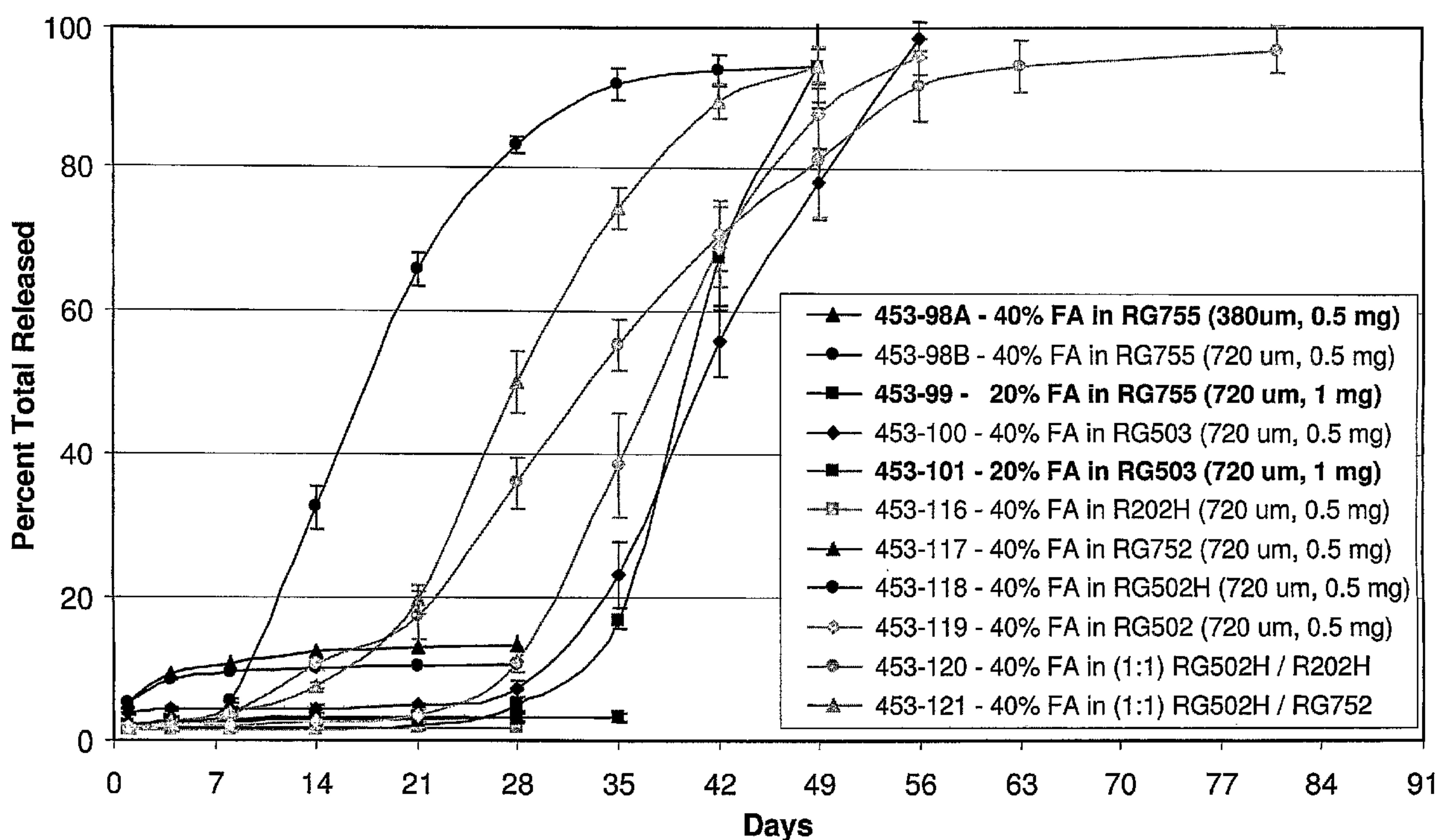
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(54) Title: STEROID INTRAOCULAR IMPLANTS HAVING AN EXTENDED SUSTAINED RELEASE FOR A PERIOD OF GREATER THAN 2 MONTHS



(57) Abrégé/Abstract:

Biocompatible intraocular implants include a steroid and a polymer associated with each other to facilitate release of the steroid into an eye for a period of time greater than about two months. The steroid may be associated with a biodegradable polymer matrix, such as a matrix of a two biodegradable polymers. Or, the steroid may be associated with a polymeric coating having one or more openings effective to permit the steroid to be released into an external environment. The implants may be placed in an eye to treat one or more ocular conditions. The steroid is released from the implant for more than about two months, and may be released for more than several years.

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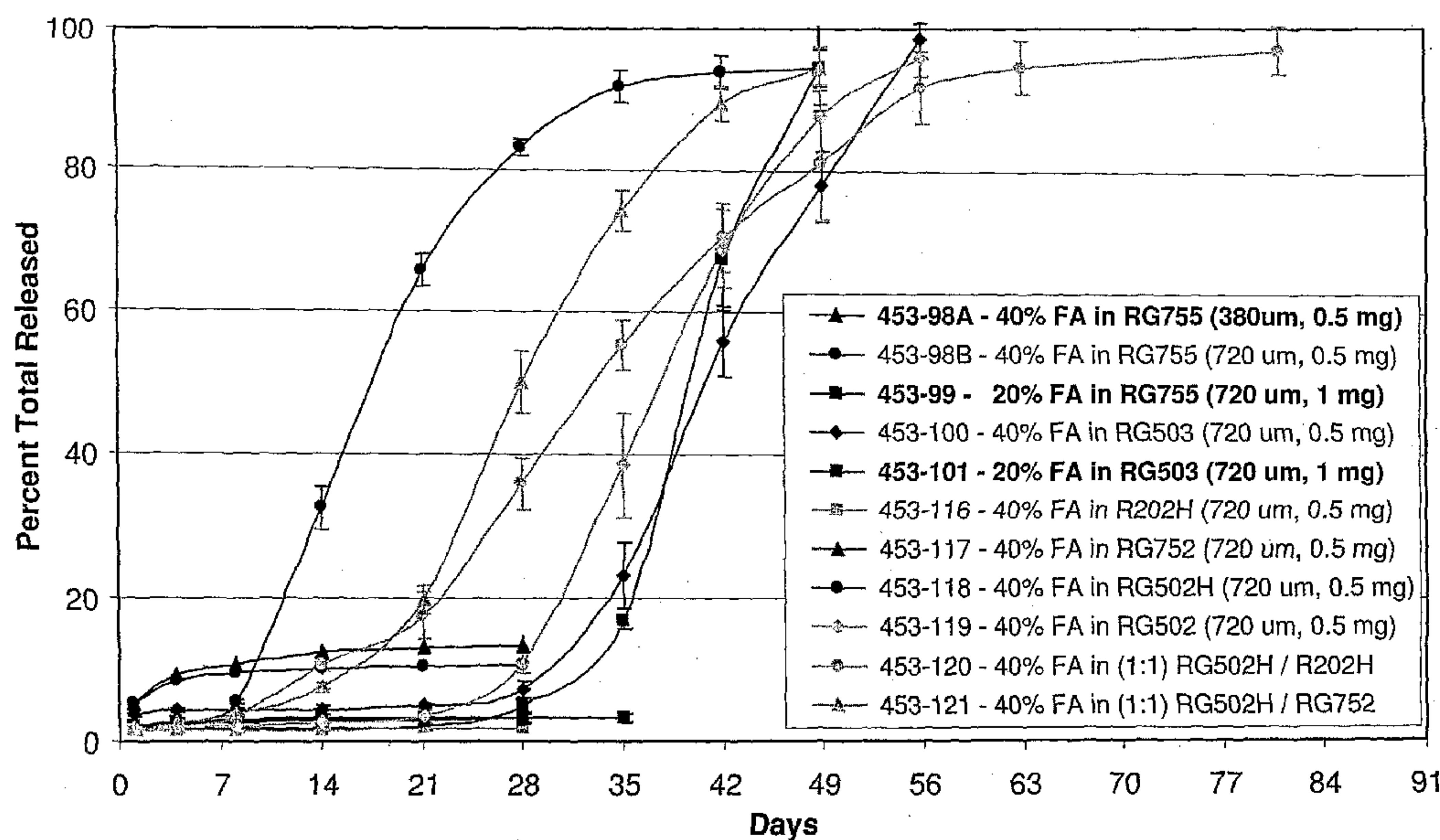
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(57) Abstract: Biocompatible intraocular implants include a steroid and a polymer associated with each other to facilitate release of the steroid into an eye for a period of time greater than about two months. The steroid may be associated with a biodegradable polymer matrix, such as a matrix of a two biodegradable polymers. Or, the steroid may be associated with a polymeric coating having one or more openings effective to permit the steroid to be released into an external environment. The implants may be placed in an eye to treat one or more ocular conditions. The steroid is released from the implant for more than about two months, and may be released for more than several years.

WO 2005/107727 A1

WO 2005/107727 A1



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WO 2005/107727

PCT/US2005/015113

STEROID INTRAOCULAR IMPLANTS HAVING AN EXTENDED SUSTAINED RELEASE FOR A PERIOD
OF GREATER THAN 2 MONTHS

by

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BACKGROUND

The present invention generally relates to devices and methods to treat an eye of a patient, and more specifically to intraocular implants that provide extended release of a therapeutic agent to an eye in which the implant is placed.

Steroids, such as the corticosteroid, fluocinolone acetonide (1,4-pregnadien-6 α , 9 α -difluoro-11 β , 16 α , 17, 21-tetrol-3, 20-dione 16, 17-acetonide), are usually given topically, systemically, or periocularly, as an injection, to treat uveitis. All three methods of delivery have drawbacks, e.g., topical corticosteroids do not treat diseases in the back of the eye, systemic corticosteroids are often associated with many unwanted side effects, and periocular injections may sometimes cause globe perforation, periocular fibrosis and ptosis.

An alternative that may circumvent the drawbacks of the above-mentioned delivery methods is to use sustained-released drug delivery systems. In 2000, Jaffe et al. reported using compressed pure fluocinolone acetonide pellets coated with

WO 2005/107727

PCT/US2005/015113

Docket D3141-CIP
17698 CIP (OCU)

silicone and polyvinyl alcohol as a fluocinolone sustained delivery device (Jaffe, G.J. et al., *Journal of Ophthalmology and Vision Surgery*, Vol 41, No. 11, October 2000). They obtained release rates of $1.9 \pm 0.25 \mu\text{g/day}$ (6 months) and $2.2 \pm 0.6 \mu\text{g/day}$ (45 days) for the 2-mg device and 15-mg device, respectively. The duration of 5 release for the 2-mg and 15-mg device was estimated to be 2.7 and 18.6 years, respectively. U.S. Patent Nos. 6,217,895 and 6,548,078 disclose sustained release implants for delivering a corticosteroid, such as fluocinolone acetonide, to an eye. However, fluocinolone acetonide intravitreal implants made by Control Delivery 10 Systems (the assignee of U.S. Patent Nos. 6,217,895 and 6,548,078) were only partially successful and led to the development of cataracts and increased 15 intraocular pressure.

In addition, intravitreal injection of triamcinolone acetonide (KENALOG®) for 15 treatments of non-infectious uveitis, and macular edema due to various retinal diseases has appeared to be safe and effective.

Additional biocompatible implants for placement in the eye have been disclosed in a number of patents, such as U.S. Pat. Nos. 4,521,210; 4,853,224; 4,997,652; 5,164,188; 5,443,505; 5,501,856; 5,766,242; 5,824,072; 5,869,079; 20 6,074,661; 6,331,313; 6,369,116; 6,699,493, and 6,726,918.

Other intravitreal therapeutic approaches are described in U.S. Publication 2005-0101582, filed October 14, 2004; and U.S. Publication 2005-0181017, filed January 19, 2005.

25

It would be advantageous to provide eye implantable drug delivery systems, such as intraocular implants, and methods of using such systems, that are capable of releasing a therapeutic agent at a sustained or controlled rate for extended periods of time and in amounts with few or no negative side effects.

30

SUMMARY

The present invention provides new drug delivery systems, and methods of using such systems, for extended or sustained drug release into an eye, for example, to achieve one or more desired therapeutic effects. The drug delivery systems are in the form of implants or implant elements that may be placed in an eye. The present systems and methods advantageously provide for extended release times of one or more therapeutic agents. Thus, the patient in whose eye the implant has been placed receives a therapeutic amount of an agent for a long or extended time period without requiring additional administrations of the agent. For example, the patient has a substantially consistent level of therapeutically active agent available for consistent treatment of the eye over a relatively long period of time, for example, on the order of at least about two months, such as between about two and about six months, or even for about one or about two years or longer after receiving an implant. Such extended release times facilitate obtaining successful treatment results.

Intraocular implants in accordance with the disclosure herein comprise a therapeutic component and a drug release sustaining component associated with the therapeutic component. In accordance with the present invention, the therapeutic component comprises, consists essentially of, or consists of, a steroid. The drug release sustaining component is associated with the therapeutic component to sustain release of a therapeutically effective amount of the steroid into an eye in which the implant is placed. The therapeutically effective amount of the steroid is released into the eye for a period of time greater than about two months after the implant is placed in the eye.

In one embodiment, the intraocular implants comprise a steroid and a biodegradable polymer matrix. The steroid is associated with a biodegradable polymer matrix that releases drug, such as by degrading, at a rate effective to sustain release of a therapeutically effective amount of the steroid from the implant

Docket D3141-CIP
17698 CIP (OCU)

for a time greater or longer than about two months from a time the implant is placed in an ocular site or region of an eye. The intraocular implant is biodegradable or bioerodible and provides a sustained release of the steroid in an eye for extended periods of time, such as for more than two months, for example for about three

5 months or more and up to about six months or more.

The biodegradable polymer component of the foregoing implants may be a mixture of biodegradable polymers, wherein at least one of the biodegradable polymers is a polylactic acid or poly(lactide-co-glycolide) polymer having a molecular weight less than 40 kiloDaltons (kD). Additionally or alternatively, the foregoing implants may comprise a first biodegradable polymer having terminal free acid groups, and a different second biodegradable polymer having terminal free acid groups. Furthermore, the foregoing implants may comprise a mixture of different biodegradable polymers, each biodegradable polymer having an inherent viscosity in a range of about 0.16 deciliters/gram (dl/g) to about 0.24 dl/g. Examples of suitable biodegradable polymers include polymers of lactic acid, glycolic acid, and mixtures thereof.

In another embodiment, intraocular implants comprise a therapeutic component that comprises a steroid, and a polymeric outer layer covering the therapeutic component. The polymeric outer layer includes one or more orifices or openings or holes that are effective to allow a liquid to pass into the implant, and to allow the steroid to pass out of the implant. The therapeutic component is provided in a core or interior portion of the implant, and the polymeric outer layer covers or coats the core. The polymeric outer layer may include one or more biodegradable portions. The implant can provide an extended release of the steroid for more or longer than about two months, and for more than about one year, and even for more than about five or about ten years.

30 The steroid of the implants disclosed herein may be corticosteroids, or other steroids that are effective in treating ocular conditions. One example of a suitable

Docket D3141-CIP
17698 CIP (OCU)

steroid is fluocinolone or fluocinolone acetonide. Another example of a suitable steroid is triamcinolone or triamcinolone acetonide. Another example of a suitable steroid is beclomethasone or beclomethasone dipropionate. In addition, the therapeutic component of the present implants may include one or more additional

5 and different therapeutic agents that may be effective in treating an ocular condition.

The implants may be placed in an ocular region to treat a variety of ocular conditions, including conditions that affect an anterior region or posterior region of an eye. For example, the implants may be used to treat many conditions of the eye,

10 including, without limitation, maculopathies and retinal degeneration, uveitis, retinitis, choroiditis, vascular diseases, and exudative diseases, proliferative disorders, infectious disorders, genetic disorders, tumors, trauma, and surgery, retinal tears or holes, and the like.

15 Kits in accordance with the present invention may comprise one or more of the present implants, and instructions for using the implants. For example, the instructions may explain how to administer the implants to a patient, and types of conditions that may be treated with the implants.

20 Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment of the present invention.

25 Additional aspects and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying drawings and examples.

DRAWINGS

Figure 1 is a graph showing the cumulative release profiles for biodegradable fluocinolone acetonide containing implants as determined in 0.9% saline at 37
5 degrees Celsius.

Figure 2 is a graph similar to Figure 1 showing the cumulative release profiles for biodegradable fluocinolone acetnonide containing implants with different combinations of biodegradable polymers.

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Figure 3 is a graph similar to Figure 1 showing the cumulative release profiles for biodegradable triamcinolone acetonide containing implants.

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Figure 4 is a graph showing the cumulative release profiles for non-sterile fluocinolone acetonide containing implants having different hole configurations.

Figure 5 is a graph showing the amount of fluocinolone released per day for the implants described in Figure 4.

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Figure 6 is a graph showing the cumulative release profiles for sterile fluocinolone acetonide containing implants having different hole configurations.

Figure 7 is a graph showing the amount of fluocinolone released per day for the implants described in Figure 6.

25

Figure 8 is a graph showing the cumulative release profiles for non-sterile fluocinolone acetonide containing implants having different hole configurations than those described in Figure 4.

30

Figure 9 is a graph showing the amount of fluocinolone released per day for the implants described in Figure 8.

Figure 10 is a graph showing the cumulative release profiles for sterile fluocinolone acetonide containing implants having hole configurations similar to those described in Figure 8.

5

Figure 11 is a graph showing the amount of fluocinolone released per day for the implants described in Figure 10.

10 Figure 12 is a graph showing the cumulative release profiles for sterile fluocinolone acetonide containing implants having different hole configurations.

Figure 13 is a graph showing the amount of fluocinolone released per day for the implants described in Figure 12.

15 Figure 14 is a graph showing the cumulative release profiles for non-sterile fluocinolone acetonide containing implants having different hole configurations.

Figure 15 is a graph showing the amount of fluocinolone released per day for the implants described in Figure 14.

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Figure 16 is a graph showing the cumulative release profiles for sterile fluocinolone acetonide containing implants described in Figure 14.

25

Figure 17 is a graph showing the amount of fluocinolone released per day for the implants described in Figure 16.

Figure 18 is a graph showing the total percent release of triamcinolone as a function of time in phosphate buffered saline for implants containing 30% triamcinolone.

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Docket D3141-CIP
17698 CIP (OCU)

Figure 19 is a graph showing the total percent release of triamcinolone as a function of time in phosphate buffered saline for implants containing 50% triamcinolone.

5 Figure 20 is a graph showing the total percent release of triamcinolone as a function of time in citrate phosphate buffer for implants containing 30% triamcinolone.

10 Figure 21 is a graph showing the total percent release of triamcinolone as a function of time in citrate phosphate buffer for implants containing 50% triamcinolone.

15 Figure 22 is a graph showing the total percent release of beclomethasone propionate as a function of time in phosphate buffered saline for implants containing 30% triamcinolone.

Figure 23 is a graph showing the total percent release of beclomethasone propionate as a function of time in phosphate buffered saline for implants containing 50% triamcinolone.

20

Figure 24 is a graph showing the total percent release of beclomethasone propionate as a function of time in citrate phosphate buffer for implants containing 30% triamcinolone.

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Figure 25 is a graph showing the total percent release of beclomethasone propionate as a function of time in citrate phosphate buffer for implants containing 50% triamcinolone.

DESCRIPTION

As described herein, controlled and sustained administration of a therapeutic agent through the use of one or more intraocular implants may improve treatment of undesirable ocular conditions. The implants comprise a pharmaceutically acceptable polymeric composition and are formulated to release one or more pharmaceutically active agents, such as steroids, over an extended period of time. The implants are effective to provide a therapeutically effective dosage of the agent or agents directly to a region of the eye to treat one or more undesirable ocular conditions. Thus, with a single administration, therapeutic agents will be made available at the site where they are needed and will be maintained for an extended period of time, rather than subjecting the patient to repeated injections or, in the case of self-administered drops, ineffective treatment with only limited bursts of exposure to the active agent or agents.

15

An intraocular implant in accordance with the disclosure herein comprises a therapeutic component and a drug release sustaining component associated with the therapeutic component. In accordance with the present invention, the therapeutic component comprises, consists essentially of, or consists of, a steroid. The drug release sustaining component is associated with the therapeutic component to sustain release of a therapeutically effective amount of the steroid into an eye in which the implant is placed. The therapeutic amount of the steroid is released into the eye for a period of time greater than about two months after the implant is placed in the eye.

25

Definitions

For the purposes of this description, we use the following terms as defined in this section, unless the context of the word indicates a different meaning.

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Docket D3141-CIP
17698 CIP (OCU)

As used herein, an "intraocular implant" refers to a device or element that is structured, sized, or otherwise configured to be placed in an eye. Intraocular implants are generally biocompatible with physiological conditions of an eye and do not cause adverse side effects. Intraocular implants may be placed in an eye
5 without disrupting vision of the eye.

As used herein, a "therapeutic component" refers to a portion of an intraocular implant comprising one or more therapeutic agents or substances used to treat a medical condition of the eye. The therapeutic component may be a
10 discrete region of an intraocular implant, or it may be homogenously distributed throughout the implant. The therapeutic agents of the therapeutic component are typically ophthalmically acceptable, and are provided in a form that does not cause adverse reactions when the implant is placed in an eye.

15 As used herein, a "drug release sustaining component" refers to a portion of the intraocular implant that is effective to provide a sustained release of the therapeutic agents of the implant. A drug release sustaining component may be a biodegradable polymer matrix, or it may be a coating covering a core region of the implant that comprises a therapeutic component.

20

As used herein, "associated with" means mixed with, dispersed within, coupled to, covering, or surrounding. With respect to intraocular implants which comprise a therapeutic component associated with a biodegradable polymer matrix, "associated with" specifically excludes biodegradable polymeric coatings that may
25 be provided on or around the matrix.

As used herein, an "ocular region" or "ocular site" refers generally to any area of the eyeball, including the anterior and posterior segment of the eye, and which generally includes, but is not limited to, any functional (e.g., for vision) or structural
30 tissues found in the eyeball, or tissues or cellular layers that partly or completely line the interior or exterior of the eyeball. Specific examples of areas of the eyeball in an

Docket D3141-CIP
17698 CIP (OCU)

ocular region include the anterior chamber, the posterior chamber, the vitreous cavity, the choroid, the suprachoroidal space, the conjunctiva, the subconjunctival space, the episcleral space, the intracorneal space, the epicorneal space, the sclera, the pars plana, surgically-induced avascular regions, the macula, and the retina.

5

As used herein, an "ocular condition" is a disease, ailment or condition which affects or involves the eye or one of the parts or regions of the eye. Broadly speaking the eye includes the eyeball and the tissues and fluids which constitute the eyeball, the periocular muscles (such as the oblique and rectus muscles) and the 10 portion of the optic nerve which is within or adjacent to the eyeball.

An anterior ocular condition is a disease, ailment or condition which affects or which involves an anterior (i.e. front of the eye) ocular region or site, such as a periocular muscle, an eye lid or an eye ball tissue or fluid which is located anterior to 15 the posterior wall of the lens capsule or ciliary muscles. Thus, an anterior ocular condition primarily affects or involves the conjunctiva, the cornea, the anterior chamber, the iris, the posterior chamber (behind the retina but in front of the posterior wall of the lens capsule), the lens or the lens capsule and blood vessels and nerve which vascularize or innervate an anterior ocular region or site.

20

Thus, an anterior ocular condition can include a disease, ailment or condition, such as for example, aphakia; pseudophakia; astigmatism; blepharospasm; cataract; conjunctival diseases; conjunctivitis; corneal diseases; corneal ulcer; dry eye syndromes; eyelid diseases; lacrimal apparatus diseases; lacrimal duct obstruction; 25 myopia; presbyopia; pupil disorders; refractive disorders and strabismus. Glaucoma can also be considered to be an anterior ocular condition because a clinical goal of glaucoma treatment can be to reduce a hypertension of aqueous fluid in the anterior chamber of the eye (i.e. reduce intraocular pressure).

30

A posterior ocular condition is a disease, ailment or condition which primarily affects or involves a posterior ocular region or site such as choroid or sclera (in a

position posterior to a plane through the posterior wall of the lens capsule), vitreous, vitreous chamber, retina, optic nerve (i.e. the optic disc), and blood vessels and nerves which vascularize or innervate a posterior ocular region or site.

5 Thus, a posterior ocular condition can include a disease, ailment or condition, such as for example, acute macular neuroretinopathy; Behcet's disease; choroidal neovascularization; diabetic uveitis; histoplasmosis; infections, such as fungal or viral-caused infections; macular degeneration, such as acute macular degeneration, non-exudative age related macular degeneration and exudative age related macular 10 degeneration; edema, such as macular edema, cystoid macular edema and diabetic macular edema; multifocal choroiditis; ocular trauma which affects a posterior ocular site or location; ocular tumors; retinal disorders, such as central retinal vein occlusion, diabetic retinopathy (including proliferative diabetic retinopathy), proliferative vitreoretinopathy (PVR), retinal arterial occlusive disease, retinal 15 detachment, uveitic retinal disease; sympathetic ophthalmia; Vogt Koyanagi-Harada (VKH) syndrome; uveal diffusion; a posterior ocular condition caused by or influenced by an ocular laser treatment; posterior ocular conditions caused by or influenced by a photodynamic therapy, photocoagulation, radiation retinopathy, epiretinal membrane disorders, branch retinal vein occlusion, anterior ischemic optic 20 neuropathy, non-retinopathy diabetic retinal dysfunction, retinitis pigmentosa, and glaucoma. Glaucoma can be considered a posterior ocular condition because the therapeutic goal is to prevent the loss of or reduce the occurrence of loss of vision due to damage to or loss of retinal cells or optic nerve cells (i.e. neuroprotection).

25 The term "biodegradable polymer" refers to a polymer or polymers which degrade in vivo, and wherein erosion of the polymer or polymers over time occurs concurrently with or subsequent to release of the therapeutic agent. Specifically, hydrogels such as methylcellulose which act to release drug through polymer swelling are specifically excluded from the term "biodegradable polymer". The terms 30 "biodegradable" and "bioerodible" are equivalent and are used interchangeably

Docket D3141-CIP
17698 CIP (OCU)

herein. A biodegradable polymer may be a homopolymer, a copolymer, or a polymer comprising more than two different polymeric units.

The term "treat", "treating", or "treatment" as used herein, refers to reduction 5 or resolution or prevention of an ocular condition, ocular injury or damage, or to promote healing of injured or damaged ocular tissue.

The term "therapeutically effective amount" as used herein, refers to the level or amount of agent needed to treat an ocular condition, or reduce or prevent ocular 10 injury or damage without causing significant negative or adverse side effects to the eye or a region of the eye.

Intraocular implants have been developed which can release drug loads over various' time periods. These implants, which when inserted into an eye, such as the 15 vitreous of an eye, provide therapeutic levels of a steroid for extended periods of time (e.g., for about 2 months or more). The implants disclosed are effective in treating ocular conditions, such as posterior ocular conditions .

In one embodiment of the present invention, an intraocular implant comprises 20 a biodegradable polymer matrix. The biodegradable polymer matrix is one type of a drug release sustaining component. The biodegradable polymer matrix is effective in forming a biodegradable intraocular implant. The biodegradable intraocular implant comprises a steroid associated with the biodegradable polymer matrix. The matrix degrades at a rate effective to sustain release of a therapeutically effective 25 amount of the steroid for a time greater than about two months from the time in which the implant is placed in ocular region or ocular site, such as the vitreous of an eye.

The steroid of the implant may be a corticosteroid. In certain embodiments, 30 the steroid may be a fluocinolone, a triamcinolone, or a mixture of fluocinolone and triamcinolone. In some embodiments, the fluocinolone is provided in the implant as

Docket D3141-CIP
17698 CIP (OCU)

fluocinolone acetonide, and the triamcinolone is provided in the implant as triamcinolone acetonide. Triamcinolone acetonide is publicly available under the tradename, KENALOG®. Another steroid useful in the present implants is beclomethasone or beclomethasone dipropionate. Thus, the present implants may 5 comprise one or more of the following: fluocinolone, fluocinolone acetonide, triamcinolone, triamcinolone acetonide, beclomethasone, or beclamethasone dipropionate.

