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(54) **DEVICE AND METHOD FOR TREATING
CONDITIONS OF A JOINT**

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(57) **ABSTRACT**

An implantable drug delivery system is provided including a mechanical member attachable to a portion of a body, a first chamber having an opening configured to receive a sustained release device, a sustained release device, and a removably attachable retainer for retaining the sustained release device in the first chamber. A method for administering a drug to a joint is provided including the steps of positioning a mechanical member in or adjacent a bone, the mechanical member configured to hold a sustained release drug delivery device bearing at least one drug, and outputting the at least one drug from the sustained release drug delivery device at a substantially controlled rate. Also provided is a sustained release device intraarticularly implantable into a joint to deliver a therapeutically effective compound within a synovial capsule of the joint such that, in one aspect, the synovial fluid concentration of the compound is greater than the plasma concentration of the compound during the prolonged lifetime of the device, thereby eliminating unwanted systemic side effects and the need for frequent and repeated administrations.

[FA] Plasma vs Synovial Fluid in Sheep

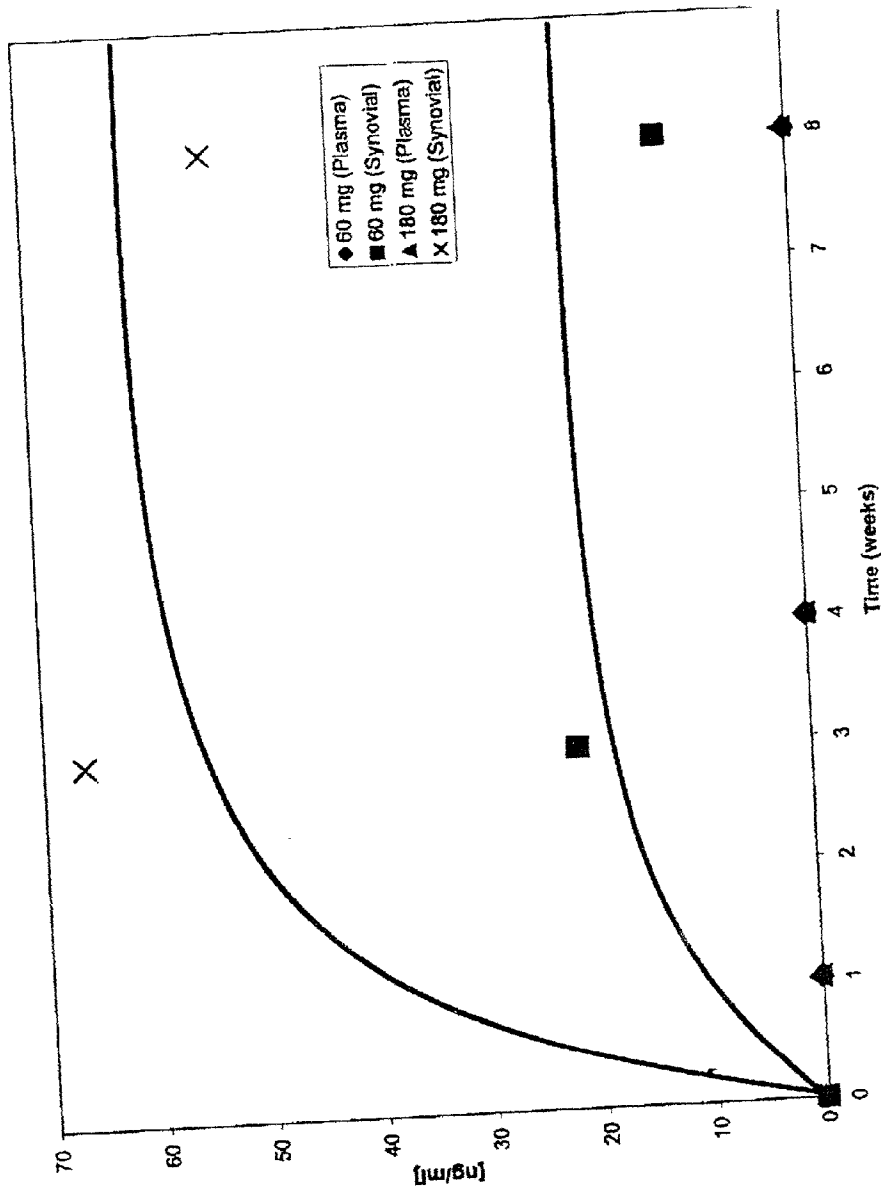


FIG. 1

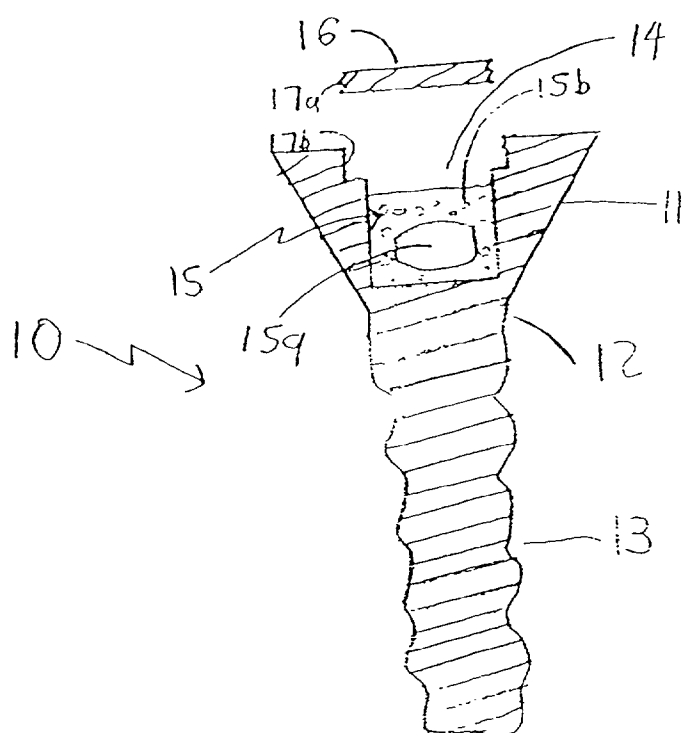


FIG. 2A

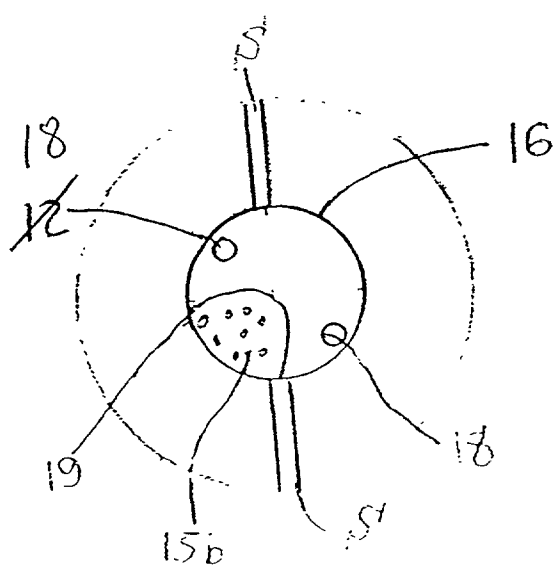


FIG. 2B

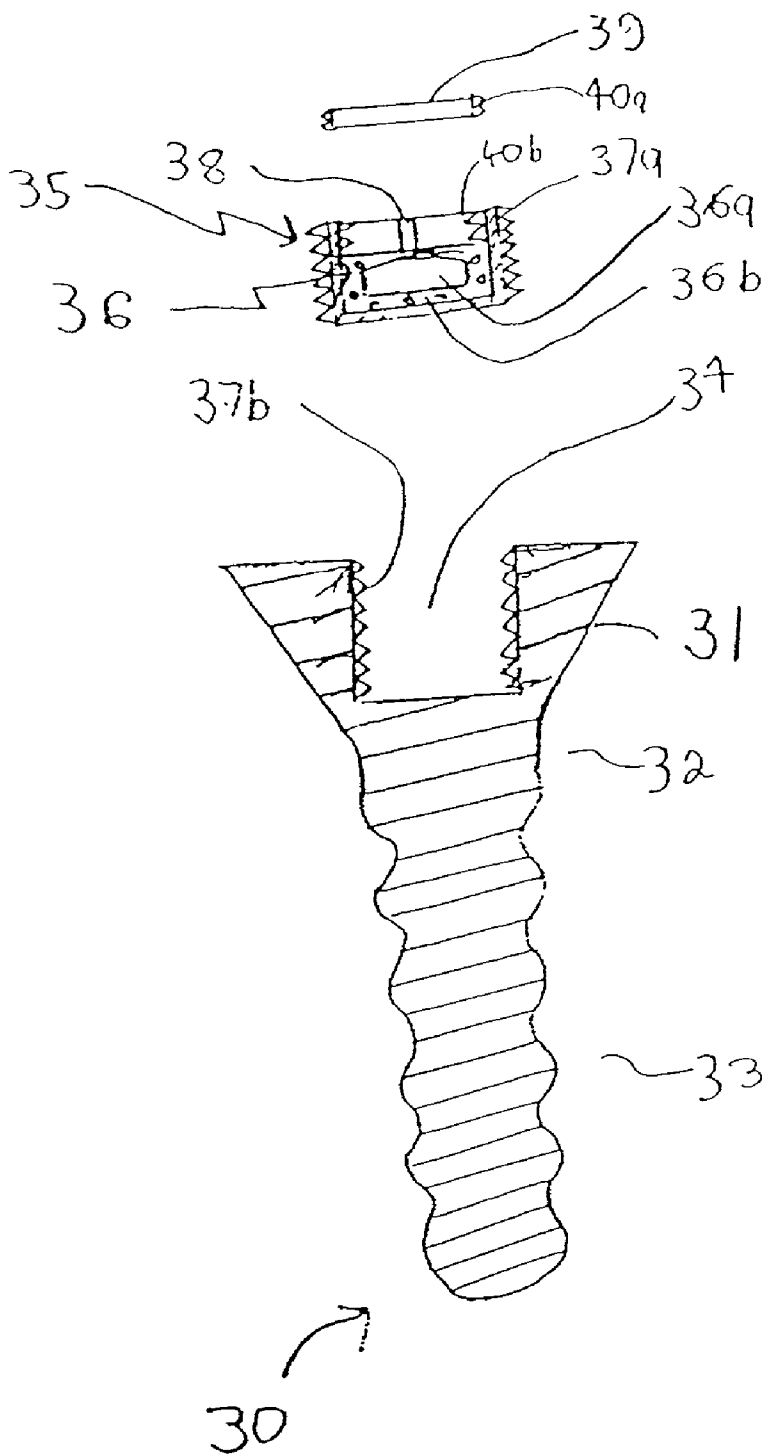


FIG. 3

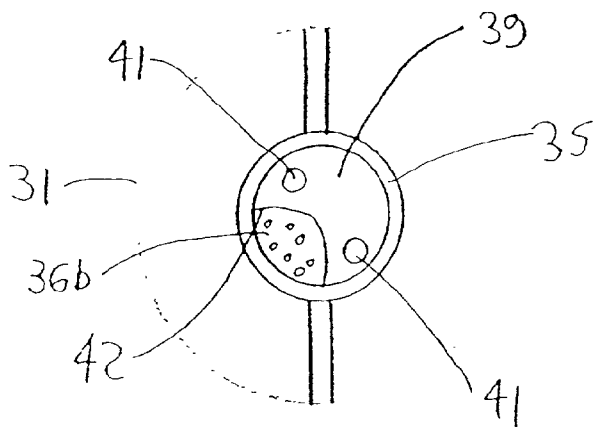


FIG. 4