The steroid may be in a particulate or powder form and entrapped by the 10 biodegradable polymer matrix. Usually, steroid particles will have an effective average size less than about 3000 nanometers. In certain implants, the particles may have an effective average particle size about an order of magnitude smaller than 3000 nanometers. For example, the particles may have an effective average particle size of less than about 500 nanometers. In additional implants, the particles 15 may have an effective average particle size of less than about 400 nanometers, and in still further embodiments, a size less than about 200 nanometers.

The steroid of the implant is preferably from about 10 to 90% by weight of the 20 implant. More preferably, the steroid is from about 50 to about 80% by weight of the implant. In a preferred embodiment, the steroid comprises about 50% by weight of the implant. In another embodiment, the steroid comprises about 70% by weight of the implant.

Suitable polymeric materials or compositions for use in the implant include 25 those materials which are compatible, that is biocompatible, with the eye so as to cause no substantial interference with the functioning or physiology of the eye. Such materials preferably are at least partially and more preferably substantially completely biodegradable or bioerodible.

30 Examples of useful polymeric materials include, without limitation, such materials derived from and/or including organic esters and organic ethers, which

Docket D3141-CIP
17698 CIP (OCU)

when degraded result in physiologically acceptable degradation products, including the monomers. Also, polymeric materials derived from and/or including, anhydrides, amides, orthoesters and the like, by themselves or in combination with other monomers, may also find use. The polymeric materials may be addition or 5 condensation polymers, advantageously condensation polymers. The polymeric materials may be cross-linked or non-cross-linked, for example not more than lightly cross-linked, such as less than about 5%, or less than about 1% of the polymeric material being cross-linked. For the most part, besides carbon and hydrogen, the polymers will include at least one of oxygen and nitrogen, advantageously oxygen. 10 The oxygen may be present as oxy, e.g. hydroxy or ether, carbonyl, e.g. non-oxo-carbonyl, such as carboxylic acid ester, and the like. The nitrogen may be present as amide, cyano and amino. The polymers set forth in Heller, Biodegradable Polymers in Controlled Drug Delivery, In: CRC Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 1, CRC Press, Boca Raton, FL 1987, pp 39-90, which 15 describes encapsulation for controlled drug delivery, may find use in the present implants.

Of additional interest are polymers of hydroxyaliphatic carboxylic acids, either homopolymers or copolymers, and polysaccharides. Polyesters of interest include 20 polymers of D-lactic acid, L-lactic acid, racemic lactic acid, glycolic acid, polycaprolactone, and combinations thereof. Generally, by employing the L-lactate or D-lactate, a slowly eroding polymer or polymeric material is achieved, while erosion is substantially enhanced with the lactate racemate.

25 Among the useful polysaccharides are, without limitation, calcium alginate, and functionalized celluloses, particularly carboxymethylcellulose esters characterized by being water insoluble, a molecular weight of about 5 kD to 500 kD, for example.

Docket D3141-CIP
17698 CIP (OCU)

Other polymers of interest include, without limitation, polyvinyl alcohol, polyesters, polyethers and combinations thereof which are biocompatible and may be biodegradable and/or bioerodible.

5 Some preferred characteristics of the polymers or polymeric materials for use in the present invention may include biocompatibility, compatibility with the therapeutic component, ease of use of the polymer in making the drug delivery systems of the present invention, a half-life in the physiological environment of at least about 6 hours, preferably greater than about one day, not significantly 10 increasing the viscosity of the vitreous, and water insolubility.

15 The biodegradable polymeric materials which are included to form the matrix are desirably subject to enzymatic or hydrolytic instability. Water soluble polymers may be cross-linked with hydrolytic or biodegradable unstable cross-links to provide useful water insoluble polymers. The degree of stability can be varied widely, depending upon the choice of monomer, whether a homopolymer or copolymer is employed, employing mixtures of polymers, and whether the polymer includes terminal acid groups.

20 Equally important to controlling the biodegradation of the polymer and hence the extended release profile of the implant is the relative average molecular weight of the polymeric composition employed in the implant. Different molecular weights of the same or different polymeric compositions may be included in the implant to modulate the release profile. In certain implants, the relative average molecular 25 weight of the polymer will range from about 9 to about 60 kD, usually from about 10 to about 54 kD, more usually from about 12 to about 45 kD, and most usually less than about 40 kD.

30 In some implants, copolymers of glycolic acid and lactic acid are used, where the rate of biodegradation is controlled by the ratio of glycolic acid to lactic acid. The most rapidly degraded copolymer has roughly equal amounts of glycolic acid and

Docket D3141-CIP
17698 CIP (OCU)

lactic acid. Homopolymers, or copolymers having ratios other than equal, are more resistant to degradation. The ratio of glycolic acid to lactic acid will also affect the brittleness of the implant, where a more flexible implant is desirable for larger geometries. The % of polylactic acid in the polylactic acid polyglycolic acid (PLGA) 5 copolymer can be 0-100%, preferably about 15-85%, more preferably about 35-65%. In some implants, a 50/50 PLGA copolymer is used.

The biodegradable polymer matrix of the intraocular implant may comprise a mixture of two or more biodegradable polymers. For example, the implant may 10 comprise a mixture of a first biodegradable polymer and a different second biodegradable polymer. One or more of the biodegradable polymers may have terminal acid groups. In certain implants, the matrix comprises a first biodegradable polymer having terminal acid groups, and a different second biodegradable polymer having terminal acid groups. The first biodegradable polymer may be a poly (D,L- 15 lactide-co-glycolide). The second biodegradable polymer may be a poly (D,L-lactide).

Release of a drug from an erodible polymer is the consequence of several mechanisms or combinations of mechanisms. Some of these mechanisms include 20 desorption from the implants surface, dissolution, diffusion through porous channels of the hydrated polymer and erosion. Erosion can be bulk or surface or a combination of both. As discussed herein, the matrix of the intraocular implant may release drug at a rate effective to sustain release of a therapeutically effective amount of the steroid for more than three months after implantation into an eye. In 25 certain implants, therapeutic amounts of the steroid are released for more than four months after implantation. For example, an implant may comprise fluocinolone, and the matrix of the implant degrades at a rate effective to sustain release of a therapeutically effective amount of fluocinolone for about three months after being placed in an eye. As another example, the implant may comprise triamcinolone, and 30 the matrix releases drug at a rate effective to sustain release of a therapeutically

Docket D3141-CIP
17698 CIP (OCU)

effective amount of triamcinolone for more than three months, such as from about three months to about six months.

Release of a drug from the present implants can also be related to the 5 amount of a drug present in the implant and the properties of the polymers of the implant, such as polymer molecular weight and ratio of glycolic acid to lactic acid. In one embodiment of the present implants, the drug, such as the steroid, is released at a first rate for a first time period that is substantially independent of the polymer properties, and the drug is released at a second rate for a second time period after 10 the first time period that is dependent on the polymer properties of the implant. For example, an implant comprises a steroid and a polymeric component that releases the steroid from the implant for a time period of about thirty days primarily due to steroid dissolution, and releases the steroid from the implant after thirty days primarily due to polymer properties.

15

One example of the biodegradable intraocular implant comprises a steroid associated with a biodegradable polymer matrix, which comprises a mixture of different biodegradable polymers. At least one of the biodegradable polymers is a polylactide having a molecular weight less than 40 kD. Such a mixture is effective in 20 sustaining release of a therapeutically effective amount of the steroid for a time period greater than about two months from the time the implant is placed in an eye. In certain embodiments, the polylactide has a molecular weight less than 20 kD. In other embodiments, the polylactide has a molecular weight of about 10 kD. The polylactide may be a poly (D,L-lactide), and the polylactide may include polymers 25 having terminal free acid groups. In one particular embodiment, the matrix of the implant comprises a mixture of poly(lactide-co-glycolide) and polylactide. Each of the poly(lactide-co-glycolide) and polylactide may have terminal free acid groups.

Another example of a biodegradable intraocular implant comprises a steroid 30 associated with a biodegradable polymer matrix, which comprises a mixture of different biodegradable polymers, each biodegradable polymer having an inherent

Docket D3141-CIP
17698 CIP (OCU)

viscosity from about 0.16 dl/g to about 0.24 dl/g. For example, one of the biodegradable polymers may have an inherent viscosity of about 0.2 dl/g. Or, the mixture may comprise two different biodegradable polymers, and each of the biodegradable polymers has an inherent viscosity of about 0.2 dl/g. The inherent 5 viscosities identified above may be determined in 0.1% chloroform at 25°C.

Other implants may include a biodegradable polymer matrix of biodegradable polymers, at least one of the polymers having an inherent viscosity of about 0.25 dl/g to about 0.35 dl/g. Additional implants may comprise a mixture of biodegradable 10 polymers wherein each polymer has an inherent viscosity from about 0.50 dl/g to about 0.70 dl/g.

The release of the steroid from the intraocular implant comprising a biodegradable polymer matrix may include an initial burst of release followed by a 15 gradual increase in the amount of the steroid released, or the release may include an initial delay in release of the steroid followed by an increase in release. When the implant is substantially completely degraded, the percent of the steroid that has been released is about one hundred. Compared to existing implants, the implants disclosed herein do not completely release, or release about 100% of the steroid, 20 until after about two months of being placed in an eye. Thus, the implants exhibit a cumulative release profile that may have a shallower slope, or a lower rate of release, for longer periods of time than existing implants.

In at least one embodiment, the present implants release the steroid into the 25 interior of the eye in an amount having a reduced toxicity relative to bolus or liquid injections of the same steroid without a polymeric component. For example, it has been reported that a single or repeated 20 mg dose of Kenalog 40 results in substantial retinal changes, including changes in the retinal pigment epithelium. Such doses may be necessary in liquid formulations to provide prolonged 30 therapeutic effects.

Docket D3141-CIP
17698 CIP (OCU)

In comparison, the present implants can provide therapeutically effective amounts of the steroid for prolonged periods of time without requiring such large doses. Thus, present implants may contain 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg of a steroid, such as triamcinolone acetonide or fluocinolone acetonide, the steroid is 5 gradually released over time without causing substantial ocular toxicity or other adverse side effects that are associated with injection of 20 mg of the steroid in a liquid formulation. Thus, in one embodiment, an intravitreal implant comprises triamcinolone acetonide and a biodegradable polymer associated with the triamcinolone acetonide in the form of an intravitreal implant that releases the 10 triamcinolone acetonide in amounts associated with a reduced toxicity relative to the toxicity associated with administering triamcinolone acetonide in a liquid composition.

It may be desirable to provide a relatively constant rate of release of the 15 steroid from the implant over the life of the implant. For example, it may be desirable for the steroid to be released in amounts from about 0.01 μ g to about 2 μ g per day for the life of the implant. However, the release rate may change to either increase or decrease depending on the formulation of the biodegradable polymer 20 matrix. In addition, the release profile of the steroid may include one or more linear portions and/or one or more non-linear portions. Preferably, the release rate is greater than zero once the implant has begun to degrade or erode.

The implants may be monolithic, i.e. having the active agent or agents 25 homogenously distributed through the polymeric matrix, or encapsulated, where a reservoir of active agent is encapsulated by the polymeric matrix. Due to ease of manufacture, monolithic implants are usually preferred over encapsulated forms. However, the greater control afforded by the encapsulated, reservoir-type implant 30 may be of benefit in some circumstances, where the therapeutic level of the drug falls within a narrow window. In addition, the therapeutic component, including the steroid, may be distributed in a non-homogenous pattern in the matrix. For example,

Docket D3141-CIP
17698 CIP (OCU)

the implant may include a portion that has a greater concentration of the steroid relative to a second portion of the implant.

In another embodiment of the present invention, an intraocular implant 5 comprises a therapeutic component, including a steroid, and a drug release sustaining component including a coating covering a core region of the implant. The therapeutic component is provided in the core region. The polymeric outer layer may be impermeable to the therapeutic component and ocular fluids. Or, the polymeric outer layer may be initially impermeable to the therapeutic component and 10 ocular fluids, but then may become permeable to the therapeutic component or ocular fluids as the outer layer degrades. Thus, the polymeric outer layer may comprise a polymer such as polytetrafluoroethylene, polyfluorinated ethylenepropylene, polylactic acid, polyglycolic acid, silicone, or mixtures thereof.

15 The foregoing implant may be understood to include a reservoir of one or more therapeutic agents, such as a steroid. In certain implants, the steroid may be a corticosteroid, such as fluocinolone or triamcinolone, as discussed above. One example of an implant including a reservoir of a therapeutic agent is described in U.S. Patent No. 6,331,313.

20

In some implants, the drug release sustaining component comprises a polymeric outer layer covering the therapeutic component, the outer layer comprises a plurality of openings or holes through which the therapeutic component may pass from the drug delivery system to an external environment of the implant, such as an 25 ocular region of an eye. The holes enable a liquid to enter into the interior of the implant and dissolve the therapeutic agent contained therein. The release of the therapeutic agent from the implant may be influenced by the drug solubility in the liquid, the size of the hole(s), and the number of holes. In certain implants, the hole size and number of holes are effective in providing substantially all of the desired 30 release characteristics of the implant. Thus, additional excipients may not be

Docket D3141-CIP
17698 CIP (OCU)

necessary to achieve the desired results. However, in other implants, excipients may be provided to further augment the release characteristics of the implant.

Various biocompatible substantially impermeable polymeric compositions 5 may be employed in preparing the outer layer of the implant. Some relevant factors to be considered in choosing a polymeric composition include: compatibility of the polymer with the biological environment of the implant, compatibility of the drug with the polymer, ease of manufacture, a half-life in the physiological environment of at least several days, no significant enhancement of the viscosity of the vitreous, and 10 the desired rate of release of the drug. Depending on the relative importance of these characteristics, the compositions can be varied. Several such polymers and their methods of preparation are well-known in the art. See, for example, U.S. Pat. Nos. 4,304,765; 4,668,506 4,959,217; 4,144,317, and 5,824,074, Encyclopedia of 15 Polymer Science and Technology, Vol. 3, published by Interscience Publishers, Inc., New York, latest edition, and Handbook of Common Polymers by Scott, J. R. and Roff, W. J., published by CRC Press, Cleveland, Ohio, latest edition.

The polymers of interest may be homopolymers, copolymers, straight, branched-chain, or cross-linked derivatives. Some exemplary polymers include: 20 polycarbamates or polyureas, cross-linked poly(vinyl acetate) and the like, ethylene-vinyl ester copolymers having an ester content of 4 to 80% such as ethylene-vinyl acetate (EVA) copolymer, ethylene-vinyl hexanoate copolymer, ethylene-vinyl propionate copolymer, ethylene-vinyl butyrate copolymer, ethylene-vinyl pentantoate copolymer, ethylene-vinyl trimethyl acetate copolymer, ethylene-vinyl diethyl acetate 25 copolymer, ethylene-vinyl 3-methyl butanoate copolymer, ethylene-vinyl 3-3-dimethyl butanoate copolymer, and ethylene-vinyl benzoate copolymer, or mixtures thereof.

Additional examples include polymers such as: poly(methylmethacrylate), poly(butylmethacrylate), plasticized poly(vinylchloride), plasticized poly(amides), 30 plasticized nylon, plasticized soft nylon, plasticized poly(ethylene terephthalate), natural rubber, silicone, poly(isoprene), poly(isobutylene), poly(butadiene),

Docket D3141-CIP
17698 CIP (OCU)

poly(ethylene), poly(tetrafluoroethylene), poly(vinylidene chloride), poly(acrylonitrile), cross-linked poly(vinylpyrrolidone), chlorinated poly(ethylene), poly(trifluorochloroethylene), poly(ethylene chlorotrifluoroethylene), poly(tetrafluoroethylene), poly(ethylene tetrafluoroethylene), poly(4,4'-isopropylidene diphenylene carbonate), polyurethane, poly(perfluoroalkoxy), poly(vinylidene fluoride), vinylidene chloride-acrylonitrile copolymer, vinyl chloride-diethyl fumarate copolymer, silicone, silicone rubbers (of medical grade such as Silastic® Medical Grade ETR Elastomer Q7-4750 or Dow Corning® MDX 4-4210 Medical Grade Elastomer); and cross-linked copolymers of polydimethylsilane 10 silicone polymers.

Some further examples of polymers include: poly(dimethylsiloxanes), ethylene-propylene rubber, silicone-carbonate copolymers, vinylidene chloride-vinyl chloride copolymer, vinyl chloride-acrylonitrile copolymer, vinylidene chloride-acrylonitrile copolymer, poly(olefins), poly(vinyl-olefins), poly(styrene), poly(halo-olefins), poly(vinyls) such as polyvinyl acetate, cross-linked polyvinyl alcohol, cross-linked polyvinyl butyrate, ethylene ethylacrylate copolymer, polyethyl hexylacrylate, polyvinyl chloride, polyvinyl acetals, plasicized ethylene vinylacetate copolymer, polyvinyl alcohol, polyvinyl acetate, ethylene vinylchloride copolymer, polyvinyl 20 esters, polyvinylbutyrate, polyvinylformal, poly(acrylate), poly(methacrylate), poly(oxides), poly(esters), poly(amides), and poly(carbonates), or mixtures thereof.

In some aspects, the implants with an outer layer coating with holes may be biodegradable wherein the outer layer degrades after the drug has been released for 25 the desired duration. The biodegradable polymeric compositions may comprise any of the above-identified biodegradable polymers or combinations thereof. In some implants, the polymer is polytetrafluoroethylene, (commercially known as Teflon®), ethyl vinyl alcohol or ethylene vinyl acetate.

30 The steroid containing implants typically exhibited desirable release times with orifices configured to have a total area of less than 1% of the total surface area

Docket D3141-CIP
17698 CIP (OCU)

of the implant. A substantially cylindrically shaped implant has a first end, a second end, and a body portion between the first end and the second end. Typically, the implants disclosed herein are sealed at the first and second ends. One or more holes are formed in the body portion of the implant. The holes typically have a 5 diameter of at least about 250 μm and less than about 500 μm . For example, holes may have a diameter of about 250 μm , 325 μm , 375 μm , or 500 μm . Smaller holes may be provided in other implants. Typically, two or three holes are provided in the implant outer layer. The holes may be spaced apart by a distance from about 1 mm to about 2 mm for implants having a length of about 7 mm to about 10 mm.

10

In one steroid-containing implant, the total area of the holes was about 0.311% of the total surface area of the implant. In another steroid-containing implant, the total area of the holes was about 0.9% of the total surface area of the implant. The area of an orifice or hole is determined by the following formula:

15

$$\text{Area} = 3.1416 \times r^2$$

where r is the radius of the orifice. The area for each orifice may be determined and added together to determine the total orifice area. The tubular 20 implant surface area may be determined by the following formula:

$$\text{Surface area} = 3.1416 \times \text{OD} \times \text{length} + 2 \times 3.1416 r_{\text{od}}^2$$

where OD is the outer diameter of a cross-section of the tubular implant, 25 length is the length of the tubular implant, and r_{od} is the radius of the cross-section of the tubular implant.

In the configurations described above, the implant is capable of releasing the steroid at concentrations less than 2 $\mu\text{g}/\text{day}$. Some implants were capable of 30 releasing the steroid at a concentration of about 0.5 $\mu\text{g}/\text{day}$. These implants are capable of providing therapeutically effective amounts of the steroid to an ocular

Docket D3141-CIP
17698 CIP (OCU)

region of an eye for more than one year, such as for more than five years, and even for about 13 years.

Examples of materials used and methods of making such implants are

5 disclosed in U.S. Patent No. 6,331,313. Briefly, a coating is formed around a core containing a therapeutic agent. The core may include a therapeutic agent associated with a biodegradable polymer matrix, or the core may be formed by filling a preformed coating, such as a tube.

10 The therapeutic agent can be deposited in a preformed coating as a dry powder, particles, granules, or as a compressed solid. The therapeutic agent may also be present in a solution. In addition, the core can comprise a mixture of a biodegradable polymer matrix and the therapeutic agent, such as the matrix containing implants described above. The polymers used in the matrix with the

15 therapeutic agent are bio-compatible with body tissues and body fluids and can be biodegradable or substantially insoluble in the body fluids. Any of the above-described biocompatible polymer compositions can be used to prepare the matrix. The amount of polymer in the core may be from about 0% to 80 wt % by weight. These polymers are commercially available and methods for preparing polymer

20 matrices are well-known in the art. See, for example, U.S. Pat. No. 5,882,682.

The biocompatible, substantially impermeable outer layer can be obtained by coating the core with a polymeric composition described above. The coat can be applied using organic solvents, and the solvents may then be vacuum stripped from

25 the coat to leave a dry coat. The polymer, at a concentration of from about 10 to about 80 weight percent is dissolved or suspended in an organic solvent at the appropriate temperature, for example for polylactic polymer, between 60 degrees to 90 degrees C. The resulting mixture can be cut, molded, injection molded, extruded, or poured or sprayed onto a pre-formed core into any shape or size for implantation.

30 The spraying can be accomplished in a rotating pan coater or in a fluidized bed coater until the desired coating thickness is achieved.

Alternatively, the core may be dip coated or melt coated. This type of coating is especially useful with waxes and oils. In another embodiment, the core may be compression coated, wherein a suitable polymeric composition may be pressed onto 5 a preformed core. In another aspect, an adhesive coat such as shellac or polyvinyl acetate phthallate (PVAP) is applied to the core prior to applying the impermeable coating in order to improve adhesion of the impermeable coating to the core. These techniques are well-known in the art. See, for example, *Handbook of Common Polymers*, by J. R. Scott and W. J. Roff, Section 64, (1971) published by CRC Press, 10 Cleveland, Ohio.

When the outer layer is injection molded or extruded into the desired shape, the cavity formed by the outer layer can be then filled with the therapeutic agent composition. Then, the ends are sealed with an end cap. At least one orifice is 15 drilled in the device. Optionally, an orifice is drilled, or preformed in the wall, or an orifice is sealed with a break-off tab that is broken open, or cut open, or the like, at the time of use.

Alternatively, the core-free device may be loaded with therapeutic agent by, 20 for example, immersing the device in a solution comprising the therapeutic agent for a time sufficient for absorption of the therapeutic agent. The device may be equipped with a hollow fiber and the therapeutic agent may be directly loaded into the fiber and the device subsequently sealed. Where the activity of the therapeutic agent will not be compromised, the therapeutic agent -filled device may then be 25 dried or partially dried for storage until use. This method may find particular application where the activity of the therapeutic agent of choice is sensitive to exposure to solvents, heat or other aspects of the conventional solvent-evaporation, molding, extrusion or other methods described above.

30 The orifice may be formed using any technique known in the art. For instance, the orifice may be made using a needle or other form of boring instrument

Docket D3141-CIP
17698 CIP (OCU)

such as a mechanical drill or a laser to remove a section of the impermeable portion of the device. Alternatively, a specially designed punch tip may be incorporated into the compressing equipment, in order to pierce through the impermeable portion at the point of compaction.

5

The holes may be made by drilling the appropriate size hole through a wall of the device using a mechanical or laser-based process. In some implants, a digital laser marking system is used to drill the holes. This system allows for an array of apertures to be drilled on both faces of a dosage form simultaneously and at rates 10 suitable for production of dosage forms. The process utilizes a digital laser marking system (for example the DigiMarkTM variable marking system, available from Directed Energy, Inc.) to produce an unlimited number of holes through the surface or coating of the dosage form, at rates practically suitable for production of dosage forms.

15

The steps involved in this laser drilling process are as follows: a digital laser marking system is focused at a laser stage; the dosage form is moved onto the laser stage of the digital laser marking system is pulsed to energize those laser tubes needed to drill the desired apertures along a linear array on the dosage form, the 20 dosage form is moved forward on the laser stage and the digital laser marking system is again pulsed as needed to produce an additional linear array of apertures; the dosage form is then removed from the laser stage.

Orifices and equipment for forming orifices are disclosed in U.S. Pat. Nos. 25 3,845,770; 3,916,899; 4,063,064 and 4,008,864. Orifices formed by leaching are disclosed in U.S. Pat. Nos. 4,200,098 and 4,285,987. Laser drilling machines equipped with photo wave length detecting systems for orienting a device are described in U.S. Pat. No. 4,063,064 and in U.S. Pat. No. 4,088,864.

30 The intraocular implants disclosed herein may have a size of between about 5 μ m and about 10 mm, or between about 10 μ m and about 1 mm for administration

Docket D3141-CIP
17698 CIP (OCU)

with a needle, greater than 1 mm, or greater than 2 mm, such as 3 mm or up to 10 mm, for administration by surgical implantation. For needle-injected implants, the implants may have any appropriate length so long as the diameter of the implant permits the implant to move through a needle. For example, implants having a 5 length of about 6 mm to about 7 mm have been injected into an eye. The implants administered by way of a needle should have a diameter that is less than the inner diameter of the needle. In certain implants, the diameter is less than about 500 μm . The vitreous chamber in humans is able to accommodate relatively large implants of varying geometries, having lengths of, for example, 1 to 10 mm. The implant may 10 be a cylindrical pellet (e. g., rod) with dimensions of about 2 mm x 0.75 mm diameter. Or the implant may be a cylindrical pellet with a length of about 7 mm to about 10 mm, and a diameter of about 0.75 mm to about 1.5 mm.

The implants may also be at least somewhat flexible so as to facilitate both 15 insertion of the implant in the eye, such as in the vitreous, and accommodation of the implant. The total weight of the implant is usually about 250-5000 μg , more preferably about 500-1000 μg . For example, an implant may be about 500 μg , or about 1000 μg . For non-human individuals, the dimensions and total weight of the 20 implant(s) may be larger or smaller, depending on the type of individual. For example, humans have a vitreous volume of approximately 3.8 ml, compared with approximately 30 ml for horses, and approximately 60-100 ml for elephants. An implant sized for use in a human may be scaled up or down accordingly for other animals, for example, about 8 times larger for an implant for a horse, or about, for example, 26 times larger for an implant for an elephant.

25

Thus, implants can be prepared where the center may be of one material and the surface may have one or more layers of the same or a different composition, where the layers may be cross-linked, or of a different molecular weight, different density or porosity, or the like. For example, where it is desirable to quickly release 30 an initial bolus of drug, the center may be a polylactate coated with a polylactate-polyglycolate copolymer, so as to enhance the rate of initial degradation.

Docket D3141-CIP
17698 CIP (OCU)

Alternatively, the center may be polyvinyl alcohol coated with polylactate, so that upon degradation of the polylactate exterior the center would dissolve and be rapidly washed out of the eye.

5 The implants, particularly the implants with the steroid associated with a biodegradable polymer matrix, may be of any geometry including fibers, sheets, films, microspheres, spheres, circular discs, plaques and the like. The upper limit for the implant size will be determined by factors such as toleration for the implant, size limitations on insertion, ease of handling, etc. Where sheets or films are employed, 10 the sheets or films will be in the range of at least about 0.5 mm x 0.5 mm, usually about 3-10 mm x 5-10 mm with a thickness of about 0.1-1.0 mm for ease of handling. Where fibers are employed, the fiber diameter will generally be in the range of about 0.05 to 3 mm and the fiber length will generally be in the range of about 0.5-10 mm. Spheres may be in the range of about 0.5 μm to 4 mm in 15 diameter, with comparable volumes for other shaped particles.

20 The size and form of the implant can also be used to control the rate of release, period of treatment, and drug concentration at the site of implantation. Larger implants will deliver a proportionately larger dose, but depending on the surface to mass ratio, may have a slower release rate. The particular size and geometry of the implant are chosen to suit the site of implantation.

25 The proportions of steroid, polymer, and any other modifiers may be empirically determined by formulating several implants with varying proportions. A USP approved method for dissolution or release test can be used to measure the rate of release (USP 23; NF 18 (1995) pp. 1790-1798). For example, using the infinite sink method, a weighed sample of the implant is added to a measured volume of a solution containing 0.9% NaCl in water, where the solution volume will be such that the drug concentration is after release is less than 5% of saturation. 30 The mixture is maintained at 37°C and stirred slowly to maintain the implants in suspension. The appearance of the dissolved drug as a function of time may be

Docket D3141-CIP
17698 CIP (OCU)

followed by various methods known in the art, such as spectrophotometrically, HPLC, mass spectroscopy, etc. until the absorbance becomes constant or until greater than 90% of the drug has been released.

5 In addition to the steroid or steroids included in the intraocular implants disclosed herein, the intraocular implants may also include one or more additional ophthalmically acceptable therapeutic agents. For example, the implant may include one or more antihistamines, one or more antibiotics, one or more beta blockers, one or more different corticosteroids, one or more antineoplastic agents, one or more 10 immunosuppressive agents, one or more antiviral agents, one or more antioxidant agents, and mixtures thereof.

15 Pharmacologic or therapeutic agents which may find use in the present systems, include, without limitation, those disclosed in U.S. Pat. Nos. 4,474,451, columns 4-6 and 4,327,725, columns 7-8.

20 Examples of antihistamines include, and are not limited to, loradatine, hydroxyzine, diphenhydramine, chlorpheniramine, brompheniramine, cyproheptadine, terfenadine, clemastine, triprolidine, carbinoxamine, diphenylpyraline, phenindamine, azatadine, tripelennamine, dexchlorpheniramine, dexbrompheniramine, methdilazine, and trimprazine doxylamine, pheniramine, pyrilamine, chiorcyclizine, thonzylamine, and derivatives thereof.

25 Examples of antibiotics include without limitation, cefazolin, cephradine, cefaclor, cephapirin, ceftizoxime, cefoperazone, cefotetan, cefuroxime, cefotaxime, cefadroxil, ceftazidime, cephalexin, cephalothin, cefamandole, cefoxitin, cefonicid, ceforanide, ceftriaxone, cefadroxil, cephradine, cefuroxime, ampicillin, amoxicillin, cyclacillin, ampicillin, penicillin G, penicillin V potassium, piperacillin, oxacillin, bacampicillin, cloxacillin, ticarcillin, azlocillin, carbenicillin, methicillin, nafcillin, 30 erythromycin, tetracycline, doxycycline, minocycline, aztreonam, chloramphenicol, ciprofloxacin hydrochloride, clindamycin, metronidazole, gentamicin, lincomycin,

Docket D3141-CIP
17698 CIP (OCU)

tobramycin, vancomycin, polymyxin B sulfate, colistimethate, colistin, azithromycin, augmentin, sulfamethoxazole, trimethoprim, and derivatives thereof.

Examples of beta blockers include acebutolol, atenolol, labetalol, metoprolol,
5 propranolol, timolol, and derivatives thereof.

Examples of other corticosteroids include cortisone, prednisolone, flurometholone, dexamethasone, medrysone, loteprednol, fluazacort, hydrocortisone, prednisone, betamethasone, prednisone, methylprednisolone,
10 riamcinolone hexacetonide, paramethasone acetate, diflorasone, fluocinonide, derivatives thereof, and mixtures thereof.

Examples of antineoplastic agents include adriamycin, cyclophosphamide, actinomycin, bleomycin, duanorubicin, doxorubicin, epirubicin, mitomycin,
15 methotrexate, fluorouracil, carboplatin, carmustine (BCNU), methyl-CCNU, cisplatin, etoposide, interferons, camptothecin and derivatives thereof, phenesterine, taxol and derivatives thereof, taxotere and derivatives thereof, vinblastine, vincristine, tamoxifen, etoposide, piposulfan, cyclophosphamide, and flutamide, and derivatives thereof.

20

Examples of immunosuppressive agents include cyclosporine, azathioprine, tacrolimus, and derivatives thereof.

Examples of antiviral agents include interferon gamma, zidovudine,
25 amantadine hydrochloride, ribavirin, acyclovir, valciclovir, dideoxycytidine, phosphonoformic acid, ganciclovir, and derivatives thereof.

Examples of antioxidant agents include ascorbate, alpha-tocopherol, mannitol, reduced glutathione, various carotenoids, cysteine, uric acid, taurine,
30 tyrosine, superoxide dismutase, lutein, zeaxanthin, cryotpxanthin, astazanthin, lycopene, N-acetyl-cysteine, carnosine, gamma-glutamylcysteine, quercitin,

Docket D3141-CIP
17698 CIP (OCU)

lactoferrin, dihydrolipoic acid, citrate, Ginkgo Biloba extract, tea catechins, bilberry extract, vitamins E or esters of vitamin E, retinyl palmitate, and derivatives thereof.

Other therapeutic agents include squalamine, carbonic anhydrase inhibitors, 5 alpha agonists, prostamides, prostaglandins, antiparasitics, antifungals, and derivatives thereof.

The amount of active agent or agents employed in the implant, individually or in combination, will vary widely depending on the effective dosage required and the 10 desired rate of release from the implant. Usually the agent will be at least about 1, more usually at least about 10 weight percent of the implant, and usually not more than about 80, more usually not more than about 40 weight percent of the implant.

In addition to the therapeutic component, the intraocular implants disclosed 15 herein may include effective amounts of buffering agents, preservatives and the like. Suitable water soluble buffering agents include, without limitation, alkali and alkaline earth carbonates, phosphates, bicarbonates, citrates, borates, acetates, succinates and the like, such as sodium phosphate, citrate, borate, acetate, bicarbonate, carbonate and the like. These agents advantageously present in amounts sufficient 20 to maintain a pH of the system of between about 2 to about 9 and more preferably about 4 to about 8. As such the buffering agent may be as much as about 5% by weight of the total implant. Suitable water soluble preservatives include sodium bisulfite, sodium bisulfate, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, phenylmercuric borate, 25 phenylmercuric nitrate, parabens, methylparaben, polyvinyl alcohol, benzyl alcohol, phenylethanol and the like and mixtures thereof. These agents may be present in amounts of from 0.001 to about 5% by weight and preferably 0.01 to about 2% by weight.

30 In some situations mixtures of implants may be utilized employing the same or different pharmacological agents. In this way, a cocktail of release profiles, giving

Docket D3141-CIP
17698 CIP (OCU)

a biphasic or triphasic release with a single administration is achieved, where the pattern of release may be greatly varied.

Additionally, release modulators such as those described in U. S. Patent No. 5,869,079 may be included in the implants. The amount of release modulator employed will be dependent on the desired release profile, the activity of the modulator, and on the release profile of the glucocorticoid in the absence of modulator. Electrolytes such as sodium chloride and potassium chloride may also be included in the implant. Where the buffering agent or enhancer is hydrophilic, it may also act as a release accelerator. Hydrophilic additives act to increase the release rates through faster dissolution of the material surrounding the drug particles, which increases the surface area of the drug exposed, thereby increasing the rate of drug bioerosion. Similarly, a hydrophobic buffering agent or enhancer dissolve more slowly, slowing the exposure of drug particles, and thereby slowing the rate of drug bioerosion.

Various techniques may be employed to produce the implants described herein. Useful techniques include, but are not necessarily limited to, solvent evaporation methods, phase separation methods, interfacial methods, molding methods, injection molding methods, extrusion methods, co-extrusion methods, carver press method, die cutting methods, heat compression, combinations thereof and the like.

Specific methods are discussed in U.S. Pat. No. 4,997,652. Extrusion methods may be used to avoid the need for solvents in manufacturing. When using extrusion methods, the polymer and drug are chosen so as to be stable at the temperatures required for manufacturing, usually at least about 85 degrees Celsius. Extrusion methods use temperatures of about 25 degrees C to about 150 degrees C, more preferably about 65 degrees C to about 130 degrees C. An implant may be produced by bringing the temperature to about 60 degrees C to about 150 degrees C for drug/polymer mixing, such as about 130 degrees C, for a time period of about

Docket D3141-CIP
17698 CIP (OCU)

0 to 1 hour, 0 to 30 minutes, or 5-15 minutes. For example, a time period may be about 10 minutes, preferably about 0 to 5 min. The implants are then extruded at a temperature of about 60 degrees C to about 130 degrees C, such as about 75 degrees C.

5

In addition, the implant may be coextruded so that a coating is formed over a core region during the manufacture of the implant.

Compression methods may be used to make the implants, and typically yield implants with faster release rates than extrusion methods. Compression methods may use pressures of about 50-150 psi, more preferably about 70-80 psi, even more preferably about 76 psi, and use temperatures of about 0 degrees C to about 115 degrees C, more preferably about 25 degrees C.

15 The implants of the present invention may be inserted into the eye, for example the vitreous chamber of the eye, by a variety of methods, including placement by forceps or by trocar following making a 2-3 mm incision in the sclera. The method of placement may influence the therapeutic component or drug release kinetics. For example, delivering the implant with a trocar may result in placement of 20 the implant deeper within the vitreous than placement by forceps, which may result in the implant being closer to the edge of the vitreous. The location of the implant may influence the concentration gradients of therapeutic component or drug surrounding the element, and thus influence the release rates (e.g., an element placed closer to the edge of the vitreous may result in a slower release rate).

25

Among the diseases/conditions which can be treated or addressed in accordance with the present invention include, without limitation, the following:

30 **MACULOPATHIES/RETINAL DEGENERATION:** Non-Exudative Age Related Macular Degeneration (ARMD), Exudative Age Related Macular Degeneration (ARMD), Choroidal Neovascularization, Diabetic Retinopathy, Acute Macular

Docket D3141-CIP
17698 CIP (OCU)

Neuroretinopathy, Central Serous Chorioretinopathy, Cystoid Macular Edema, Diabetic Macular Edema.

UVEITIS/RETINITIS/CHOROIDITIS: Acute Multifocal Placoid Pigment

5 Epitheliopathy, Behcet's Disease, Birdshot Retinochoroidopathy, Infectious (Syphilis, Lyme, Tuberculosis, Toxoplasmosis), Intermediate Uveitis (Pars Planitis), Multifocal Choroiditis, Multiple Evanescent White Dot Syndrome (MEWDS), Ocular Sarcoidosis, Posterior Scleritis, Serpiginous Choroiditis, Subretinal Fibrosis and Uveitis Syndrome, Vogt-Koyanagi-Harada Syndrome.

10

VASCULAR DISEASES/EXUDATIVE DISEASES: Retinal Arterial Occlusive Disease, Central Retinal Vein Occlusion, Disseminated Intravascular Coagulopathy, Branch Retinal Vein Occlusion, Hypertensive Fundus Changes, Ocular Ischemic Syndrome, Retinal Arterial Microaneurysms, Coat's Disease, Parafoveal Telangiectasis, Hemi-Retinal Vein Occlusion, Papillophlebitis, Central Retinal Artery Occlusion, Branch Retinal Artery Occlusion, Carotid Artery Disease (CAD), Frosted Branch Angitis, Sickle Cell Retinopathy and other Hemoglobinopathies, Angioid Streaks, Familial Exudative Vitreoretinopathy, Eales Disease.

20

TRAUMATIC/SURGICAL: Sympathetic Ophthalmia, Uveitic Retinal Disease, Retinal Detachment, Trauma, Laser, PDT, Photocoagulation, Hypoperfusion During Surgery, Radiation Retinopathy, Bone Marrow Transplant Retinopathy.

25

PROLIFERATIVE DISORDERS: Proliferative Vitreal Retinopathy and

Epiretinal Membranes, Proliferative Diabetic Retinopathy.

30

INFECTIOUS DISORDERS: Ocular Histoplasmosis, Ocular Toxocariasis, Presumed Ocular Histoplasmosis Syndrome (POHS), Endophthalmitis, Toxoplasmosis, Retinal Diseases Associated with HIV Infection, Choroidal Disease Associated with HIV Infection, Uveitic Disease Associated with HIV Infection, Viral Retinitis, Acute Retinal Necrosis, Progressive Outer Retinal Necrosis, Fungal Retinal

Docket D3141-CIP
17698 CIP (OCU)

Diseases, Ocular Syphilis, Ocular Tuberculosis, Diffuse Unilateral Subacute Neuroretinitis, Myiasis.

GENETIC DISORDERS: Retinitis Pigmentosa, Systemic Disorders with
5 Accosiated Retinal Dystrophies, Congenital Stationary Night Blindness, Cone
Dystrophies, Stargardt's Disease and Fundus Flavimaculatus, Best's Disease,
Pattern Dystrophy of the Retinal Pigmented Epithelium, X-Linked Retinoschisis,
Sorsby's Fundus Dystrophy, Benign Concentric Maculopathy, Bietti's Crystalline
Dystrophy, pseudoxanthoma elasticum.

10

RETINAL TEARS/HOLES: Retinal Detachment, Macular Hole, Giant Retinal
Tear.

TUMORS: Retinal Disease Associated with Tumors, Congenital Hypertrophy
15 of the RPE, Posterior Uveal Melanoma, Choroidal Hemangioma, Choroidal
Osteoma, Choroidal Metastasis, Combined Hamartoma of the Retina and Retinal
Pigmented Epithelium, Retinoblastoma, Vasoproliferative Tumors of the Ocular
Fundus, Retinal Astrocytoma, Intraocular Lymphoid Tumors.

20 MISCELLANEOUS: Punctate Inner Choroidopathy, Acute Posterior Multifocal
Placoid Pigment Epitheliopathy, Myopic Retinal Degeneration, Acute Retinal
Pigment Epithelitis and the like.

In one embodiment, an implant, such as the implants disclosed herein, is
25 administered to a posterior segment of an eye of a human or animal patient, and
preferably, a living human or animal. In at least one embodiment, an implant is
administered without accessing the subretinal space of the eye. For example, a
method of treating a patient may include placing the implant directly into the
posterior chamber of the eye. In other embodiments, a method of treating a patient
30 may comprise administering an implant to the patient by at least one of intravitreal

Docket D3141-CIP
17698 CIP (OCU)

injection, subconjunctival injection, sub-tenon injections, retrobulbar injection, and suprachoroidal injection.

In at least one embodiment, a method of treating a posterior ocular condition 5 comprises administering one or more implants containing one or more steroids, as disclosed herein to a patient by at least one of intravitreal injection, subconjunctival injection, sub-tenon injection, retrobulbar injection, and suprachoroidal injection. A syringe apparatus including an appropriately sized needle, for example, a 22 guage neele, a 27 gauge needle or a 30 gauge needle, can be effectively used to inject the 10 composition with the posterior segment of an eye of a human or animal. Repeat injections are often not necessary due to the extended release of the steroid from the implants.

The present implants provide prolonged therapy to patients in need of ocular 15 therapy. As discussed herein, the present implants can release a steroid for at least about 2 months after placement in the vitreous of an eye of a patient. In certain implants, the steroid, and/or other therapeutic agents, can be released for at least about one year, for example for about three years. In additional implants, the steroid can be released at therapeutically effective amounts for more than three years, such 20 as for about five years.

In another aspect of the invention, kits for treating an ocular condition of the eye are provided, comprising: a) a container comprising an extended release 25 implant comprising a therapeutic component including a steroid, such as fluocinolone or triamcinolone, and drug release sustaining component; and b) instructions for use. Instructions may include steps of how to handle the implants, how to insert the implants into an ocular region, and what to expect from using the implants.

30 In view of the disclosure herein, one embodiment of a biodegradable intraocular implant comprises a steroid, such as triamcinolone acetonide,

Docket D3141-CIP
17698 CIP (OCU)

fluocinolone acetonide, dexamethasone, and the like, and a biodegradable polymeric component, and substantially no polyvinyl alcohol. Such an implant may be useful in treating uveitis, including non-infectious uveitis, and other ocular disorders, including macular edema, age-related macular degeneration, and the 5 disorders described herein. Advantageously, these implants can be placed in the vitreous of an eye of a patient, and can provide one or more therapeutic benefits with relatively few or no side effects. For example, the steroid, such as fluocinolone acetonide, can be released from the implant without the patient developing cataracts, vitreous hemorrhage, retinal neovascularization, and/or ocular 10 hypertension.

In another embodiment, the implant can comprise a steroid, such as fluocinolone acetonide, and the implant can have a form other than a tablet. For example, the implant can be in the form of a rod, sphere, and the like. In certain 15 implants, the implant is an extruded element as compared to a compressed tablet. The implant may include an adhesive component effective in retaining the implant in a fixed position in the eye. For example, certain implants, such as non-tablet implants, may include a polyvinyl alcohol suture. Other implants, including compressed tablets, may include an adhesive component that is free of polyvinyl 20 alcohol. For example, a hydrogel material may be used to affix the implant in the eye of a patient.

In a further embodiment, an implant can comprise a steroid, such as fluocinolone acetonide or triamcinolone acetonide, and an intraocular pressure 25 reducing agent, such as an alpha-2 adrenergic agonist. These implants may be particularly useful in preventing an increase in intraocular pressure associated with release of the steroid from the implant into the eye.

In another embodiment, a steroid containing intraocular tablet may comprise 30 a polyvinyl alcohol coating over the tablet body, and be substantially free of a

Docket D3141-CIP
17698 CIP (OCU)

silicone component. Some examples of useful coatings include those described above.

EXAMPLES

5 The following non-limiting examples provide those of ordinary skill in the art with specific preferred drug delivery systems, methods of making such systems, and methods to treat conditions within the scope of the present invention. The following examples are not intended to limit the scope of the invention.

10 Example 1

Manufacture and testing of implants containing flucinolone and a biodegradable polymer matrix

15 Fluocinolone acetonide was combined with a polymer in a stainless steel mortar and mixed using the Turbula shaker set at 96RPM for 15 minutes. The powder of the fluocinolone and polymer was scraped off the walls of the steel mortar and then mixed again for an additional 15 minutes. The powder blend was heated at temperatures ranging from 110°C to 160°C, depending on the polymer used, for a 20 total of 30 minutes, forming a polymer/drug melt. The melt was pelletized, then loaded into the barrel and extruded into filaments, and finally the filaments were cut into about 0.5 mg or about 1 mg size implants. The implants had a weight range from about 450 µg to about 550 µg, or from about 900 µg to about 1100 µg. The 1 mg size implants had a length of about 2 mm and a diameter of about 0.72 mm.

25 Each implant was placed in a 20 ml screw cap vial with 10 ml of 0.9% saline. The vials were placed in a shaking water bath at 37°C. 9 ml aliquots were removed and replaced with equal volume of fresh media on day 1, 4, 7 and every week thereafter. The in-vitro release testing was performed on each lot of implants in six 30 replicates.

Docket D3141-CIP
17698 CIP (OCU)

The drug assays were performed by HPLC, consisting of a Waters 2690 Separation Module (or 2696) and Waters 2996 Photodiode Array Detector. A Varian Microsorb-MV™ 100 Å C18 column was used for separation and the detector was 5 set at 254 nm. The mobile phase was (50:50) acetonitrile/0.005M sodium acetate (pH = 4.0). The flow rate was 1.00 ml/min and the total run time for was 6 minutes. The release rate was determined by calculating the amount of drug released in a given volume of medium over time in μ g/day.

10 A total of 20 fluocinolone acetonide formulations were prepared, as shown in Table 1. The polymers used were Boehringer Ingelheim Resomers RG755, RG503, R202H, RG502H, and RG502. The inherent viscosities were about 0.6, 0.4, 0.2, 0.2, and 0.2 dl/g, respectively. The average molecular weights were 40000, 28300, 6500, 8400, and 11400 daltons, respectively.

15

Table 1. Fluocinolone Acetonide Formulations

Formulation	Lot	FA (w/w)	Polymer	I.V. (dl/g)	Melt T	Extru T (core)	Nozzle	DDS Size
1	453-98A	40%	RG755	0.6	160 °C	122 °C	380 μ m	0.5 mg
2	453-98B	40%	RG755	0.6	160 °C	122 °C	720 μ m	0.5 mg
3	453-99	20%	RG755	0.6	160 °C	116 °C	720 μ m	1 mg
4	453-100	40%	RG503	0.4	150 °C	116 °C	720 μ m	0.5 mg
5	453-101	20%	RG503	0.4	150 °C	106 °C	720 μ m	1 mg
6	453-116	40%	R202H	0.2	110 °C	90 °C	720 μ m	0.5 mg
7	453-117	40%	RG752	0.2	110 °C	90 °C	720 μ m	0.5 mg
8	453-118	40%	RG502H	0.2	110 °C	84 °C	720 μ m	0.5 mg
9	453-119	40%	RG502	0.2	110 °C	92 °C	720 μ m	0.5 mg
10	453-120	40%	(1:1) RG502H / R202H	0.2	110 °C	85 °C	720 μ m	0.5 mg
11	453-121	40%	(1:1) RG502H / RG752	0.2	110 °C	83 °C	720 μ m	0.5 mg
12	453-128	60%	(3:1) RG502H / R202H	0.2	110 °C	95 °C	720 μ m	0.5 mg
13	453-129	60%	(3:1) RG502H / RG752	0.2	110 °C	101 °C	720 μ m	0.5 mg
14	453-130	60%	(3:1) RG502H / RG502	0.2	110 °C	101 °C	720 μ m	0.5 mg
15	453-131	60%	(1:1) RG502H / R202H	0.2	110 °C	101 °C	720 μ m	0.5 mg
16	453-137	40%	(1:2) RG502H / R202H	0.2	110 °C	88 °C	720 μ m	1 mg
17	453-138	40%	(1:2) RG502H / RG752	0.2	110 °C	85 °C	720 μ m	1 mg
18	453-139	40%	(1:2) RG502H / RG502	0.2	120 °C	85 °C	720 μ m	1 mg
19	453-140	40%	(1:2) RG502H / RG503	n.a.	120 °C	99 °C	720 μ m	1 mg
20	453-141	40%	(1:2) RG502H / RG755	n.a.	120 °C	99 °C	720 μ m	1 mg

Docket D3141-CIP
17698 CIP (OCU)

FA = Fluocinolone Acetonide

I.V. = inherent viscosity

Melt T = melting temperature

Extru T = extrusion temperature

5 Nozzle = nozzle diameter (μm)

DDS size = drug delivery system size (i.e., the weight of an individual implant)

Of the 20 formulations prepared, 16 were screened for release testing (formulations # 1-11 and 16-20). Initially, the release medium was 10 mL phosphate buffer-saline (PBS) with 1 mL replacement at each time point, but almost no release was observed up to three weeks. The release medium was subsequently changed to PBS with 9 mL replacement, but the release was inconsistent and with unacceptably high standard deviations. Finally, the release medium was switched to 0.9% saline with 9 mL replacement at each time point. The release profiles are 15 shown in Figures 1 and 2.

Most of the fluocinolone acetonide formulations released the total drug load in approximately 2-3 months. Of the 16 formulations, 11 formulations exhibited release for about two months. Of the 11 formulations, 6 formulations exhibited release for 20 about three months.

In particular, all formulations prepared with Resomer RG755 (453-98A, 453-98B, and 453-99) and RG752 (453-117) showed almost no release after day 4 and their release studies were stopped after 1 month.

25

Formulations prepared with RG503 (453-100 and 453-101) and RG502 (453-119) showed a delay of 3-4 weeks before releasing 100% between day 49 and day 56.

30

The formulation prepared with RG502H (453-118) appeared to be the fastest, on day 49.

The formulation prepared with a (1:1) mixture of RG502H and R202H led to the longest release, up to 84 days.

5 Finally, the formulation prepared with a (1:1) mixture of RG502H and RG752 appeared to be slower than the one prepared with RG502H (453-118) at first, but eventually ended up having complete release at day 49.

10 Based on these data, it was concluded that a mixture of RG502H and other polymers with slower release will provide a formulation with longer release and relatively closer to zero-order kinetics. One formulation with desirable release properties was a 1:2 mixture of RG502H and R202H, which led to a release of 94% of the fluocinolone after 84 days.

15 Example 2

Manufacture and testing of implants containing triamcinolone and a biodegradable polymer matrix

20 Triamcinolone acetonide was combined with a polymer in a stainless steel mortar and mixed using the Turbula shaker set at 96RPM for 15 minutes. The powder of the fluocinolone and polymer was scraped off the walls of the steel mortar and then mixed again for an additional 15 minutes. The powder blend was heated at temperatures ranging from 110°C to 160°C, depending on the polymer used, for a 25 total of 30 minutes, forming a polymer/drug melt. The melt was pelletized, then loaded into the barrel and extruded into filaments, and finally the filaments were cut into about 0.5 mg or about 1 mg size implants. The implants had a weight range from about 450 µg to about 550 µg, or from about 900 µg to about 1100 µg. The 1 mg size implants had a length of about 2 mm and a diameter of about 0.72 mm.

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Docket D3141-CIP
17698 CIP (OCU)

The testing of the triamcinolone implants was performed as described in Example 1.

A total of 16 triamcinolone acetonide formulations were prepared, as shown in 5 Table 2. The polymers used were Boehringer Ingelheim Resomers RG755, RG503, R202H, RG502H, and RG502. The inherent viscosities were 0.6, 0.4, 0.2, 0.2, and 0.2 dl/g, respectively. The average molecular weights were 40000, 28300, 6500, 8400, and 11400 daltons, respectively.

10 Table 2. Triamcinolone Acetonide Formulations

Formulation	Lot	TA (w/w)	Polymer	I.V. (dl/g)	Melt T	Extru T (core)	Nozzle	DDS Size
1	453-96	50%	RG755	0.6	160 °C	122 °C	720 µm	1 mg
2	453-97	50%	RG503	0.4	150 °C	116 °C	720 µm	1 mg
3	453-112	50%	RG502	0.2	110 °C	105 °C	720 µm	1 mg
4	453-113	50%	RG502H	0.2	110 °C	90 °C	720 µm	1 mg
5	453-114	50%	RG752	0.2	110 °C	95 °C	720 µm	1 mg
6	453-115	50%	R202H	0.2	110 °C	96 °C	720 µm	1 mg
7	453-122	50%	(1:1) RG502H / RG752	0.2	110 °C	83 °C	720 µm	1 mg
8	453-123	50%	(1:1) RG502H / R202H	0.2	110 °C	85 °C	720 µm	1 mg
9	453-125	60%	(3:1) RG502H / RG502	0.2	110 °C	92 °C	720 µm	1 mg
10	453-126	60%	(3:1) RG502H / R202H	0.2	110 °C	92 °C	720 µm	1 mg
11	453-127	60%	(3:1) RG502H / RG752	0.2	110 °C	95 °C	720 µm	1 mg
12	453-132	60%	(1:1) RG502H / R202H	0.2	110 °C	108 °C	720 µm	1 mg
13	453-133	50%	(1:1) RG502H / RG502	0.2	110 °C	99 °C	720 µm	1 mg
14	453-134	50%	(1:1) RG502H / RG755	N/A	110 °C	110 °C	720 µm	1 mg
15	453-135	50%	(1:1) RG502H / RG503	N/A	110 °C	110 °C	720 µm	1 mg
16	453-136	50%	(3:1) RG502H / RG502	0.2	110 °C	88 °C	720 µm	1 mg

TA = Triamcinolone Acetonide

I.V. = inherent viscosity

25 Melt T = melting temperature

Extru T = extrusion temperature

Nozzle = nozzle diameter (µm)

DDS size = drug delivery system size (i.e., the weight of an individual implant)

Docket D3141-CIP
17698 CIP (OCU)

Of the 16 formulations prepared, 8 were screened for release testing (formulations # 1-8). The same problem was encountered with the release medium as that of fluocinolone. The release medium was switched to 0.9% saline with 9 mL replacement at each time point. The release profiles are shown in Figure 3.

5

Certain triamcinolone acetonide formulations had release periods of about 4-6 months. Of the eight formulations, five formulations exhibited 4 or more months of release, and two formulations exhibited release for more than 5 months.

10 Formulations prepared with RG755 (453-96), RG752 (453-114) and R202H (453-115) showed essentially zero to very slow release.

The formulation prepared with RG502H (453-113) had the fastest and perhaps smoothest release profile with minimal delay lasting close to 4 months.

15

The formulation prepared with RG502 (453-112) showed an equally fast release of 4 months, but there was a 2-3 weeks lag time.

20 The formulation prepared with RG503 (453-97) showed a release longer than 4 months, but it also had 4 weeks lag time.

25 Similar to the formulations in Example 1, the formulation prepared with a (1:1) mixture of RG502H and R202H lot (453-123) led to a desirable release profile approaching 5 to 6 months. This release profile was the most linear and the longest (>140 days).

30 Based on the data of Examples 1 and 2, polymer blends appeared to achieve a more desired controlled release rate relative to single polymers. Using a slow degrading poly(D,L-lactide), such as R202H, and mixing it with a fast degrading poly(D,L-lactide-co-glycolide), such as RG502H, is effective in controlling the release rate of both fluocinolone and triamcinolone acetonide.

Example 3

Manufacture and *in vitro* testing of implants containing fluocinolone and a
polymeric coating

5

Silicone tubing (Specialty Silicone Fabricators, Inc, SSF-METN-755, P.N. OP-2) was cut to either 10 mm or 7 mm tubes to form an implant element. Holes of various sizes were drilled (Photomachining, Inc) in the cut tubes. The configuration of each tube was characterized by the number of holes, the diameter of holes and 10 the distance between the holes, as well as the tube length and the sterility of the tube. Each drilled tube was glued on one end with silicone adhesive (Nusil Silicone Technology, MED-1511), and dried for 72 hours at ambient temperature and then packed with fluocinolone acetonide. Each of the 10 mm long tube contained 4 to 5 mg of fluocinolone, while each of the 7 mm long tubes contained 2 to 3 mg of 15 fluocinolone. Finally, the other end of each tube was glued and dried for 72 hours. The implants did not include any additional excipients or release modifiers. A total of 30 different tube configurations were tested and are described in Table 3.

Docket D3141-CIP
17698 CIP (OCU)

Table 3. Fluocinolone Reservoir Delivery Technology Configurations

Configuration	Lot #	# Hole / Diam / Distance	Average Drug Load (µg)	Before or After γ Sterilization	Tube Length	Number of Replicates
1	257-172-1	2 hole - 250 µm - 2 mm	4526 (n = 3)	BS	1 cm	3
2	257-172-4	2 hole - 500 µm - 2 mm	4667 (n = 3)	BS	1 cm	3
3	257-172-7	3 hole - 250 µm - 2 mm	4508 (n = 3)	BS	1 cm	3
4	257-172-10	3 hole - 500 µm - 2 mm	4437 (n = 3)	BS	1 cm	3
5	267-33-1	2 hole - 250 µm - 2 mm	4699 (n = 1)	AS	1 cm	1
6	267-33-2	3 hole - 250 µm - 2 mm	4536 (n = 1)	AS	1 cm	1
7	267-33-3	2 hole - 500 µm - 2 mm	4457 (n = 1)	AS	1 cm	1
8	267-33-4	3 hole - 500 µm - 2 mm	4214 (n = 1)	AS	1 cm	1
9	267-140	2 hole - 375 µm - 2 mm	5228 (n = 3)	BS	1 cm	3
10	267-140	2 hole - 460 µm - 2 mm	4466 (n = 3)	BS	1 cm	3
11	267-140	3 hole - 325 µm - 2 mm	4867 (n = 3)	BS	1 cm	3
12	267-140	3 hole - 375 µm - 2 mm	4566 (n = 3)	BS	1 cm	3
13	285-1AS	2 hole - 375 µm - 2 mm	4663 (n = 3)	AS	1 cm	3
14	285-1AS	2 hole - 460 µm - 2 mm	4806 (n = 3)	AS	1 cm	3
15	285-1AS	3 hole - 325 µm - 2 mm	5168 (n = 3)	AS	1 cm	3
16	285-1AS	3 hole - 375 µm - 2 mm	4981 (n = 3)	AS	1 cm	3
17	285-54	2 hole - 250 µm - 2 mm	2804 (n = 3)	AS	0.7 cm	3
18	285-54	2 hole - 500 µm - 2 mm	2428 (n = 3)	AS	0.7 cm	3
19	285-54	3 hole - 375 µm - 2 mm	3068 (n = 3)	AS	0.7 cm	3
20	285-54	3 hole - 500 µm - 2 mm	2899 (n = 3)	AS	0.7 cm	3
21	285-126C	2 hole - 250 µm - 1 mm	2770 (n = 3)	BS	0.7 cm	3
22	285-126C	2 hole - 375 µm - 1 mm	2591 (n = 3)	BS	0.7 cm	3
23	285-126C	2 hole - 375 µm - 2 mm	3245 (n = 3)	BS	0.7 cm	3
24	285-126C	2 hole - 500 µm - 1 mm	2819 (n = 3)	BS	0.7 cm	3
25	285-126C	3 hole - 500 µm - 1.5 mm	2955 (n = 3)	BS	0.7 cm	3
26	285-126D	2 hole - 250 µm - 1 mm	2615 (n = 3)	AS	0.7 cm	3
27	285-126D	2 hole - 375 µm - 1 mm	2970 (n = 3)	AS	0.7 cm	3
28	285-126D	2 hole - 375 µm - 2 mm	2932 (n = 3)	AS	0.7 cm	3
29	285-126D	2 hole - 500 µm - 1 mm	2619 (n = 3)	AS	0.7 cm	3
30	285-126D	3 hole - 500 µm - 1.5 mm	2498 (n = 3)	AS	0.7 cm	3

Each of the 30 implants was placed into a 5 mL centrifuge vial with cap containing 1 mL of phosphate buffer-saline, pH 7.4 (PBS) at 37°C. Total replacement with equal volume of fresh medium was performed on day 1, 4, 7, 14, 28, and every week thereafter. Drug assay was performed on a Waters HPLC system, which included a 2690 (or 2696) Separation Module, and a 2996 Photodiode Array Detector. A Rainin C18, 4.6 x 100 mm column was used for separation and detector was set at 254 nm. The mobile phase was (50:50) acetonitrile-0.005M NaOAc/HOAc, pH 4.0 with flow rate of 1 mL/min and a total run time of 10 min per sample. Release rates were determined by calculating the amount of drug being released in a given volume of medium over time and

Docket D3141-CIP
17698 CIP (OCU)

expressed in $\mu\text{g}/\text{day}$. The release testing was performed on all 30 configurations in three replicates, except for configurations # 5 to 8, for which only one sample of each was tested.

5 The implants studied varied in the number of holes (2 or 3), hole sizes (250, 325, 375, 460, or 500 μm), distance between the holes (1 mm, 1.5 mm, or 2 mm), length of the implant (1 cm or 0.7 cm), and before or after gamma sterilization, as presented in Table 3.

10 In general, all 30 implants exhibited an initial burst of drug release on the first day then tapered off to day 7 or later, and finally gradually settled into an equilibrium release range starting after day 14. The first eight configurations were 1 cm in length with drug load of approximately $4.5 \text{ mg} \pm 0.2 \text{ mg}$ in each device, as shown in Table 3. Configurations 1 through 4 were non-sterile, while configurations 5 through 15 8 were sterile. The cumulative amount released (μg) as a function of time and the amount of release (μg) per day as a function of time are presented in Figures 4 through 7.

20 Configuration #1 (2 hole-250 μm), #2 (2 hole-500 μm), #3 (3 hole-250 μm), and #4 (3 hole-500 μm) gave an average release of 0.63 ± 0.23 , 1.72 ± 0.52 , 0.94 ± 0.30 , and $2.82 \mu\text{g}/\text{day} \pm 0.41 \mu\text{g}/\text{day}$, respectively from day 14 to day 487. These results were compared to their sterile counterparts, configuration #5, #6, #7, and #8, which gave an average release of 0.88, 1.10, 2.48, and $2.84 \mu\text{g}/\text{day}$, respectively from day 14 to day 448. A good correlation between the number of holes in a 25 configuration and its average daily release was observed for the first four configurations. For example, configuration #3 has 3 holes and configuration #1 has two holes of the same diameter as #3, and configuration #3 released 1½ times more fluocinolone per day than configuration #1. Similar results were obtained with configuration #4 and configuration #2.

Docket D3141-CIP
17698 CIP (OCU)

In configuration #5 (2 hole-250 μm), #6 (2 hole-500 μm), #7 (3 hole-250 μm), and #8 (3 hole-500 μm), we see approximately a three fold increase in the release rates between configuration #7 and #5, and also between configuration #8 and #6. This was a two-fold increase comparing to the non-sterile counterparts.

5 Configuration # 5 (2 holes-250 μm) released an average of 1 $\mu\text{g}/\text{day}$, and configuration # 7 (2 holes-500 μm) released an average of 3 $\mu\text{g}/\text{day}$.

Configurations #9 (2 hole-375 μm), #10 (2 hole-460 μm), #11 (3 hole-325 μm), and #12 (3 hole-375 μm) were made and were non-sterile, while configurations 10 13 through 16 were the sterile counterparts. The cumulative amount released (μg) as a function of time and the amount of release (μg) per day as a function of time are presented in Figures 8 through 11. Results from day 14 to day 397 showed an average release of 1.02 ± 0.25 , 1.22 ± 0.29 , 1.06 ± 0.21 , and $1.50 \pm 0.39 \mu\text{g}/\text{day}$ for configurations 9, 10, 11, and 12, respectively. Similarly, the data for configurations 15 13, 14, 15, and 16, which were the sterile counterparts, showed an average release of 1.92 ± 0.23 , 2.29 ± 0.33 , 1.94 ± 0.18 , and $3.15 \pm 0.64 \mu\text{g}/\text{day}$, respectively. Each of the sterile configurations appeared to be releasing twice as fast as its non-sterile counterpart.

20 Configuration # 13 (2 hole-375 μm -2 mm apart) exhibited an average release of $1.92 \pm 0.23 \mu\text{g}/\text{day}$ from day 14 through day 376. Likewise, configuration #15 (3 hole-325 μm – 2 mm apart) achieved an average release of $1.94 \pm 0.18 \mu\text{g}/\text{day}$ from day 14 through day 376. In the same period of time, configurations # 14 and # 16 achieved an average release of $2.29 \mu\text{g} \pm 0.33 \mu\text{g}/\text{day}$ and $3.15 \mu\text{g} \pm 0.64 \mu\text{g}/\text{day}$, respectively. Furthermore, configurations # 13 and #15 achieved a total release of $16.02 \% \pm 0.78 \%$ and $14.22 \% \pm 1.13 \%$, respectively, after 376 days. Based on the release rate, the predicted life span of configurations # 13 and #15 are 6.4 and 7.24 years, respectively.

Implants were also manufactured to provide a fluocinolone release rate of about 0.5 $\mu\text{g}/\text{day}$. Tubular implants were manufactured to have a length of about 0.7 cm filled with approximately $2.8 \text{ mg} \pm 0.34 \text{ mg}$ of drug and are identified as configurations 17, 18, 19, and 20. The cumulative amount of fluocinolone released (math) as a function of time and the amount of release (math) per day as a function of time are presented in Figures 12 and 13, respectively.

The results showed an average release of 0.95 ± 0.14 , 1.71 ± 0.55 , 1.93 ± 0.56 , and $2.76 \pm 0.27 \mu\text{g}/\text{day}$, for configurations 17, 18, 19, and 20, respectively, from day 14 through day 329. Since the length of the tube for configurations 17, 18, 19, and 20 was shortened from 1.0 cm to 0.7 cm, approximately 0.15 cm of silicone tubing was removed from both ends. As a result, the holes became much closer to the end of the tube, to the extent that the glue almost touched the circumference of the holes during preparation. It was not clear whether this affected the release profiles. To circumvent this potential problem, configurations with holes much closer to each other toward the center and away from the ends were prepared.

The last ten configurations were 0.7 cm in length with drug load of approximately $2.69 \text{ mg} \pm 0.36 \text{ mg}$ in each device. Configurations 21 through 25 were pre-sterile, while configurations 26 through 30 were sterile. The cumulative amount released (math) as a function of time and the amount of release (math) per day as a function of time are presented in Figures 14 through 17.

Results from day 14 to day 289 showed an average release of 1.01 ± 0.23 , 1.76 ± 0.57 , 1.73 ± 0.30 , 3.0 ± 1.26 , and $3.32 \pm 1.06 \mu\text{g}/\text{day}$ for configurations 21, 22, 23, 23, and 25, respectively. Similarly, the data for configurations 26, 27, 28, 29, and 30, which were the sterile counterparts, showed an average release of 0.48 ± 0.03 , 0.85 ± 0.09 , 0.82 ± 0.08 , 1.19 ± 0.15 , and $1.97 \pm 0.69 \mu\text{g}/\text{day}$, respectively, from day 14 through day 289. Configuration # 26 (2 holes-250 μm -1 mm apart) achieved an average release of 0.5 $\mu\text{g}/\text{day}$ (e.g., $0.48 \pm 0.03 \mu\text{g}/\text{day}$ from day 14

Docket D3141-CIP
17698 CIP (OCU)

through day 289) and a total release of $5.76\% \pm 0.32\%$ over 289 days or close to 9 1/2 months. Based on its release rate, it has a life span of 13.75 years. In general, the non-sterile configurations are approximately twice as fast as the sterile counterparts.

5

Example 4

Manufacture and *in vivo* testing of intraocular implants containing fluocinolone and a polymer coating

10 An *in vivo* study was conducted with an implant as shown by configuration # 29 in Example 3. The implant was manufactured as described in Example 3. Configuration # 29 achieved an average release of $1.19 \pm 0.15 \mu\text{g}/\text{day}$, and a total release of $14.28\% \pm 1.59\%$ over 289 days when tested *in vitro*.

15 The *in vivo* study was conducted on four rabbits. The fluocinolone-containing implants were surgically implanted into the posterior segment (i.e., the vitreous) of the right eye (OD) and left eye (OS) of each rabbit. The aqueous humor (15 - 20 μL) and the vitreous humor (150 - 200 μL) were withdrawn for the first two rabbits, while the sampling for the remaining two rabbits was determined by a sampling schedule 20 wherein the sampling days were days 7, 14, 21, 40, and 60, 90, and 120. The results of the *in vivo* study are shown in Table 4.

Table 4. Fluocinolone acetonide Levels in Vitreous Humor of Rabbit Eyes

Posterior Segment	Fluocinolone (ng/mL)						
Day	7	14	21	40	60	90	120
8408D	242.00						
8408S	88.60						
8399D	9.08	6.84	3.06		4.56	10.26	15.18
8399S	44.00	74.20	85.80		83.60	75.60	44.00
8407D		105.80	87.20		135.80	68.60	57.20
8407S		16.64	6.78		14.92	6.62	3.46
8397D				44.00	42.20	32.40	24.20
8397S				40.80	22.60	23.00	24.80
Average	95.92	50.87	45.71	42.40	50.61	36.08	28.14
SD	102.68	47.16	47.13	2.26	50.19	29.46	19.49

5 The mean vitreous levels of fluocinolone were relatively higher in the first week and then remained at approximately between 30 and 50 ng/mL beyond the second week. Fluocinolone acetonide was not detected at any time point in the anterior chamber of all eyes.

10 Thus, by way of Examples 3 and 4, implants have been developed that can deliver fluocinolone at a substantially constant release rate of 2 $\mu\text{g}/\text{day}$ or 0.5 $\mu\text{g}/\text{day}$ for extended periods of time (e.g., for over 1-2 years).

15 Configuration # 29 (2 hole-500 μm -1 mm) was used in the *in vivo* study and fluocinolone acetonide concentrations were measured between 0.026 $\mu\text{g}/\text{mL}$ to 0.096 $\mu\text{g}/\text{mL}$ over 120 days in the vitreous, while essentially no level was found in the aqueous humor.

20 It was noticed that the release profiles differed depending on when the implants were sterilized. For some configurations, the before sterilization release rates are about twice as fast as the after sterilization ones, and in other configurations, the reverse was observed. It is possible that sterilization may change the size of the holes in the implants. Two animals developed cataracts after day 120.

Example 5

Treatment of uveitis with an intraocular implant containing fluocinolone associated with a biodegradable polymer matrix.

5

A 48 year old female presents with posterior uveitis. She complains of sensitivity to light and ocular pain. An implant containing 250 μ g of fluocinolone acetonide and 250 μ g of a combination of biodegradable polymers (R502H and R202H at a 1:2 ratio, as described above in Example 1) is placed in the vitreous of both of the woman's eyes using a trocar. After about 2 days, the woman begins to notice a decrease in ocular pain and light sensitivity. She also notices a decreased blurring of vision, and a decrease in floaters. Substantial relief from the uveitis symptoms is obtained within about 7 days, and persists for about three months.

15

Example 6

Treatment of uveitis with an intraocular implant containing fluocinolone associated with a polymeric coating.

A 62 year old male presents with posterior uveitis. An implant containing 250 μ g of fluocinolone acetonide with a polymeric coating having two 500 μ m diameter holes spaced 1 mm apart is implanted into the vitreous of both of the patient's eyes using a trocar. The patient reports a decrease in pain and improvement in vision within a week after implantation. The improvements persist for about two years. No cataracts develop over that time.

25

Example 7

Treatment of macular edema with a steroid containing intraocular implant.

A 53 year old male with macular edema is treated by injecting a biodegradable implant into the vitreous of each of the patient's eyes using a syringe with a needle. The implants contain 500 μ g of fluocinolone acetonide and 500 μ g of

Docket D3141-CIP
17698 CIP (OCU)

PLGA. The patient reports a decrease in pain and improvement in vision within a week after implantation. The improvements persist for about two years. No cataracts develop over that time.

5

Example 8

Treatment of macular degeneration with with a steroid containing intraocular implant.

A 82 year old female diagnosed with macular degeneration in her right eye is 10 treated by intravitreal placement of a biodegradable implant containing 600 μ g of fluocinolone acetonide and 500 μ g of PLGA. The implant is placed near the fovea without interfering with the patient's vision. Further ophthalmic diagnosis indicates that macular degeneration is suspended, and the patient does not perceive further vision loss associated with macular degeneration. Throughout the treatment, 15 intraocular pressure remains within acceptable limits.

Example 9

Effects of polymer properties and drug load on intraocular implants

20 This example describes effects of poly (lactide-co-glycolide) (PLGA) polymer properties and drug load on in-vitro drug release profiles of steroids from polymeric implants. More specifically, this example describes the effects of polymer molecular weight (MW), lactide-glycolide (LG) ratio, and steroid load on the release profile of triamcinolone acetonide (TA) or beclomethasone dipropionate (BD) from poly (D, L- 25 lactide-co-glycolide) polymer implants containing triamcinolone acetonide (TA) or beclomethasone dipropionate (BD).

30 Drug release profiles of the present implants are related to the molecular weight (MW) of the polymer, such as PLGA in this example, the lactide-glycolide ratio (LG) of the polymer, and the drug load or amount of drug in the implant. Steroid release from the implants was examined in phosphate buffered saline (pH

Docket D3141-CIP
17698 CIP (OCU)

7.4; PBS) or citrate phosphate buffer containing 0.1% cetyltrimethylammonium bromide (pH 5.4; CTAB).

In short, the implants were made by melt extrusion, and the steroid release 5 from the implant was assayed by HPLC after incubation at 37 °C in phosphate buffered saline pH 7.4 or citrate phosphate buffer with 0.1% cetyltrimethylammonium bromide pH 5.4. Triamcinolone release from the implants was monitored for 90 days, and beclomethasone dipropionate release from implants was monitored for 35 days.

10

The results of these experiments show that both steroids release much faster in the citrate buffer compared to the phosphate buffer. During the first 30 days, the release profiles of the two steroids are very similar even though triamcinolone acetonide is about 150 times more water soluble than beclomethasone dipropionate. 15 Polymer properties have a minor effect on the release profile in this time frame or portion of the release profile (e.g., within approximately the first 30 days). In this early phase, the release appears to be controlled by the drug dissolution. The polymer properties become more important after the first 30 days or during a second time frame or portion of the release profile as the polymer's hydrolysis rate 20 differences become more important.

Triamcinolone acetonide was obtained from Pharmacia Upjohn Co. Beclomethasone dipropionate was obtained from Sigma. PLGA polymers RG502, RG504, RG752, and RG755 were obtained from Boehringer-Ingelheim Pharma 25 GmbH & Co. (Germany). Saline solution (0.9% NaCl) was obtained from VWR Scientific. Cetyltrimethylammonium bromide (CTAB) was obtained from Aldrich.

The following equipment was used: a ball mill (model mm200; F. Kurt Retsch GmbH & Co., Germany); a turbula shaker (model T2F Nr. 990720, Glen Mills, Inc., 30 New Jersey); a piston extruder obtained from APS Engineering, Inc.; a compactor (model A-1024, Jamesville Tool & Manufacturing, Inc., Milton Wisconsin); a shaking

Docket D3141-CIP
17698 CIP (OCU)

water bath (model 50, Precision Scientific, Winchester, VA); a high pressure liquid chromatograph (HPLC, model Alliance 2695, Equipped with a Waters 2497 Dual Wavelength Absorbance Detector, Waters, Inc., Milford, MA); and an oven (model 1330F, VWR Scientific, Cornelius, OR).

5

In this example, implants were produced by an extrusion process. Steroids and polymer(s) were combined in a stainless steel ball-mill capsule along with two stainless steel mixing balls. The capsule was placed on the ball mill for five minutes at 20 cps. The capsule was removed from the ball mill and the content was stirred 10 with a spatula; then placed back on the ball mill. This was repeated for two more five-minute cycles. The ball-mill capsule was then placed on a Turbula mixer for five minutes at 20 cps. The content of the capsule was transferred in small increments to an extruder barrel fitted with a die using a spatula and a small stainless steel funnel. After each increment, the powder was compacted in the extruder barrel with 15 the compactor set at 50 psi. When the extruder barrel was full, it is transferred to the extruder and the extruder was heated to temperature and allowed to equilibrate. The polymer steroid mixture was extruded through the die at 0.025 in/min.; the resulting filament was cut into approximately four-inch lengths and placed into a 60-mL screw cap vial, which was placed in a laminated foil pouch with a desiccant pack.

20

The experimental conditions for the extrusions are shown in Table 5 and Table 6 for triamcinolone acetonide and beclamethasone dipropionate, respectively.

Docket D3141-CIP
17698 CIP (OCU)

Table 5 Triamcinolone Acetonide /PLGA Extrusion Parameters

Polymer	Polymer ratio, %	Drug Load, %	Compactor Press, psi	Diameter of Die, um	Extrusion Speed, "/min	Extrusion Temp, °C
RG752	100	30	50	720	0.0025	95
RG752	100	50	50	720	0.0025	96
RG755	100	30	50	720	0.0025	97
RG755	100	50	50	720	0.0025	96
RG502	100	30	50	720	0.0025	97
RG502	100	50	50	720	0.0025	98
RG504	100	30	50	720	0.0025	94
RG504	100	50	50	720	0.0025	98
RG755	100	50	50	720	0.0025	101
RG752	100	30	50	720	0.0025	87

Table 6 Beclomethasone/PLGA Extrusion Parameters

5

Polymer	Polymer ratio, %	Drug Loading, %	Compactor Press, psi	Diameter of Die, um	Extrusion Speed, "/min	Extrusion Temp*, °C
RG755	100	30	50	720	0.0025	94
RG755	100	50	50	720	0.0025	99-109
RG752	100	30	50	720	0.0025	95-100
RG752	100	50	50	720	0.0025	96
RG504	100	30	50	720	0.0025	98
RG504	100	50	50	720	0.0025	104-114
RG502	100	30	50	720	0.0025	89-99
RG502	100	50	50	720	0.0025	95-96
RG755	100	50	50	720	0.0025	95
RG752	100	30	50	720	0.0025	95

* The mixture of API and polymer were left in the extruder at 90°C for 10 min before extrusion was started.

The extruded filaments were cut into 1-mg weight rod-shaped implants (rods).

10 Each rod was placed in a 60-mL vial with 50 mL of phosphate buffered saline pH 7.4 or citrate phosphate buffer pH 5.4 with 0.1% cetyltrimethylammonium bromide (CTAB) in an oscillating water bath (50 rpm) at 37 °C. At each time point, the released steroid was assayed (n=6) by HPLC, and the solution was removed from

Docket D3141-CIP
17698 CIP (OCU)

the vial and replaced with fresh buffer. The steroid release was measured after the following days: 1, 4, 7, 14, 21, 28, 35, 48 69, 77, and 90.

5 Triamcinolone acetonide (TA) released from the PLGA (poly (lactide-co-glycolide) polymer implant was assayed by HPLC (Waters, Milford, MA) employing a Waters Symmetry C18, 4.6 x 75 mm, 3 μ m column. The mobile phase was acetonitrile-water (35:65, v/v) with a flow rate of 1.0 mL/min and an injection volume of 20 μ L. Ultraviolet detection of TA was done at 243 nm. The total run time was 10 min and the TA retention time was 4.0 min. Quantization was based on peak area 10 and a triamcinolone acetonide standardization curve.

15 Beclomethasone dipropionate (BD) released from the PLGA polymer implant was assayed by HPLC (Waters, Milford, MA) employing a Discovery HS F5 C18, 4.6 x 150 mm, 5 μ m column. The mobile phase was acetonitrile-water (85:15), v/v with a flow rate of 0.8 mL/min and an injection volume of 30 μ L. Ultraviolet detection of BD was done at 240 nm. The total run time was 5 min and BD retention time was 2.5 min. Quantization was based on peak area and a BD standardization curve.

20 The results from the design were analyzed qualitatively at three times during the dissolution – early, middle and late.

The triamcinolone acetonide release results are shown in Tables 7-10 and in Figures 18 to 21, respectively.

25 As shown, TA released into the CTAB buffer faster than it was released into the PBS buffer. Drug release rate can also be effected by pH and surfactant which can alter the polymer's hydrolysis rate and thereforethe drug release rate.

30 The drug load in the polymer has the largest positive effect on the drug release rate compared to MW and LG ratio for the first 30 days. After the first 30 days, the LG ratio dominated the drug release rate and showed a negative effect. In

Docket D3141-CIP
17698 CIP (OCU)

other words, a higher LG ratio resulted in a slower drug release. Without wishing to be bound by any particular theory or mechanism of action, these effects may be related to high drug loading early in the dissolution resulting in more available drug at the polymeric implant's surface. As drug becomes less available, the drug 5 release rate may be controlled by the hydrolysis of the polymer, which is faster for the lower LG ratio polymer.

Molecular weight of the polymer had a positive effect on drug release rate especially later in the dissolution – faster release was observed with higher MW 10 polymers. While not wishing to be bound by any particular theory or mechanism of action, this may occur because the lower MW polymer pack more densely, and the higher MW polymer hydrolyze faster. Overall, the data show that early drug release is controlled by the drug load but the later in time drug release rate is controlled by the polymer hydrolysis rate.

15

Table 7 Triamcinolone Release Results in Phosphate Buffered Saline pH 7.4 for 30% Drug Load

	Total release (%)					Standard Deviation					
	755-30	752-30	504-30	502-30	752-30R		755-30	752-30	504-30	502-30	752-30R
1	1.08	0.81	1.75	0.74	0.46		0.08	0.12	0.14	0.04	0.09
4	1.40	1.02	2.13	0.94	0.49		0.05	0.11	0.13	0.04	0.03
7	1.56	1.08	2.29	1.00	0.59		0.04	0.04	0.06	0.04	0.03
14	1.70	1.10	2.47	1.11	0.60		0.03	0.02	0.07	0.05	0.02
21	1.92	1.28	2.86	1.47	0.69		0.03	0.03	0.03	0.01	0.04
28	2.05	1.37	4.14	2.77	0.97		0.05	0.03	0.19	0.02	0.11
35	2.08	1.41	9.73	4.60	1.06		0.02	0.03	1.09	0.09	0.05
48	2.22	1.98	13.74	7.73	1.65		0.12	0.03	0.83	0.33	0.10
69	14.03	4.42	21.70	11.70	3.98		1.87	0.06	2.09	0.73	0.25
90	20.94	7.82	36.46	21.22	7.05		0.34	0.94	3.05	3.10	0.53

20

Table 8 Triamcinolone Release Results in Phosphate Buffered Saline pH 7.4 for 50% Drug Load

Docket D3141-CIP
17698 CIP (OCU)

Total release (%)

	755-50	752-50	504-50	502-50	755-50R
1	1.83	2.01	1.88	1.97	2.20
4	2.93	2.32	2.56	2.57	3.75
7	3.68	2.44	2.74	2.84	4.62
14	4.66	2.58	2.93	3.09	5.68
21	5.23	2.73	3.16	3.46	6.21
28	5.60	2.87	4.29	4.23	6.62
35	5.75	2.98	6.37	4.92	6.84
48	5.92	3.70	8.07	7.44	7.04
69	7.69	5.35	14.47	10.79	7.84
90	9.42	7.38	39.38	33.66	8.59

Standard Deviation

	755-50	752-50	504-50	502-50	755-50R
1	0.35	0.15	0.72	0.09	0.16
4	0.09	0.05	0.32	0.08	0.14
7	0.15	0.05	0.10	0.04	0.16
14	0.12	0.06	0.08	0.05	0.11
21	0.09	0.03	0.09	0.03	0.04
28	0.05	0.06	0.56	0.08	0.05
35	0.01	0.05	1.01	0.04	0.03
48	0.04	0.09	1.58	2.65	0.03
69	0.79	0.25	3.75	2.60	0.08
90	0.47	0.37	2.45	3.63	0.08

Table 9 Triamcinolone Release Results in Citrate Phosphate Buffer pH 5.4 for 30% Drug Load

5

Total release (%)

	755-30	752-30	504-30	502-30	752-30R
1	1.79	1.93	2.50	1.07	0.69
4	2.18	1.93	2.85	1.12	0.74
7	2.35	2.22	3.03	1.13	0.86
14	2.61	3.05	3.23	1.21	0.94
21	3.00	4.62	4.73	1.59	0.96
28	3.45	12.44	16.60	7.99	1.00
35	3.57	12.59	45.16	25.70	1.00
48	4.05	12.99	94.39	77.56	1.46
69	18.96	42.24	95.24	83.21	45.40
77	58.09	83.17			63.83
90	92.97	96.82			79.93

Standard Deviation

	755-30	752-30	504-30	502-30	752-30R
1	0.19	1.11	0.12	0.05	0.05
4	0.03	0.00	0.02	0.04	0.03
7	0.06	0.26	0.04	0.02	0.01
14	0.05	1.18	0.02	0.03	0.03
21	0.21	2.06	0.04	0.02	0.02
28	0.27	3.92	0.27	0.64	0.03
35	0.07	0.06	2.99	2.69	0.00
48	0.27	0.04	3.90	2.92	0.04
69	0.48	3.20	0.50	3.24	2.29
77	2.48	6.49			2.71
90	3.88	5.73			4.08

Table 10 Triamcinolone Release Results in Citrate Phosphate Buffer pH 5.4 for 50% Drug Load

10

Total release (%)

	755-50	752-50	504-50	502-50	755-50R
1	4.32	3.14	4.10	3.10	5.63
4	7.96	3.38	5.77	4.08	9.39
7	13.26	3.46	6.24	4.42	11.52
14	16.75	3.60	6.79	4.77	14.79
21	19.60	3.80	10.34	5.25	16.43
28	21.91	3.90	20.94	9.17	17.21
35	23.75	4.02	41.21	16.58	17.59
48	24.50	5.02	82.11	71.13	18.38
69	43.48	33.38	91.91	85.27	27.09
77	58.17	54.68			35.62
90	85.58	75.87			54.43

Standard Deviation

	755-50	752-50	504-50	502-50	755-50R
1	1.01	0.63	0.14	0.14	1.76
4	0.76	0.09	0.36	0.08	0.09
7	5.93	0.05	0.17	0.03	0.07
14	1.16	0.03	0.13	0.03	0.15
21	1.23	0.03	0.32	0.03	0.12
28	2.78	0.02	0.14	0.55	0.11
35	2.20	0.03	1.66	3.08	0.06
48	0.34	0.19	3.58	13.62	0.10
69	8.47	7.52	4.47	1.67	1.65
77	1.78	7.97			1.13
90	5.86	11.33			4.57

The beclomethasone dipropionate release results are shown in Tables 11-14 and are plotted in Figures 22 to 25, respectively.

Docket D3141-CIP
17698 CIP (OCU)

In these experiments, beclomethasone dipropionate release was examined for about one month. In this early timeframe (e.g., within about 1 month), the release profiles for BD and TA were similar even though BD is about 150 times less soluble than TA. Changing to an acidic media increased the amount of released BD slightly but not as much as the same medium change did for TA. The BD release did not increase with increase drug load in the phosphate buffer, but did in the CTAB buffer. The response to increasing LG ratio was the same for both steroids for the first month. The effect is relatively small in the first 30 days but increasing the LG ratio decreases the amount of drug released. The effect of MW was different for the two steroids; triamcinolone's release increased slightly with higher MW in both media, whereas beclomethasone's release decreased in PBS and increased in CTAB with increasing MW.

15 Table 11 Beclomethasone Dipropionate Release Results in Phosphate
Buffered Saline pH 7.4 for 30% Drug Load

Total release (%)					
	755-30	752-30	504-30	502-30	752-30R
1	0.31	0.34	1.23	1.46	0.72
4	1.86	3.07	2.90	2.75	2.27
7	2.64	3.74	3.64	3.52	3.22
14	3.03	4.36	4.12	3.95	3.58
21	3.56	4.92	4.80	4.61	4.13
28	4.11	5.32	6.09	5.53	4.62
35	4.45	5.80	6.82	6.68	5.03
48					
69					
90					

Standard Deviation					
	755-30	752-30	504-30	502-30	752-30R
1	0.05	0.41	0.35	0.06	0.19
4	0.57	0.28	0.48	0.34	0.22
7	0.12	0.43	0.28	0.26	0.22
14	0.17	0.09	0.16	0.21	0.28
21	0.27	0.18	0.18	0.08	0.11
28	0.14	0.44	0.51	0.16	0.12
35	0.16	0.16	0.13	0.11	0.15
48					
69					
90					

20 Table 12 Beclomethasone Dipropionate Release Results in Phosphate
Buffered Saline pH 7.4 for 50% Drug Load

Docket D3141-CIP
17698 CIP (OCU)

Total release (%)						Standard Deviation					
	755-50	752-50	504-50	502-50	755-50R		755-50	752-50	504-50	502-50	755-50R
1	0.11	0.18	0.70	1.01	0.75	1	0.07	0.09	0.24	0.30	0.07
4	0.78	1.95	2.22	2.00	1.84	4	0.37	0.19	0.16	0.14	0.17
7	1.13	2.78	2.57	2.50	2.34	7	0.12	0.10	0.30	0.18	0.16
14	1.29	3.19	2.91	2.75	2.72	14	0.04	0.09	0.08	0.08	0.08
21	1.62	3.68	3.25	3.21	3.20	21	0.09	0.08	0.20	0.10	0.04
28	1.88	4.15	3.87	3.72	3.56	28	0.15	0.11	0.12	0.16	0.08
35	2.02	4.42	4.22	4.36	3.75	35	0.08	0.17	0.15	0.19	0.03
48						48					
69						69					
90						90					

Table 13 Beclomethasone Dipropionate Release Results in Citrate Phosphate Buffer pH 5.4 for 30% Drug Load

5

Total release (%)						Standard Deviation					
	755-30	752-30	504-30	502-30	752-30R		755-30	752-30	504-30	502-30	752-30R
1	0.28	1.20	2.16	1.28	1.37	1	0.16	0.22	0.23	0.25	0.10
4	1.44	1.54	3.16	1.59	1.50	4	0.24	0.11	0.22	0.16	0.11
7	2.15	1.87	3.90	2.04	1.93	7	0.15	0.09	0.17	0.03	0.08
14	2.62	2.06	4.53	2.39	2.27	14	0.09	0.21	0.08	0.11	0.06
21	3.05	2.35	7.45	3.68	2.54	21	0.09	0.05	0.24	0.16	0.16
28	3.32	2.50	12.51	7.09	2.82	28	0.10	0.22	0.74	0.29	0.07

Table 14 Beclomethasone Dipropionate Release Results in Citrate Phosphate Buffer pH 5.4 for 50% Drug Load

10

Total release (%)						Standard Deviation					
	755-50	752-50	504-50	502-50	755-50R		755-50	752-50	504-50	502-50	755-50R
1	2.01	0.47	3.07	2.16	3.80	1	0.36	0.06	0.74	0.37	0.42
4	6.26	1.77	6.01	3.16	7.64	4	0.63	0.24	0.51	0.27	0.61
7	9.00	2.55	7.48	3.98	10.30	7	0.54	0.18	0.17	0.16	0.58
14	12.40	3.51	8.45	4.73	13.49	14	0.49	0.66	0.15	0.18	0.65
21	14.16	4.06	10.59	6.04	15.06	21	0.26	0.15	0.28	0.12	0.22
28	15.07	4.44	15.31	9.21	15.95	28	0.13	0.12	0.79	0.29	0.08

Based on these results, the release of low water soluble steroids from PLGA implants is primarily limited by the dissolution of the steroid in the first thirty days, and not the loading or amount of the steroid, or the polymer matrix properties. In the early part of the dissolution (e.g., during the first portion of the drug release profile), the release rates of the two steroids are very similar even though their solubilities are quite different. During this period the drug release rate appears to be controlled by the steroid dissolution with the polymer properties having a minor effect. Later in

WO 2005/107727

PCT/US2005/015113

Docket D3141-CIP
17698 CIP (OCU)

the dissolution (e.g., during a second portion of the drug release profile), the steroid release is more dependent on polymer properties as the hydrolysis rates of the polymers become more important. Changing to a lower pH media with a lower surface tension increases the amount released for both steroids.

5

The present invention also encompasses the use of any and all possible combinations of the therapeutic agents disclosed herein in the manufacture of a medicament, such as a drug delivery system or composition comprising such a drug delivery system, to treat one or more ocular conditions, including those identified 10 above.

We claim:

1. A biodegradable intraocular implant comprising:
a steroid dispersed within a biodegradable polymer matrix that releases drug at a rate effective to sustain release of a therapeutically effective amount of the steroid from the implant for a time greater than about two months from a time in which the implant is placed in an ocular site or region of an eye, wherein the polymer matrix comprises a mixture of a biodegradable poly(D,L-lactide-co-glycolide) and a biodegradable poly(D,L-lactide).
2. The implant of claim 1, wherein the steroid is a corticosteroid.
3. The implant of claim 1, wherein the steroid is a fluocinolone, a triamcinolone, or a mixture thereof.
4. The implant of claim 1, further comprising an ophthalmically acceptable therapeutic agent in addition to the steroid.
5. The implant of claim 1 wherein the biodegradable poly (D,L-lactide-co-glycolide) and the biodegradable poly (D,L-lactide) have terminal acid groups.
6. The implant of claim 1, wherein the matrix releases drug at a rate effective to sustain release of a therapeutically effective amount of the steroid from the implant for more than three months from the time the implant is placed in the vitreous of the eye.
7. The implant of claim 1, wherein the matrix releases drug at a rate effective to sustain release of a therapeutically effective amount of the steroid from the implant for more than four months from the time the implant is placed in the vitreous of the eye.
8. The implant of claim 1, wherein the steroid is fluocinolone, and the matrix releases drug at a rate effective to sustain release of a therapeutically effective amount of fluocinolone for about three months.
9. The implant of claim 1, wherein the steroid is triamcinolone, and the matrix releases drug, at a rate effective to sustain release of a therapeutically effective amount of triamcinolone for more than three months.

10. The implant of claim 9, wherein the matrix releases drug at a rate effective to sustain release of triamcinolone for about three months to about six months.
11. The implant of claim 1, wherein the poly (D,L-lactide) has a molecular weight less than 40 kD.
12. The implant of claim 11, wherein the poly (D,L-lactide) has a molecular weight less than 20 kD.
13. The implant of claim 11, wherein the poly (D,L-lactide) has a molecular weight of about 10 kD.
14. The implant of claim 11, wherein the poly (D,L-lactide) has terminal free acid groups.
15. The implant of claim 11, wherein the poly (D,L-lactide-co-glycolide) and the poly (D,L-lactide) each have terminal free acid groups.
16. The implant of claim 1, wherein each biodegradable polymer has an inherent viscosity of in a range of about 0.16 dl/g to about 0.24 dl/g.
17. The implant of claim 16, wherein each of the biodegradable polymers has an inherent viscosity of about 0.2 dl/g.
18. The implant of claim 1 which is formed by an extrusion process.
19. The implant of claim 1, wherein the intraocular implant is structured for intravitreal placement in an eye of an individual.
20. The implant of claim 19, wherein the steroid is a dexamethasone, a fluocinolone, a triamcinolone, a beclomethasone, fluocinolone acetonide, triamcinolone acetonide, beclomethasone dipropionate, a salt thereof, or a mixture thereof.
21. The biodegradable intraocular implant of claim 1, wherein the biodegradable polymer matrix is substantially free of silicone and the intraocular implant is structured

for placement in the vitreous of an eye of a patient.

22. The implant of claim 21, wherein the steroid is a dexamethasone, a fluocinolone, a triamcinolone, a beclomethasone, fluocinolone acetonide, triamcinolone acetonide, beclomethasone dipropionate, a salt thereof, or a mixture thereof.
23. The implant of claim 21 which is in the form of a tablet.
24. The implant of claim 21, further comprising an adhesion member to affix the implant in the vitreous of the eye.
25. A method for making the biodegradable intraocular implant of claim 1, comprising the step of: extruding a mixture of the steroid and the biodegradable polymer matrix to form a biodegradable material that releases drug at a rate effective to sustain release of a therapeutically effective amount of the steroid from the implant for a time greater than about two months from a time in which the implant is placed in an ocular site or region of an eye.
26. The method of claim 25, wherein the steroid is a corticosteroid.
27. The method of claim 25, wherein the steroid is a fluocinolone or a triamcinolone.
28. The method of claim 25, further comprising a step of mixing the steroid with the polymer matrix before the extrusion step.
29. The method of claim 25, wherein the steroid and the polymer matrix are in a powder form.
30. The method of claim 25, wherein the polymer matrix comprises a mixture of biodegradable polymers, at least one of the biodegradable polymers is a polylactide having a molecular weight less than 40 kD.
31. The method of claim 25, wherein the polymer matrix comprises a first biodegradable polymer having terminal free acid groups, and a different second

biodegradable polymer having terminal free acid groups.

32. The method of claim 25, wherein the polymer matrix comprises a mixture of different biodegradable polymers, each biodegradable polymer having an inherent viscosity in a range of about 0.16 dl/g to about 0.24 dl/g.
33. A medicament, which is the implant of claim 1, for treating an ocular condition of a patient with a therapeutically effective amount of the steroid to the patient for at least about two months.
34. The medicament of claim 33, wherein the ocular condition is an inflammation of the eye.
35. The medicament of claim 33, wherein the implant is for placement in the posterior of the eye.
36. The medicament of claim 33, wherein the implant is for placement in the eye with a trocar.
37. The medicament of claim 33, wherein the implant is for placement in the eye with a syringe.
38. The medicament of claim 33, wherein a further therapeutic agent is for administration in addition to the steroid to the patient.
39. Use of the biodegradable ocular implant of any one of claims 1 to 24 for treating an ocular condition responsive to treatment with a steroid for at least about two months.
40. Use of the biodegradable ocular implant of any one of claims 1 to 24 for the production of a medicament for treating an ocular condition responsive to treatment with a steroid for at least about two months.
41. The use of claim 39 or 40, wherein the ocular condition is an inflammation of the eye.

42. The use of claim 39 or 40, wherein the implant is for placement in the posterior of the eye.
43. The use of claim 39 or 40, wherein the implant is for placement in the eye with a trocar.
44. The use of claim 39 or 40, wherein the implant is for placement in the eye with a syringe.
45. The use of claim 39 or 40, wherein a further therapeutic agent is included in the implant for administration in addition to the steroid to the patient.

(Sheet 1 of 25)

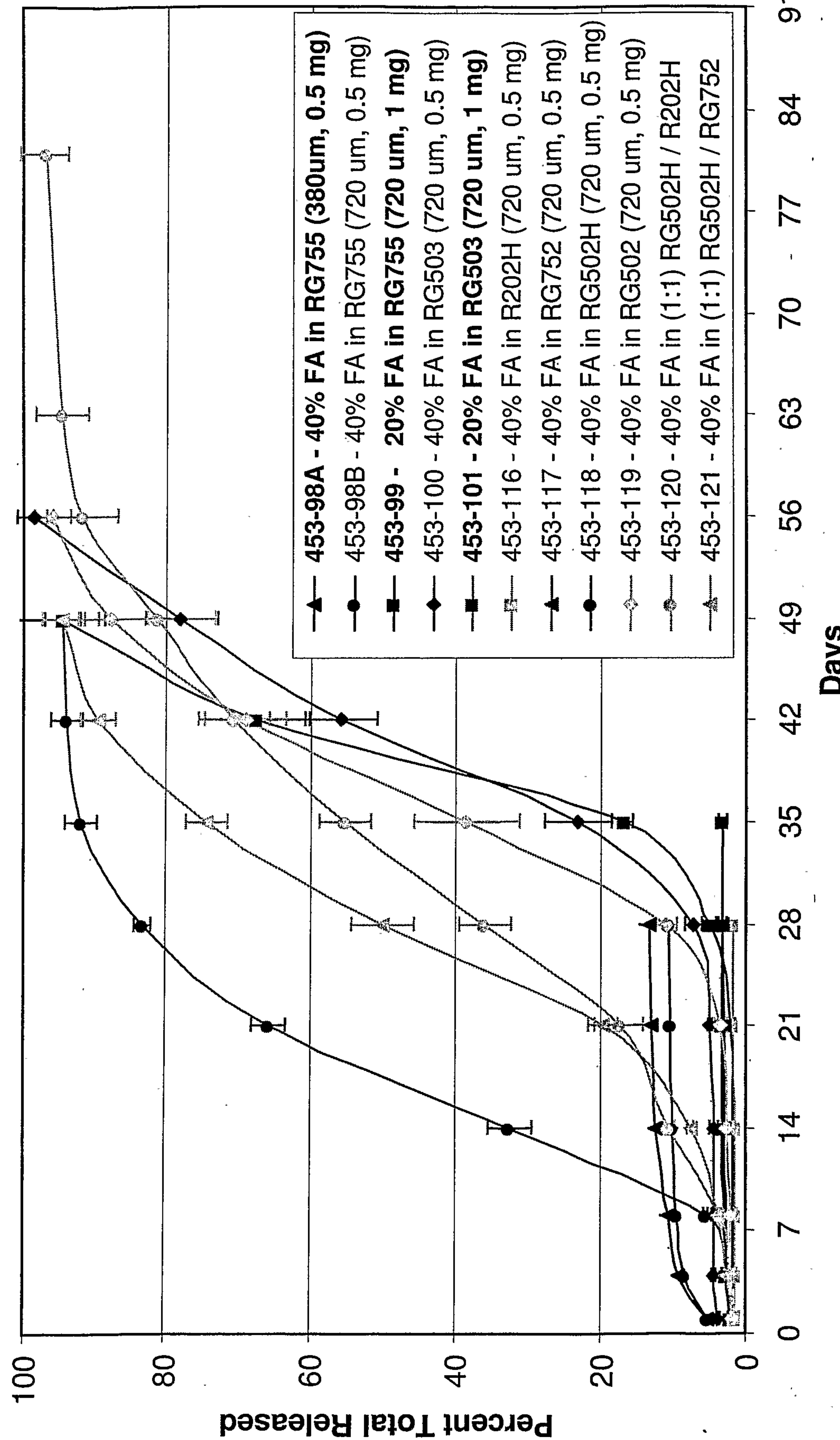


FIG. 1

(Sheet 2 of 25)

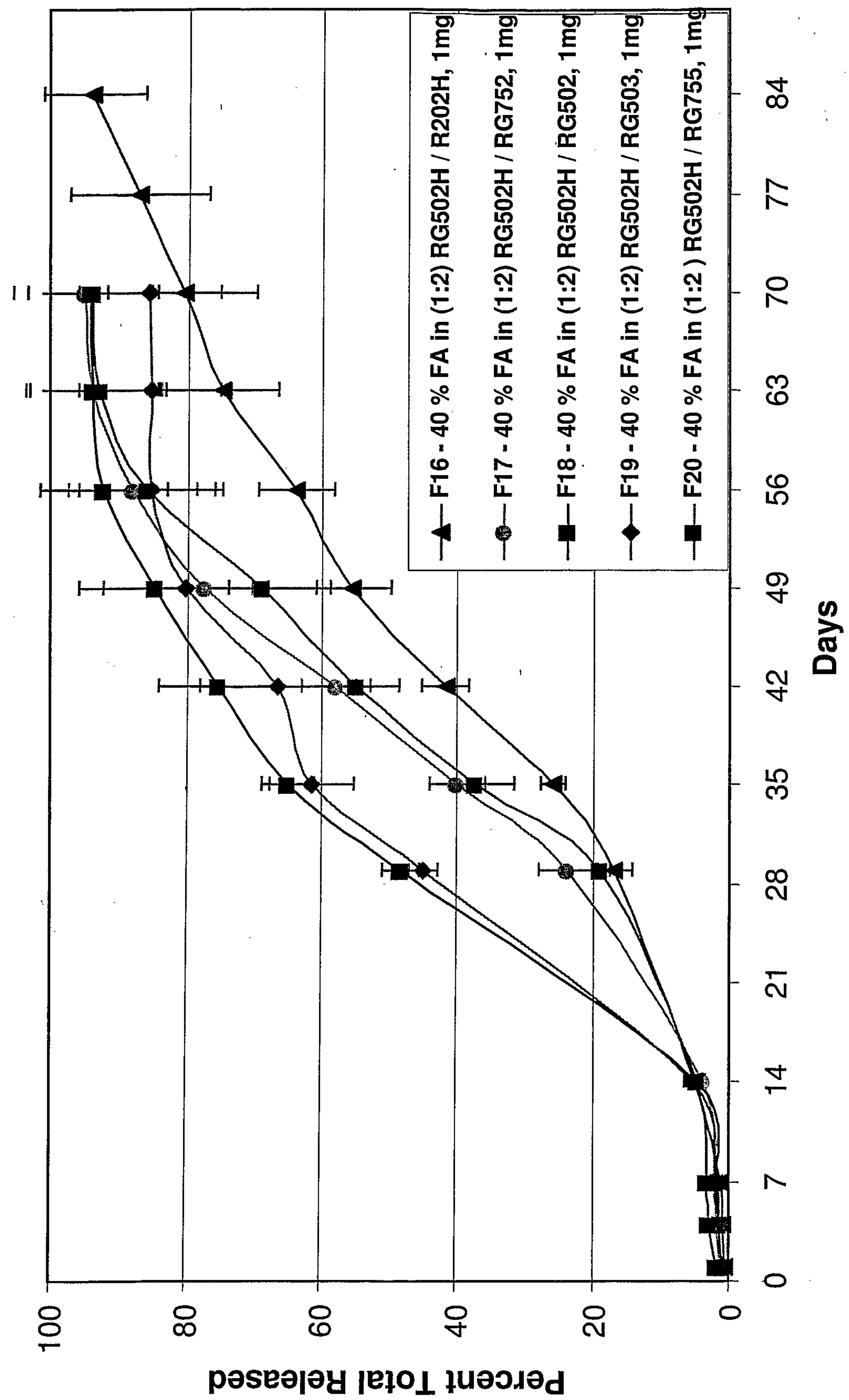


FIG. 2

(Sheet 3 of 25)

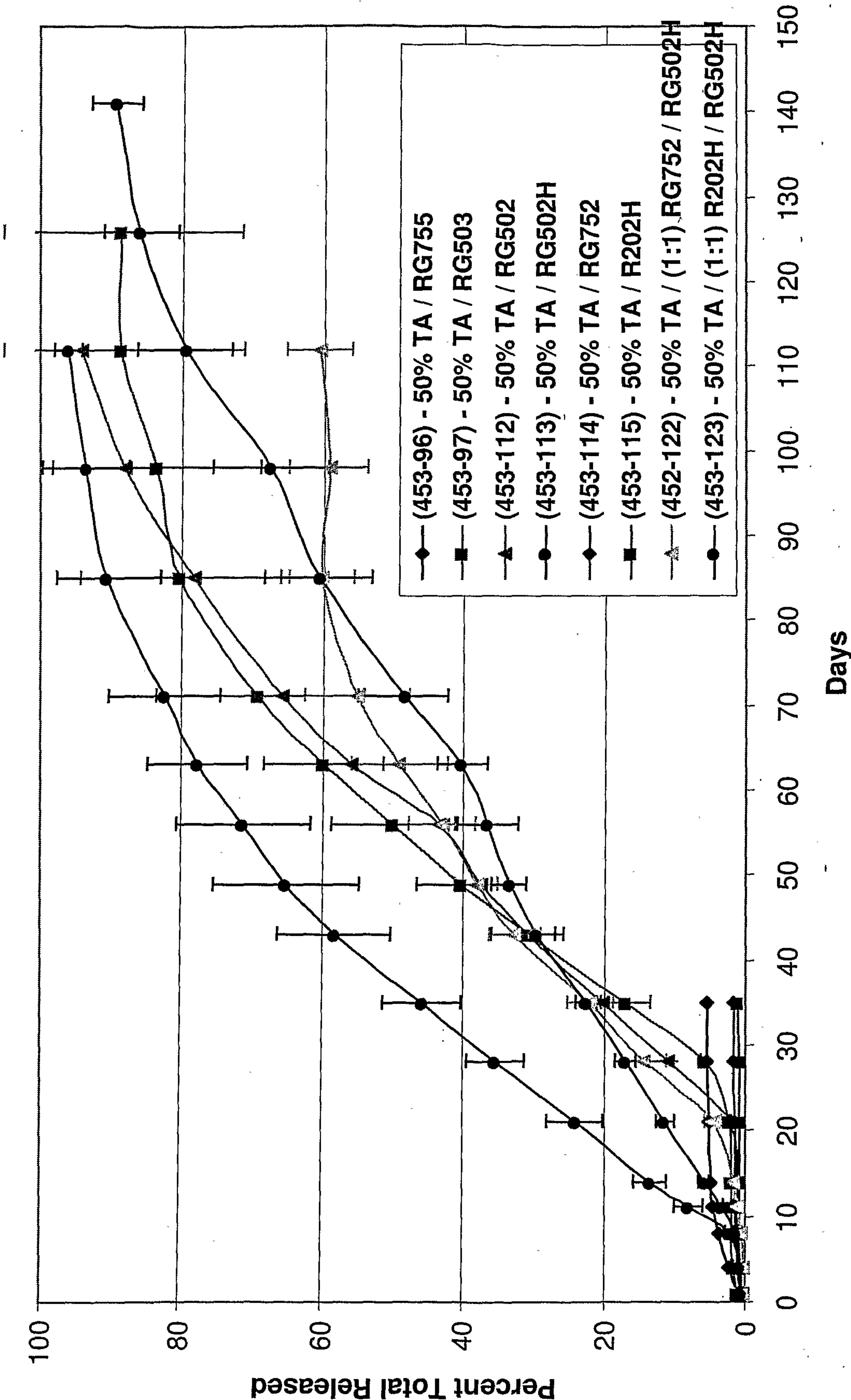


FIG. 3

(Sheet 4 of 25)

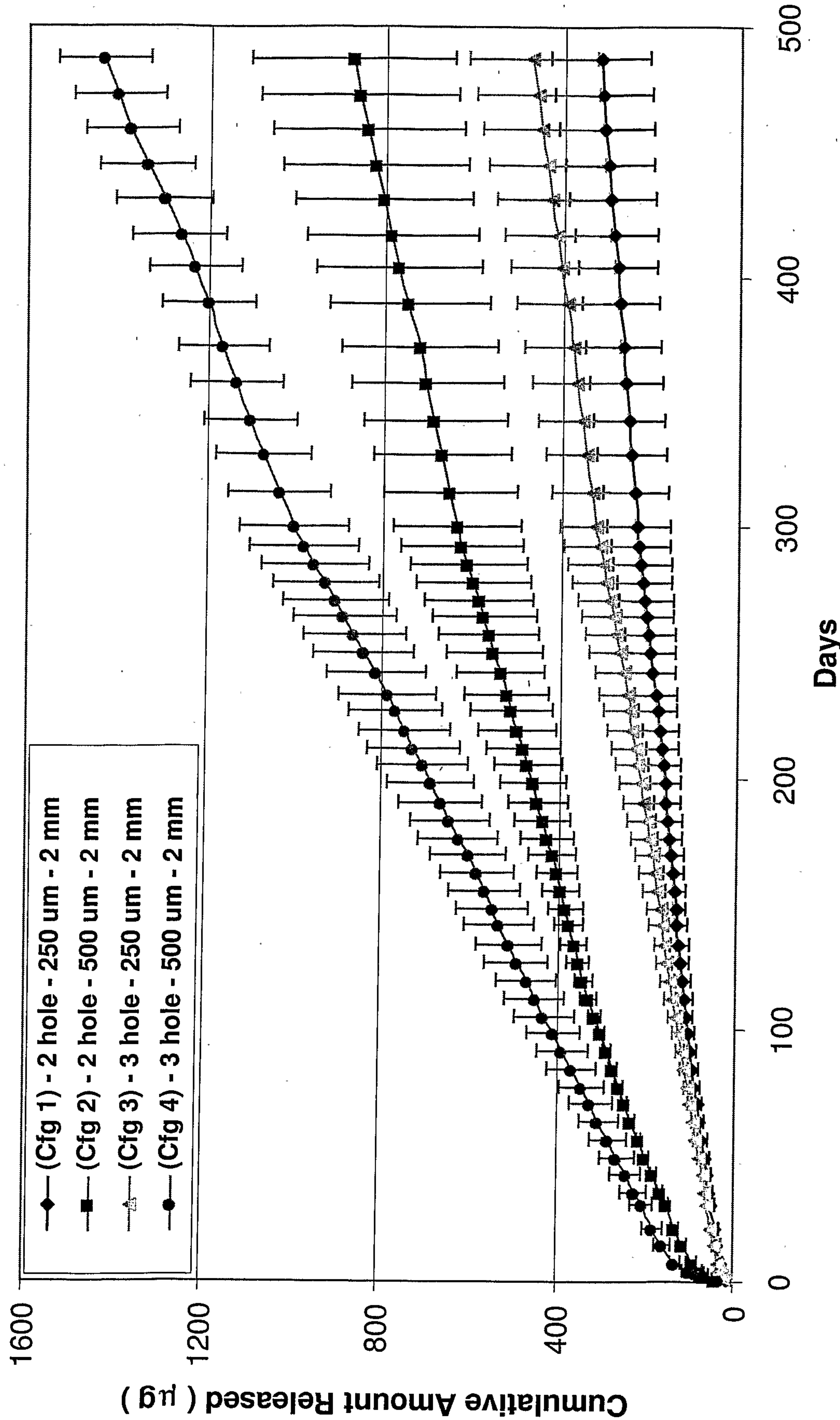


FIG. 4

(Sheet 5 of 25)

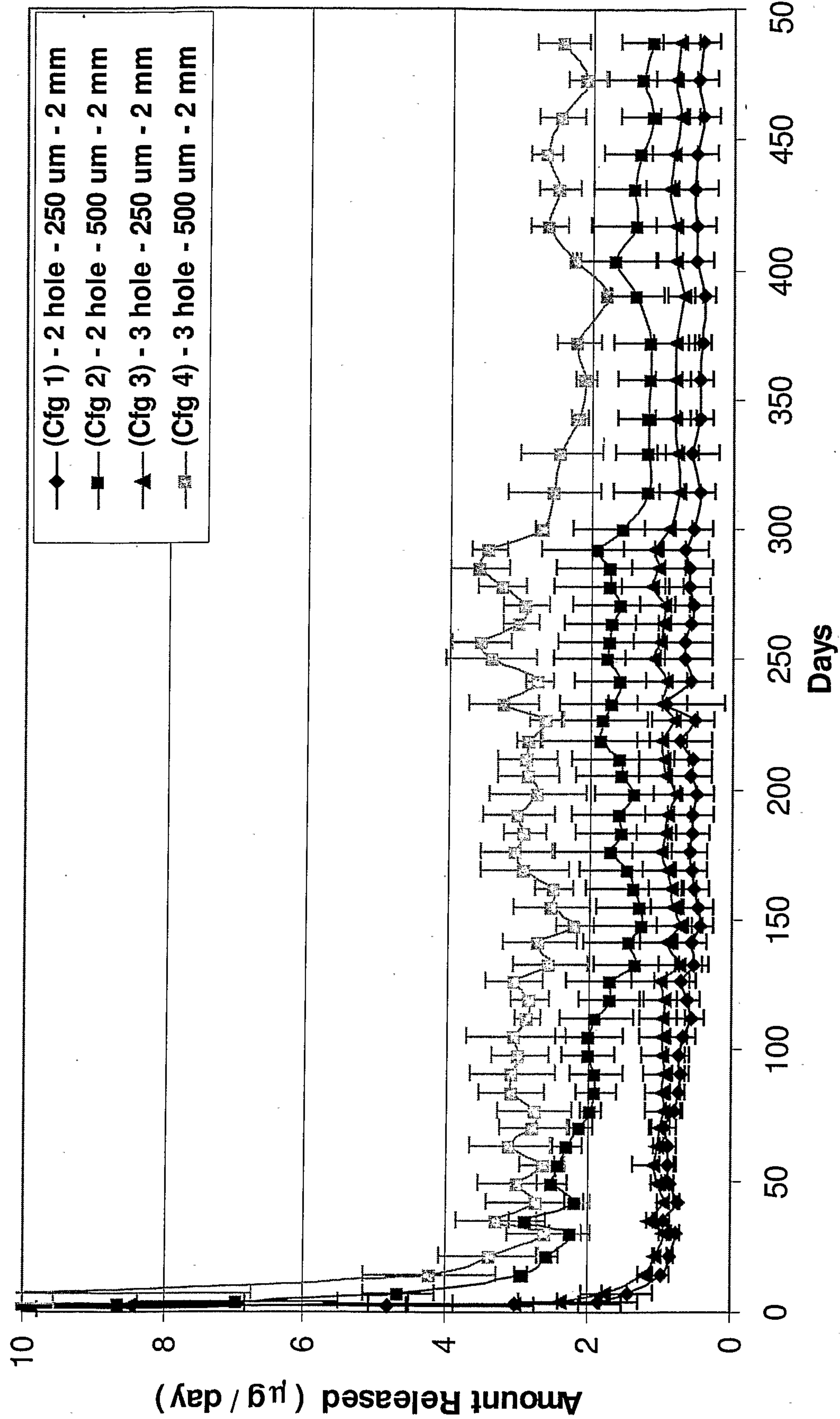


FIG. 5

(Sheet 6 of 25)

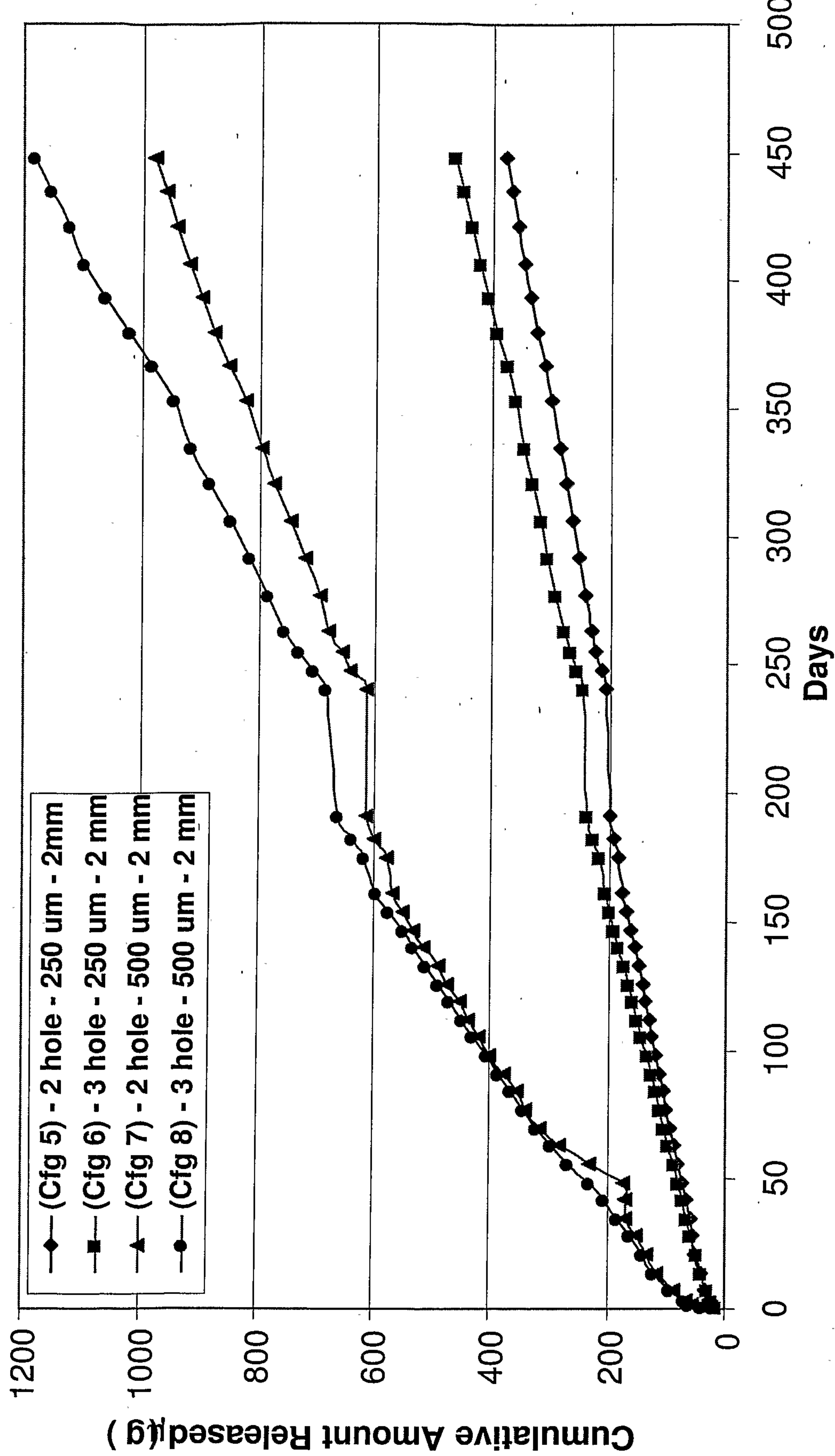


FIG. 6

(Sheet 7 of 25)

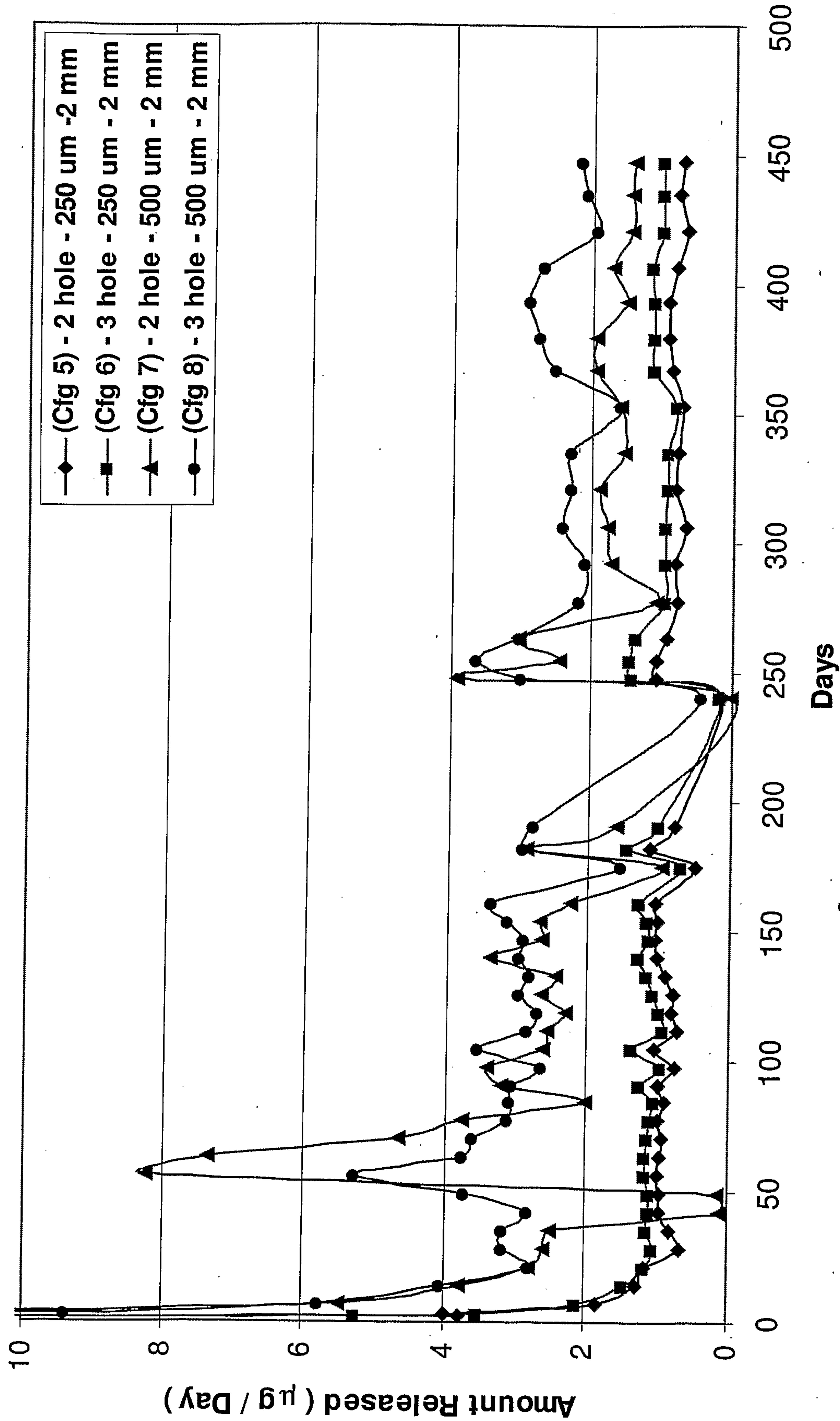


FIG. 7

(Sheet 8 of 25)

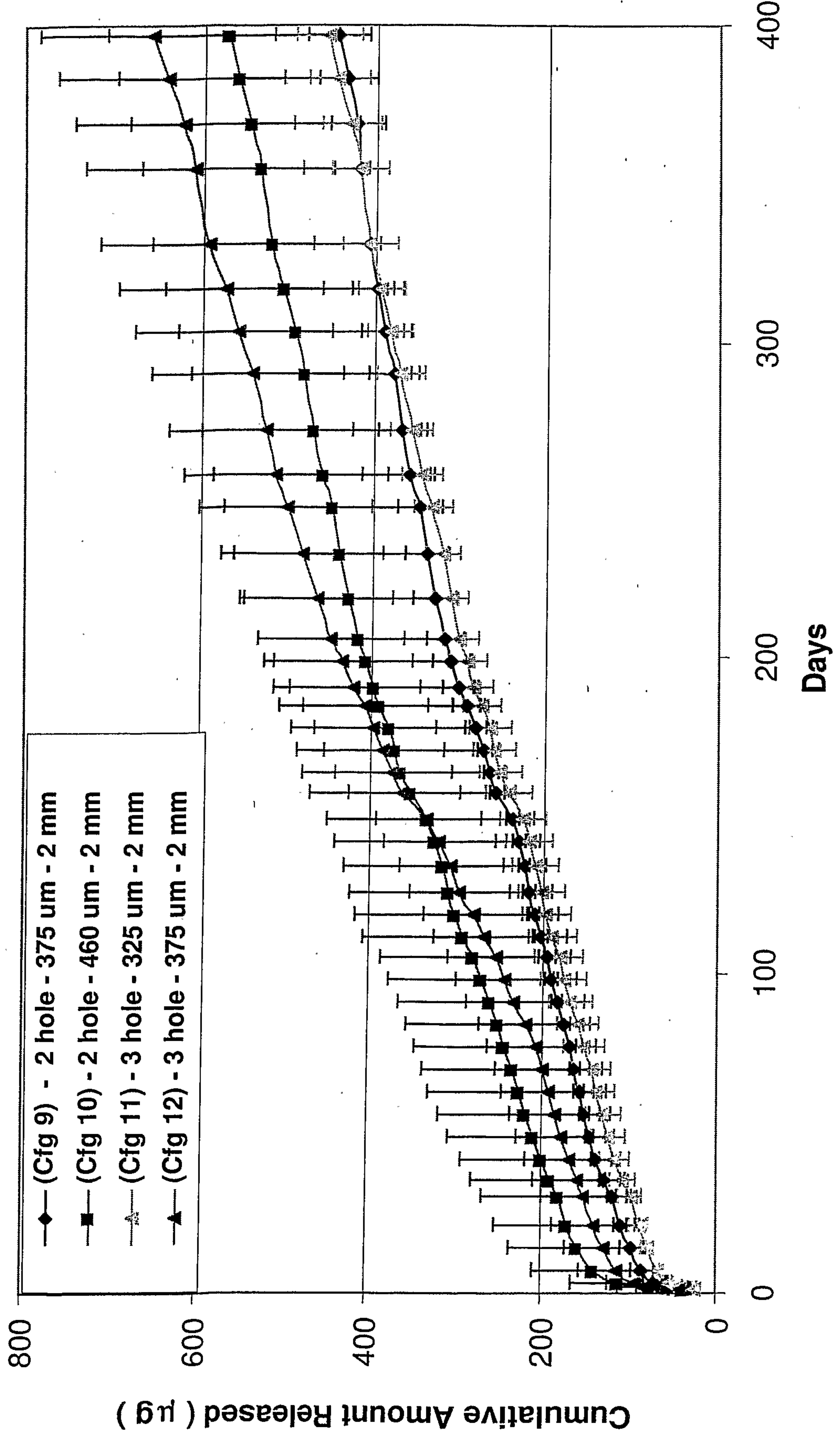


FIG. 8

(Sheet 9 of 25)

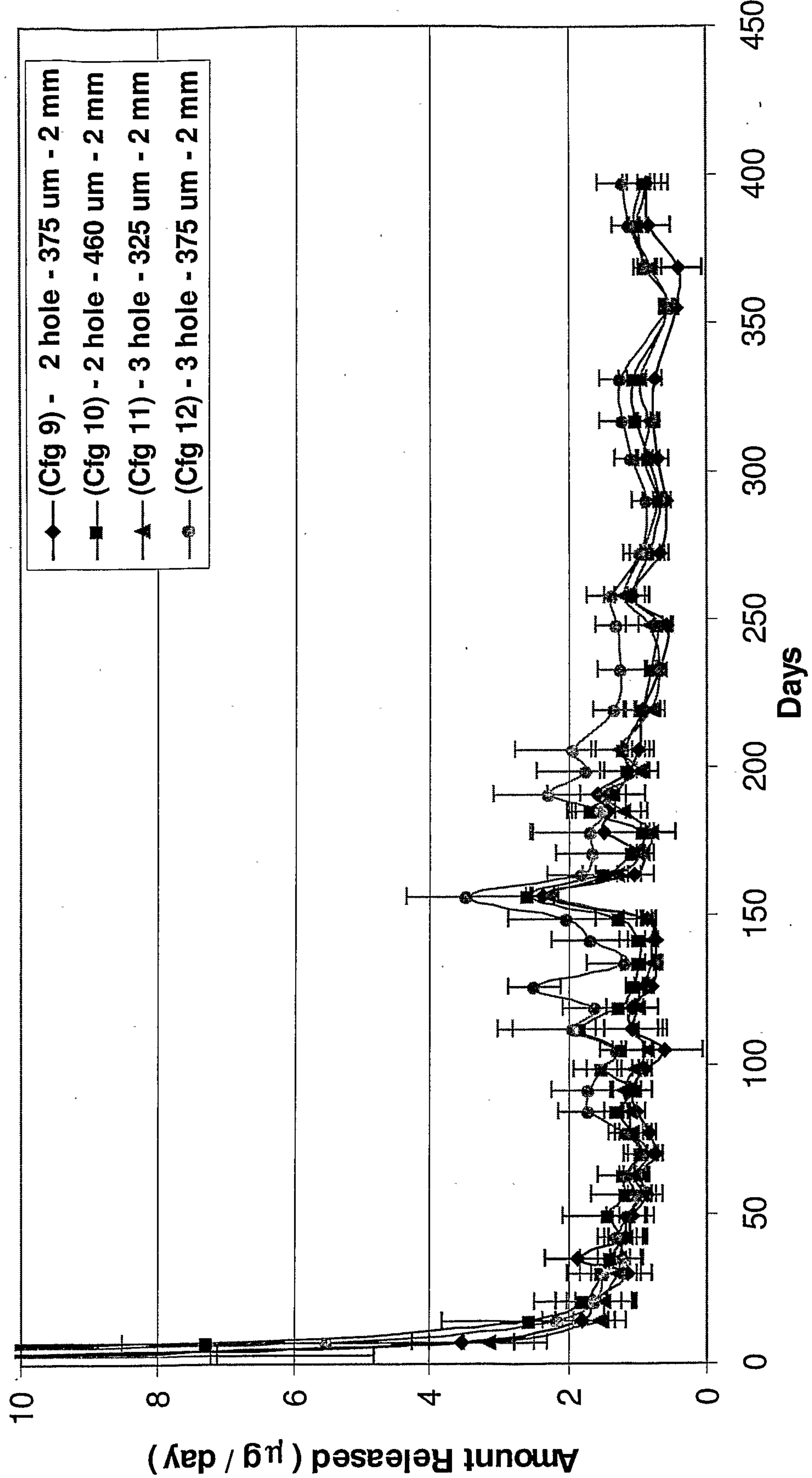


FIG. 9

(Sheet 10 of 25)

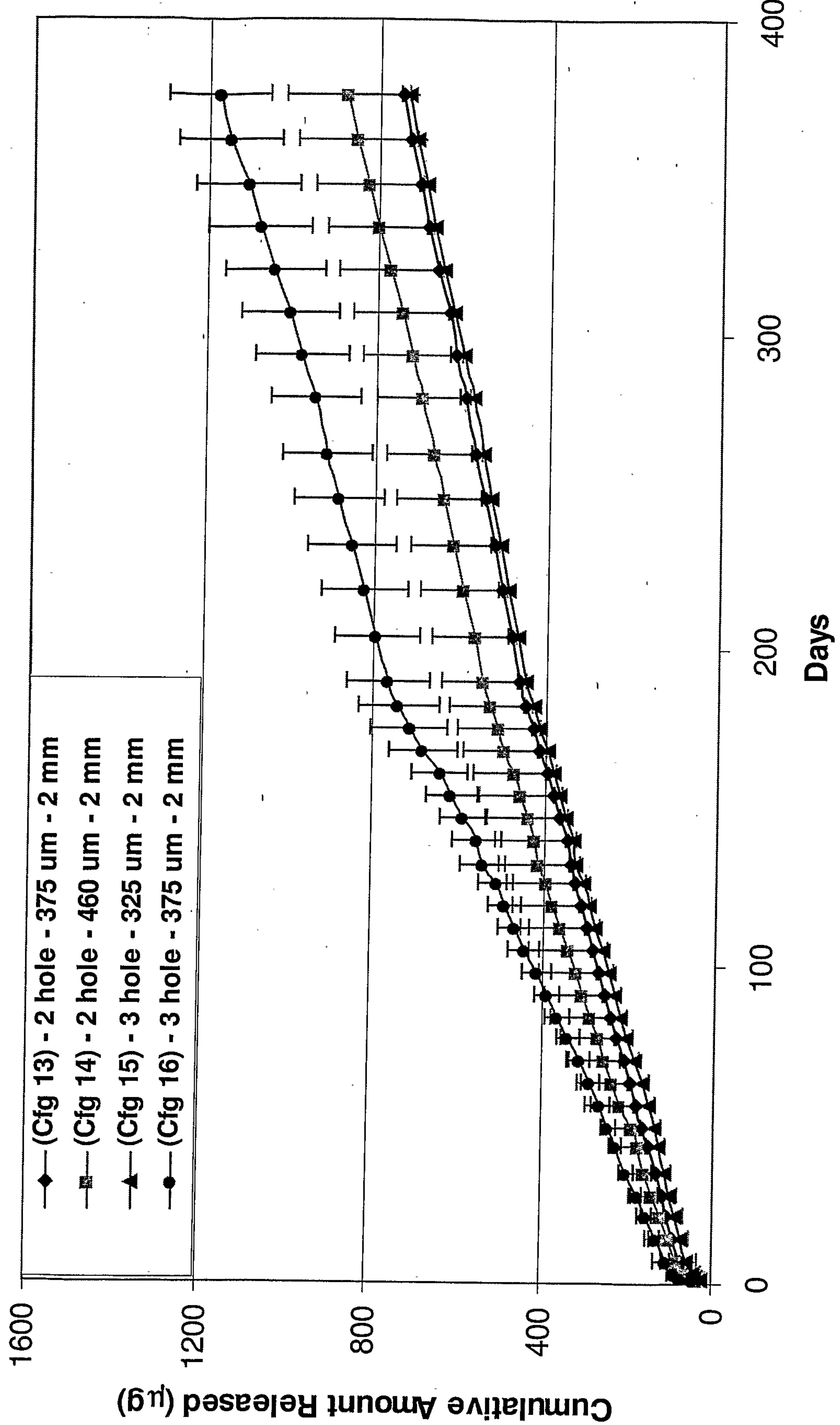


FIG. 10

(Sheet 11 of 25)

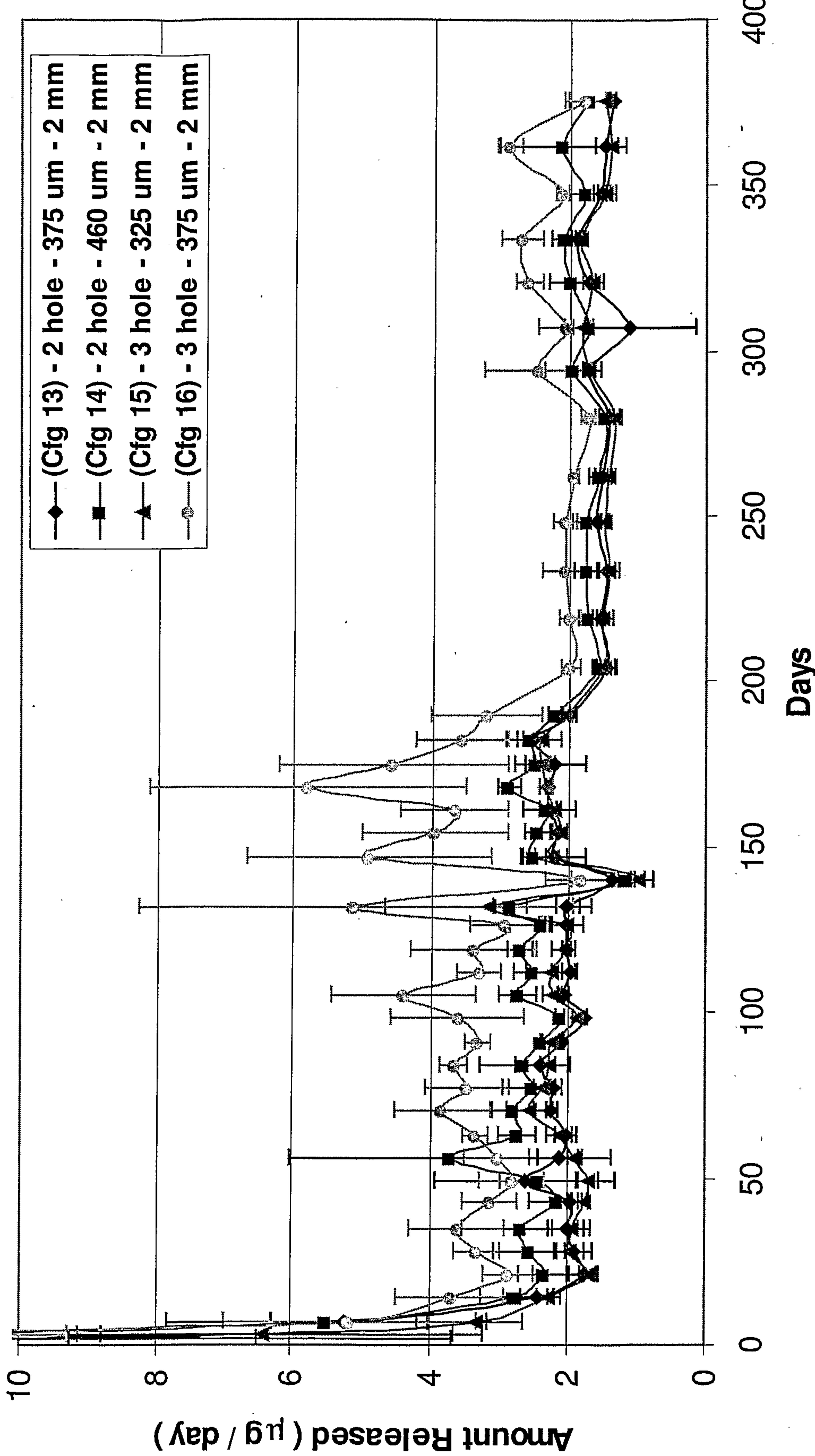


FIG. 11

(Sheet 12 of 25)

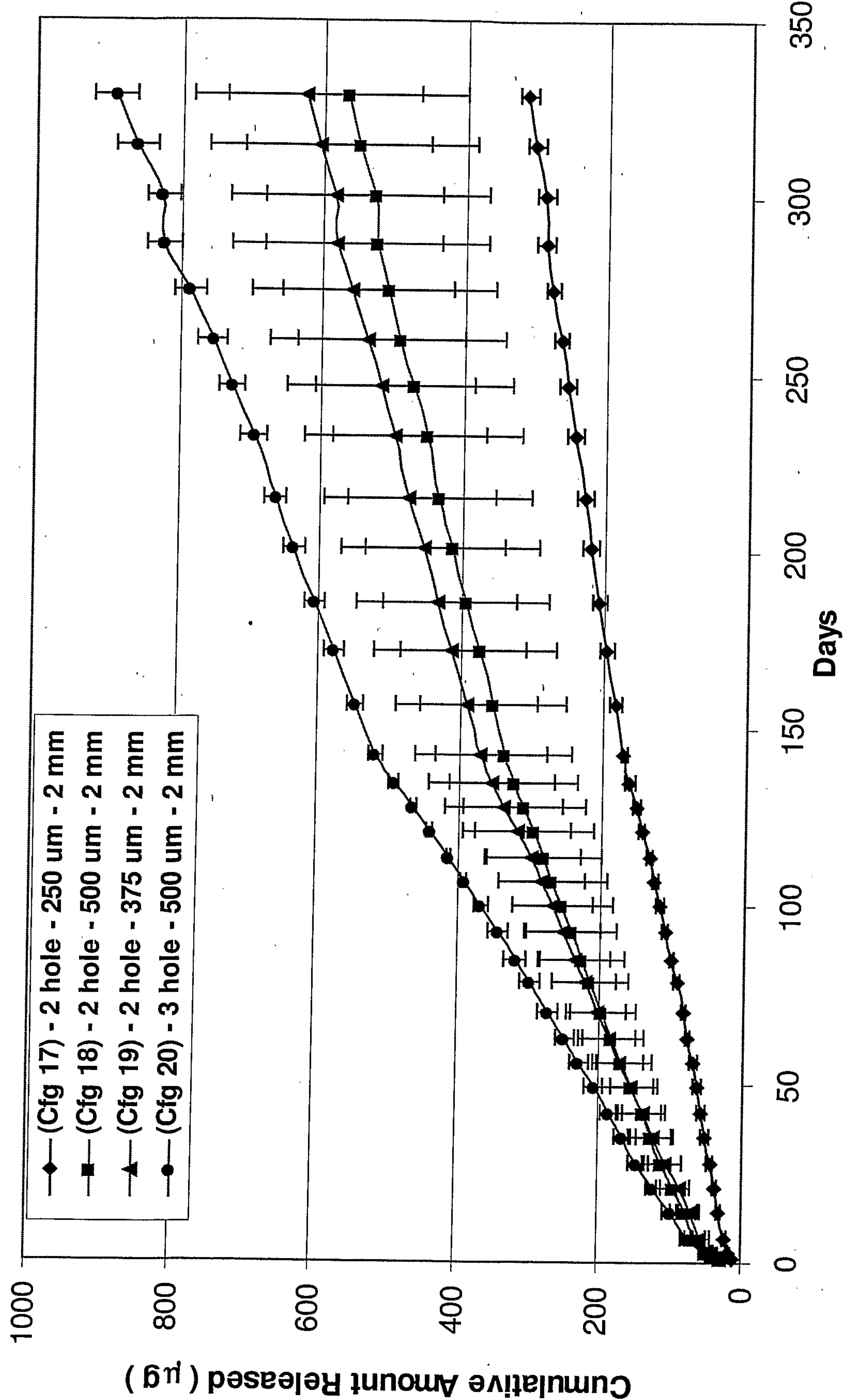


FIG. 12

(Sheet 13 of 25)

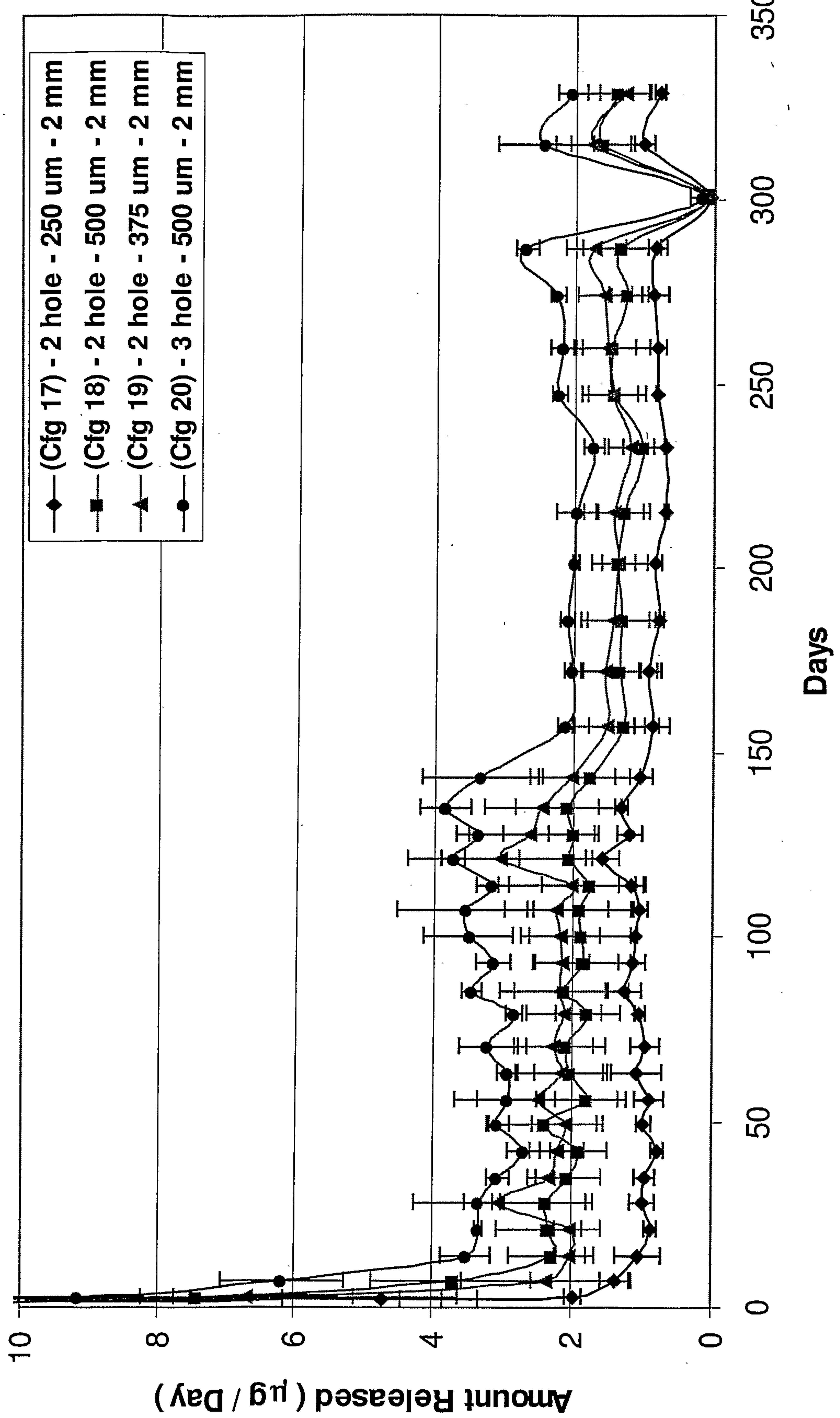


FIG. 13

(Sheet 14 of 25)

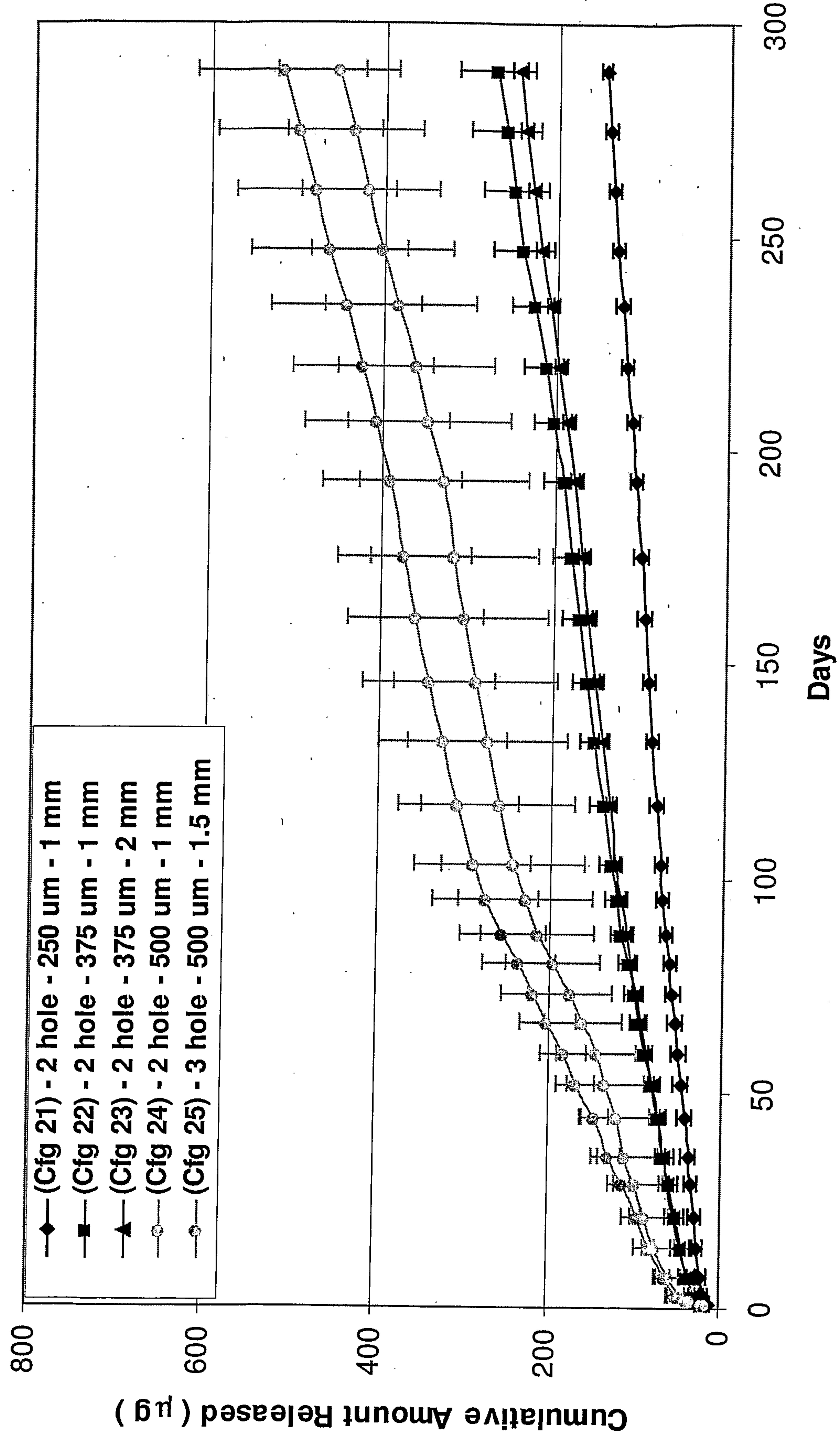


FIG. 14

(Sheet 15 of 25)

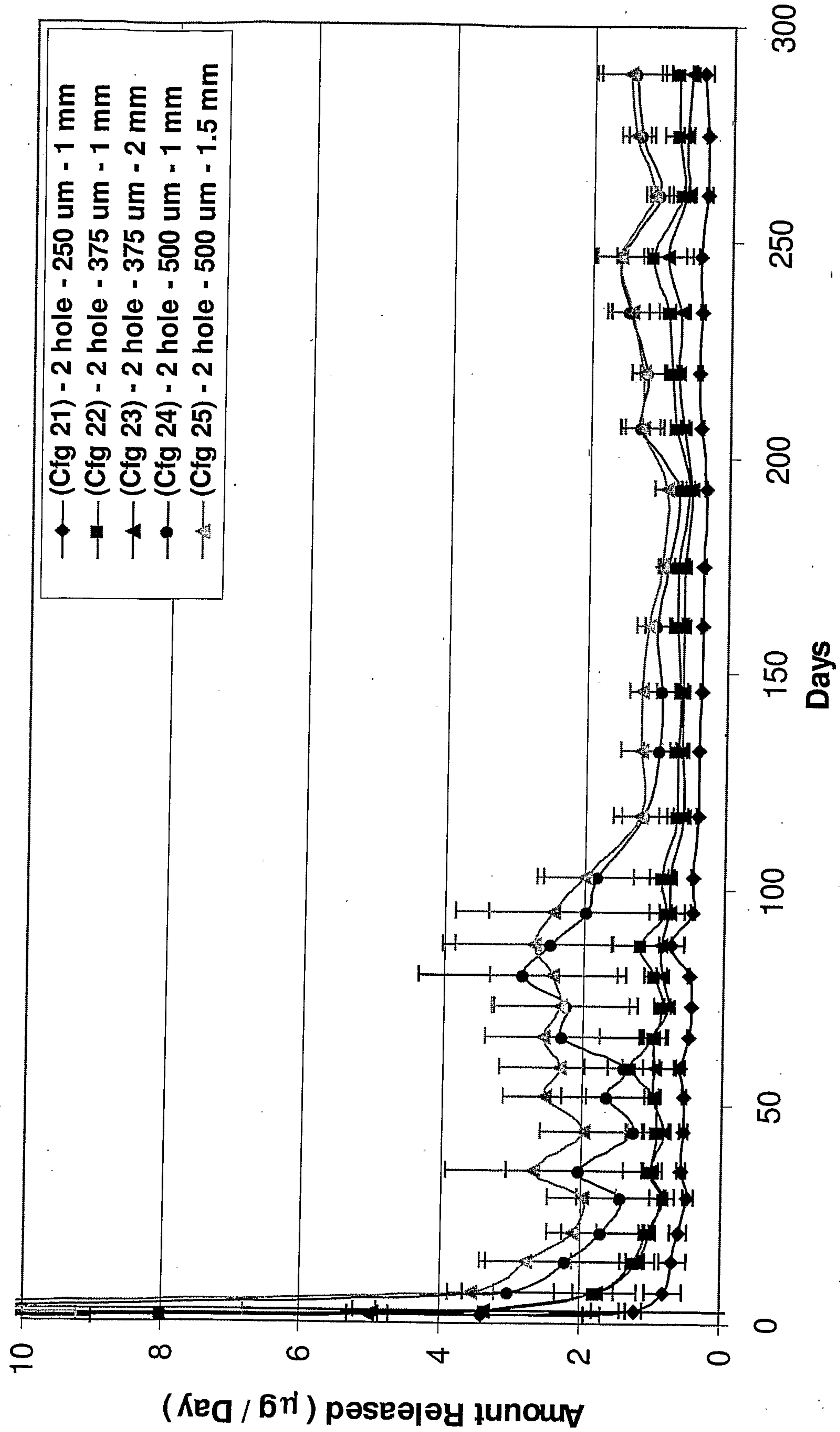


FIG. 15

(Sheet 16 of 25)

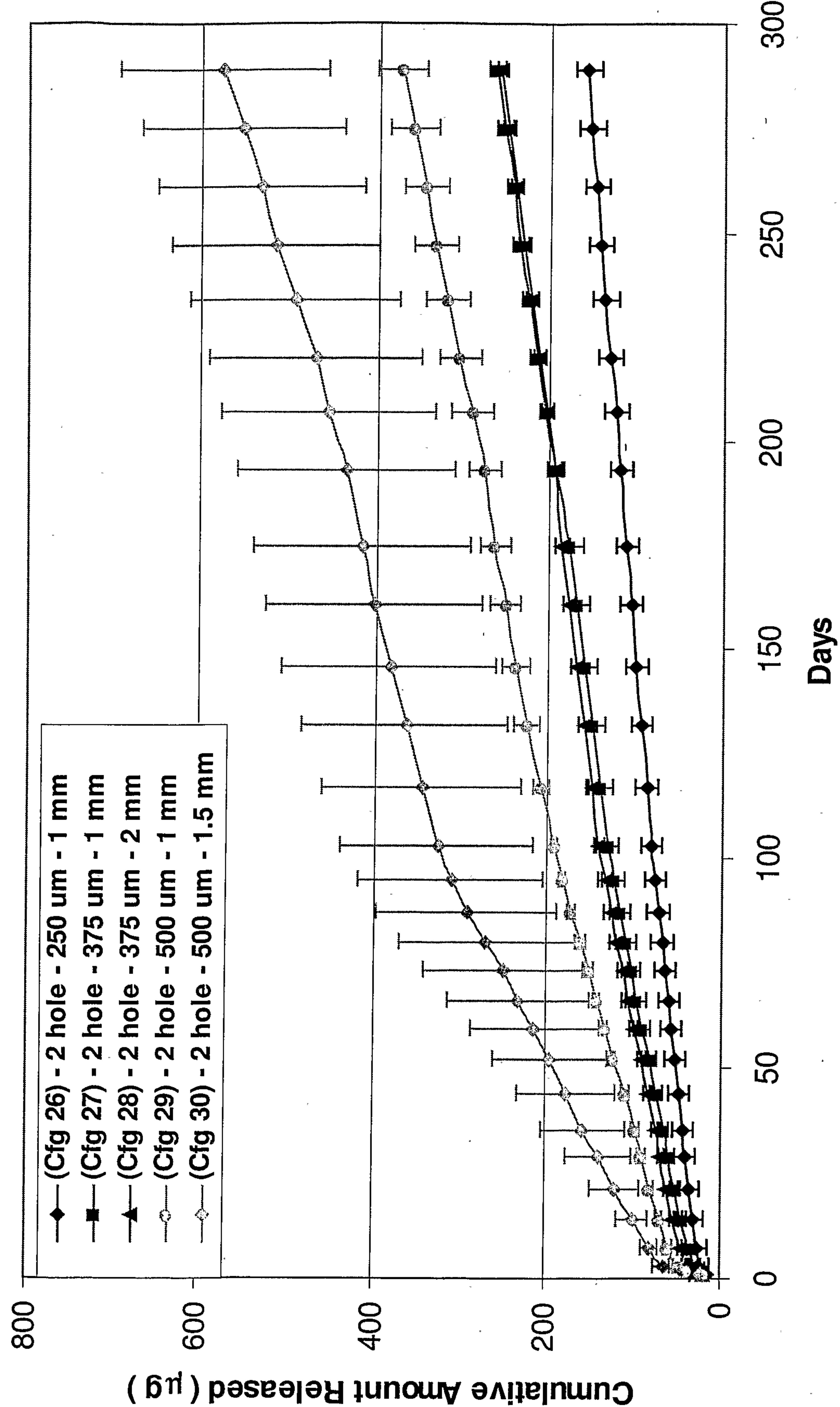


FIG. 16

(Sheet 17 of 25)

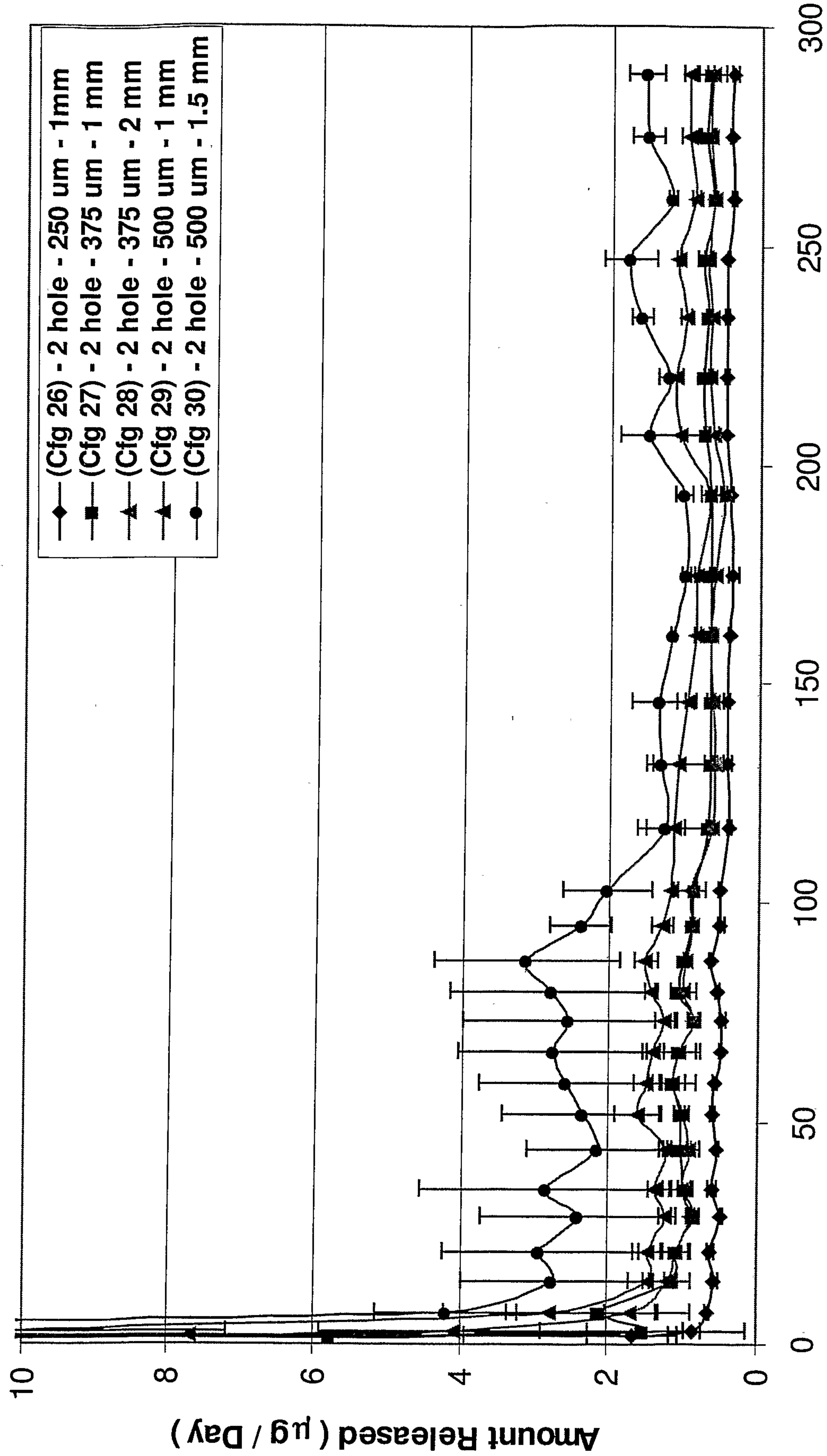


FIG. 17

(Sheet 18 of 25)

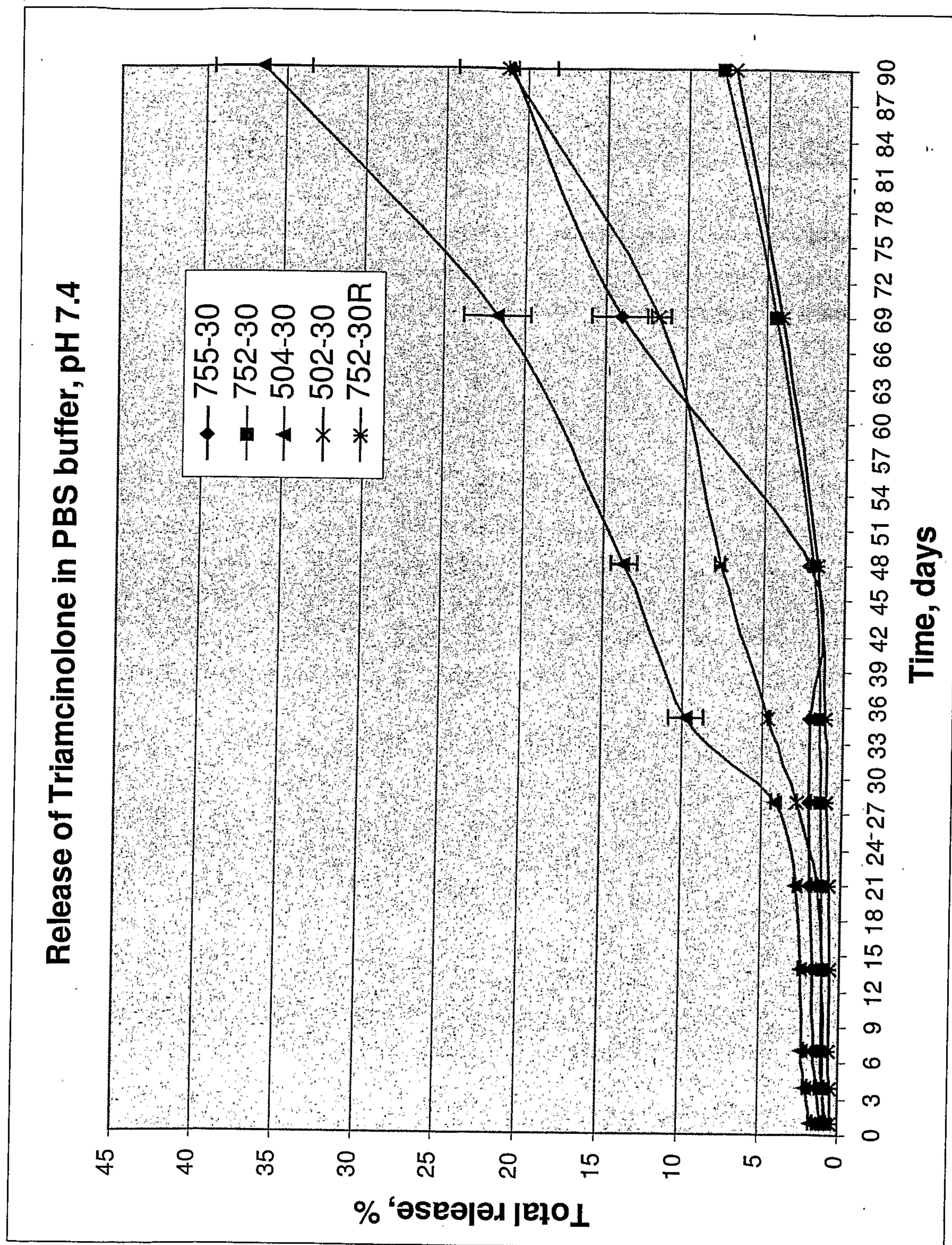


FIG. 18

(Sheet 19 of 25)

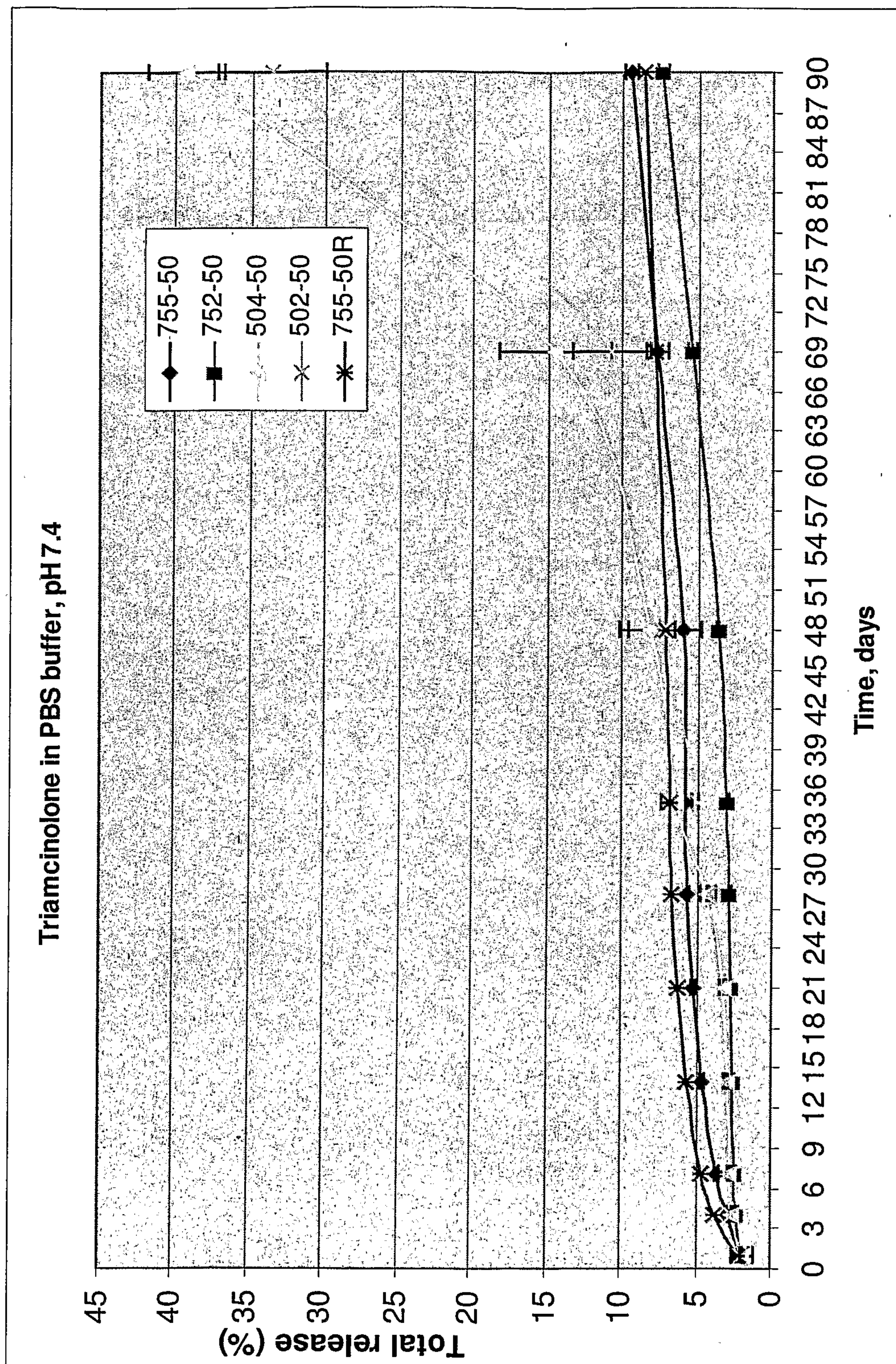


FIG. 19

(Sheet 20 of 25)

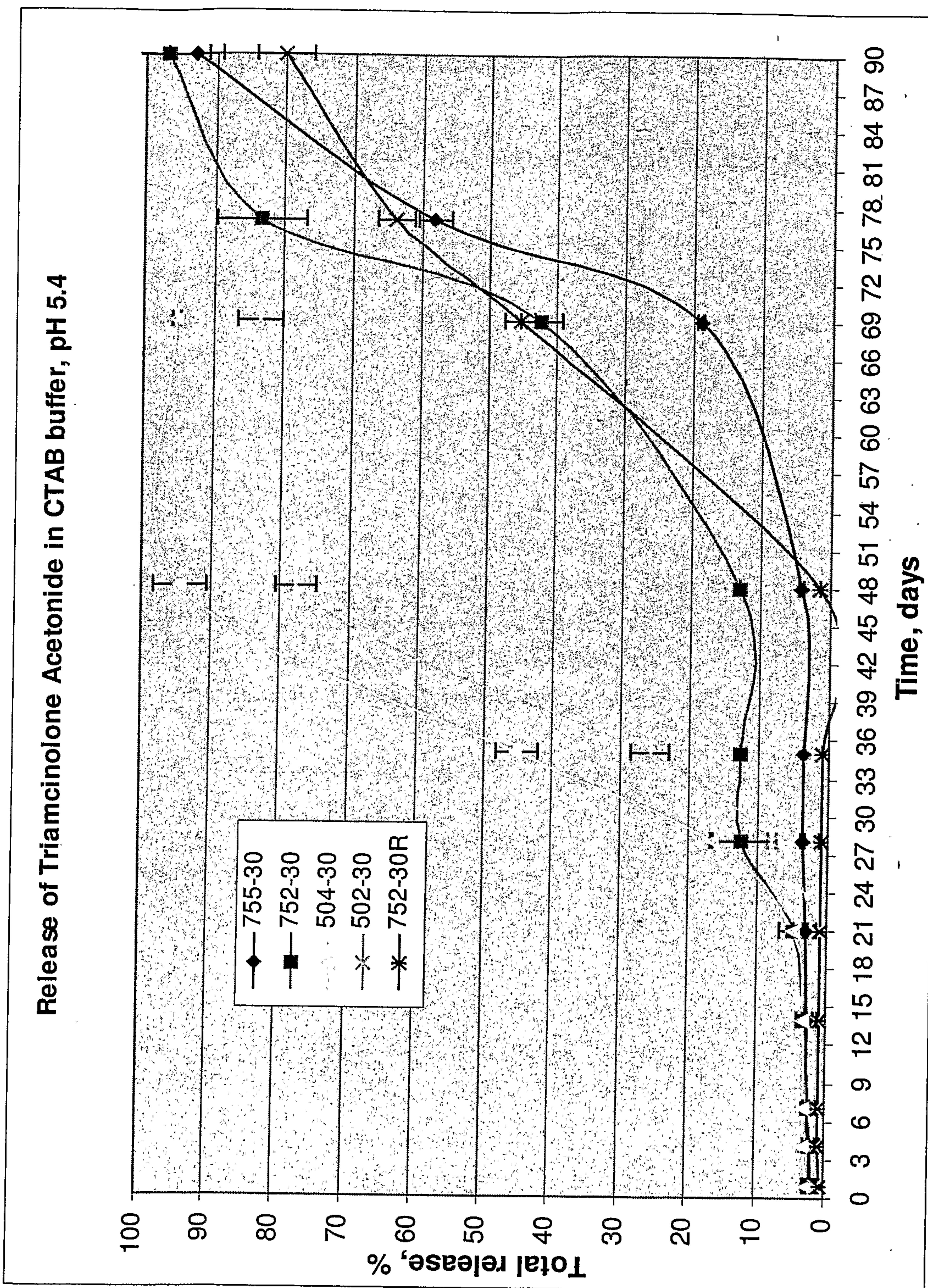


FIG. 20

(Sheet 21 of 25)

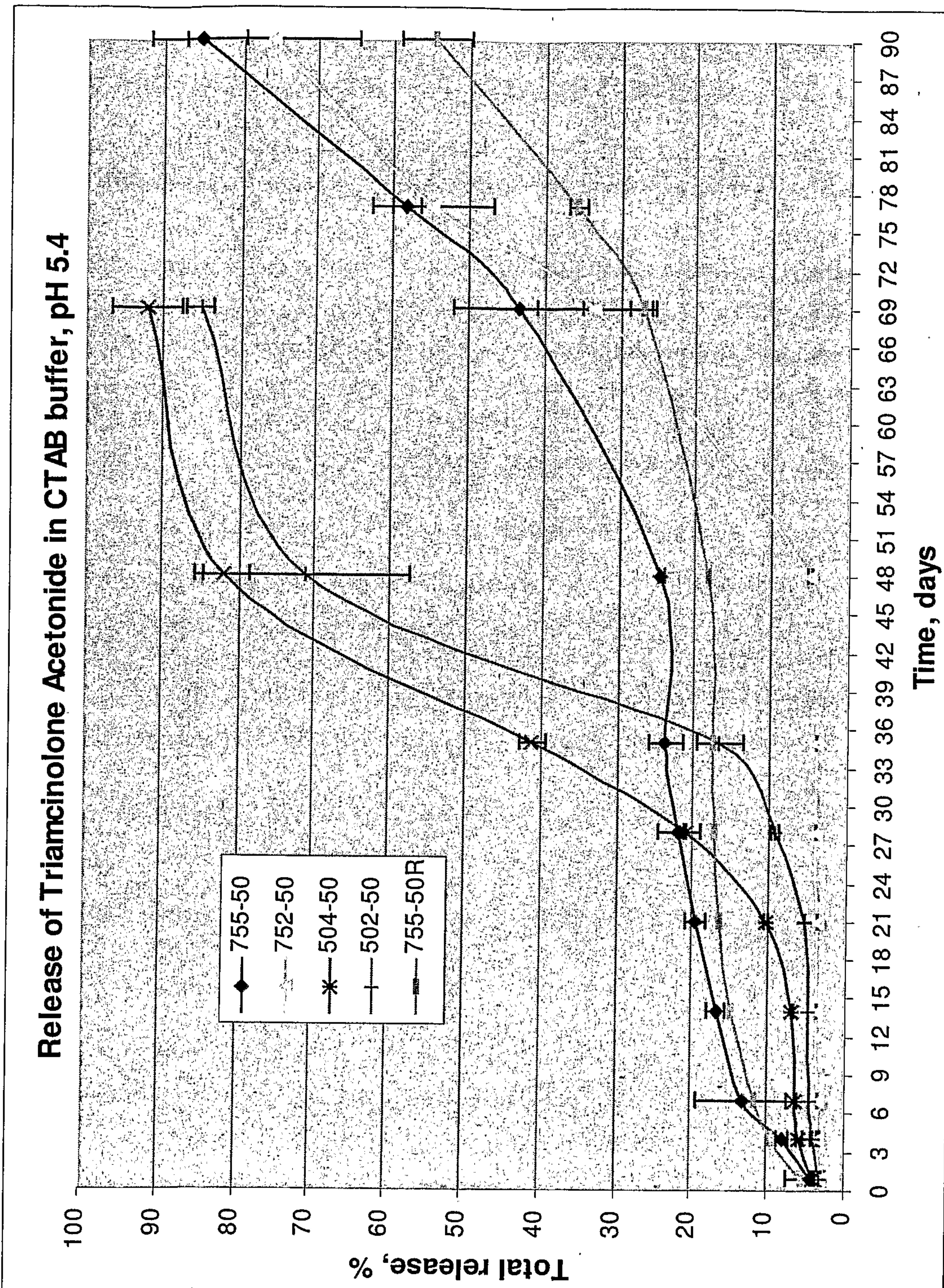


FIG. 21

(Sheet 22 of 25)

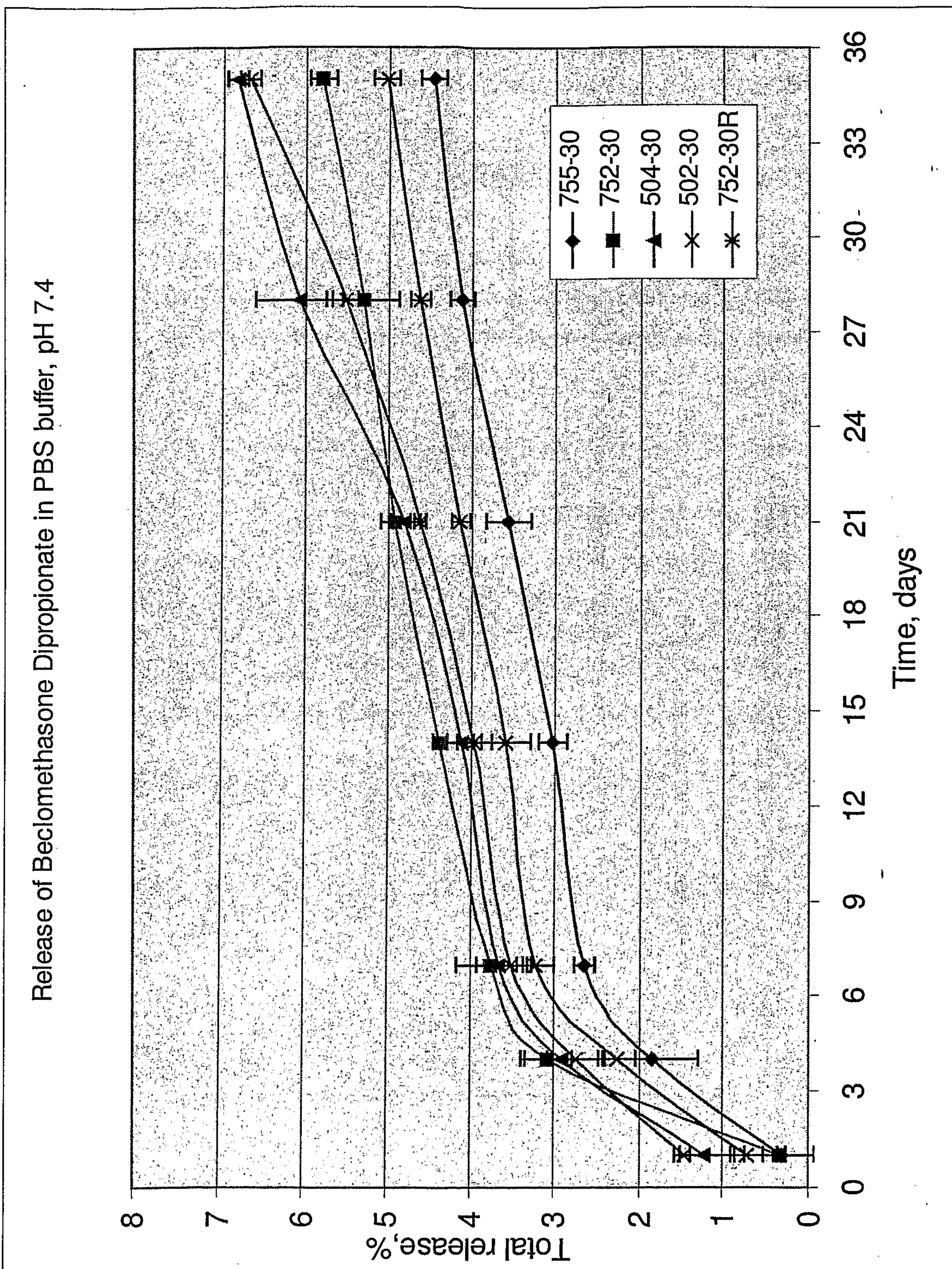


FIG. 22

(Sheet 23 of 25)

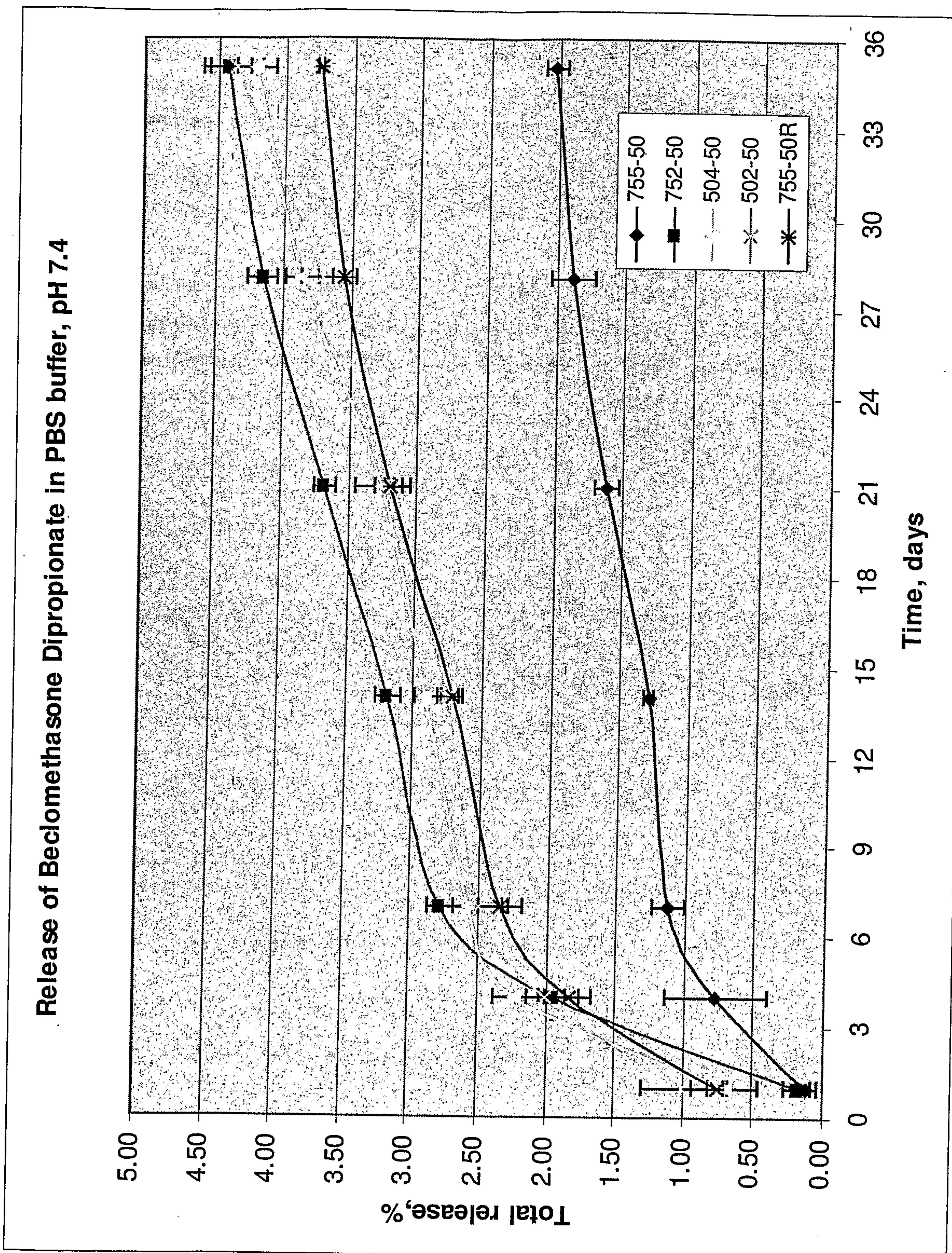


FIG. 23

(Sheet 24 of 25)

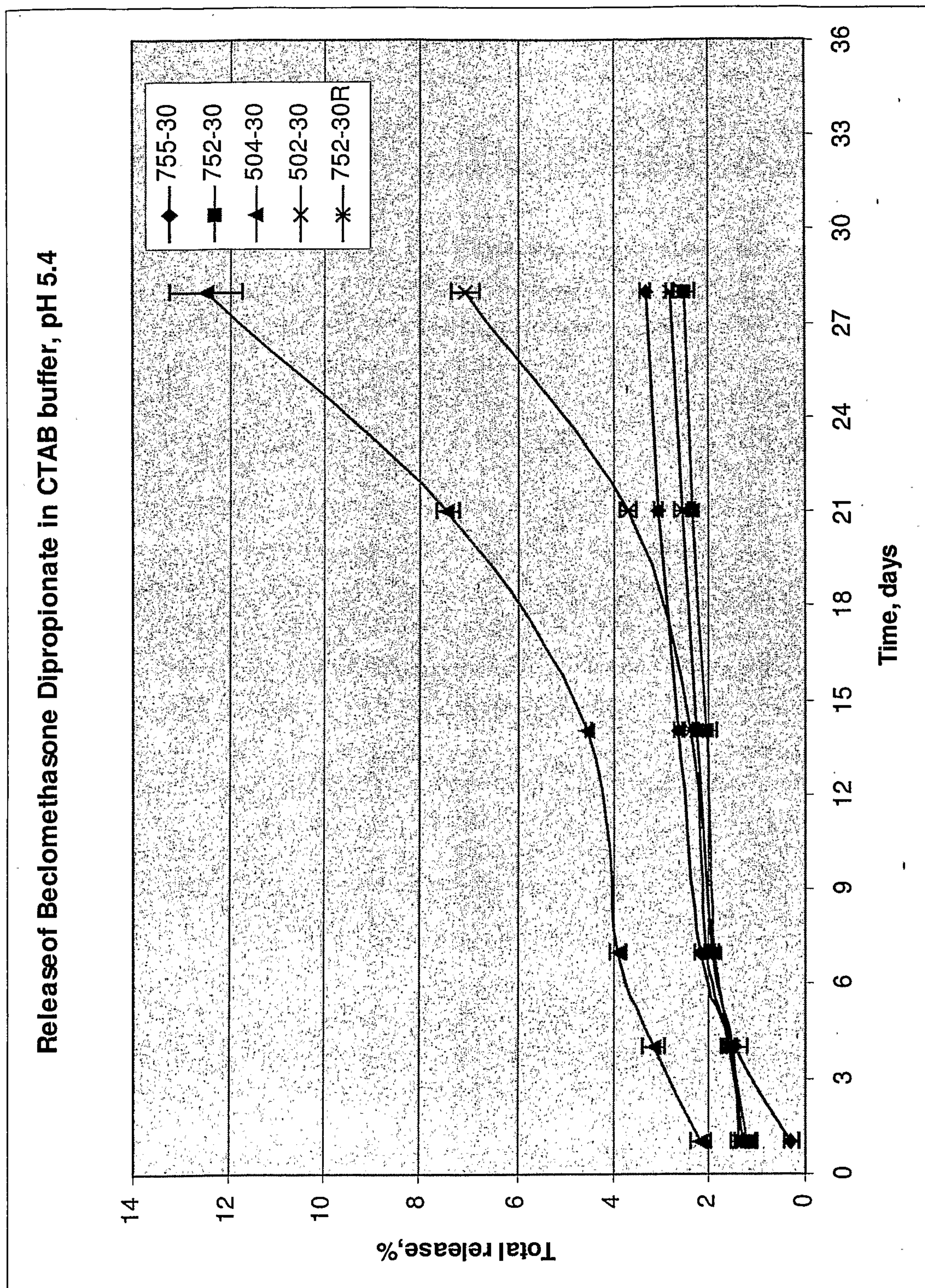


FIG. 24

(Sheet 25 of 25)

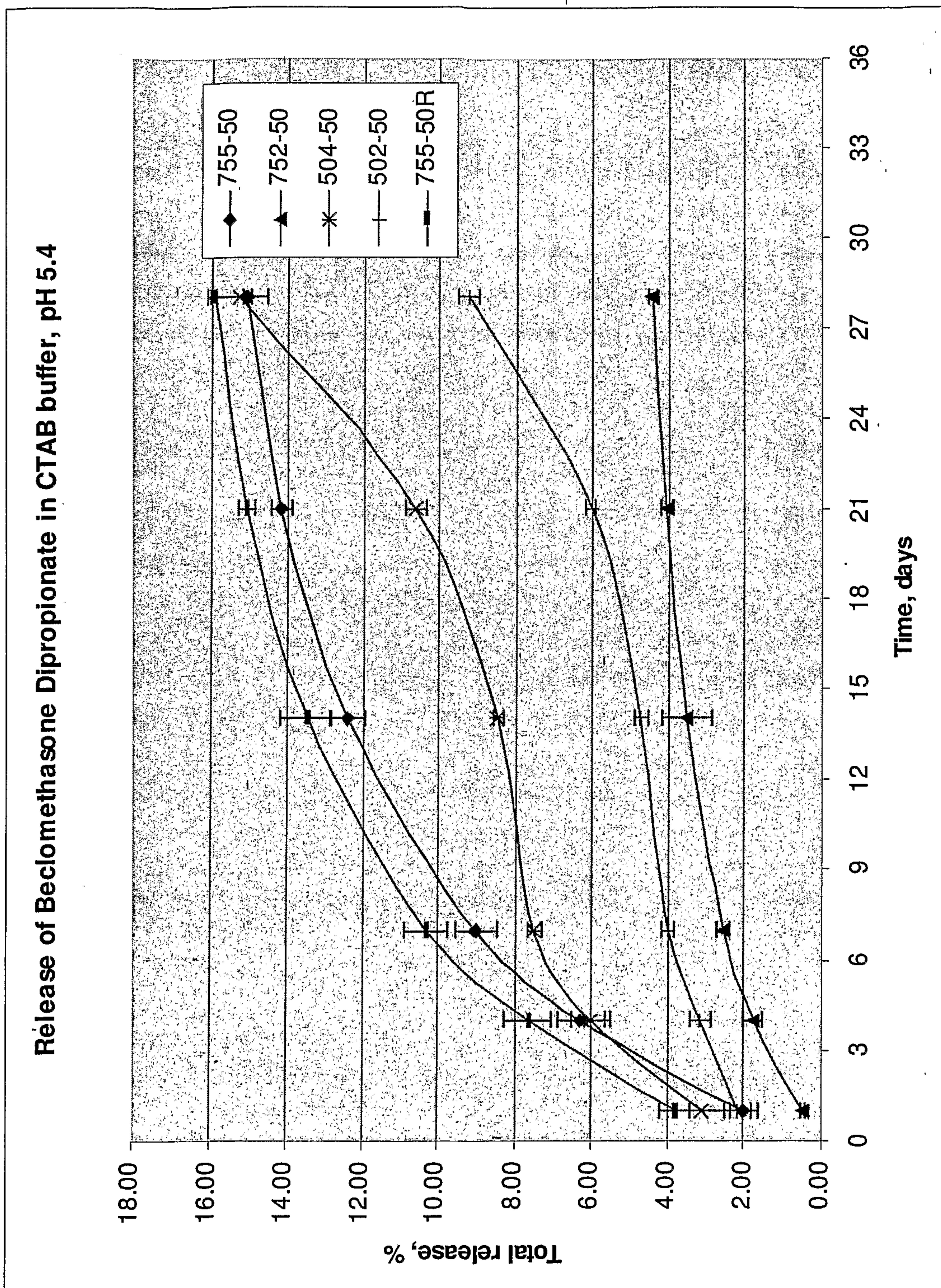


FIG. 25

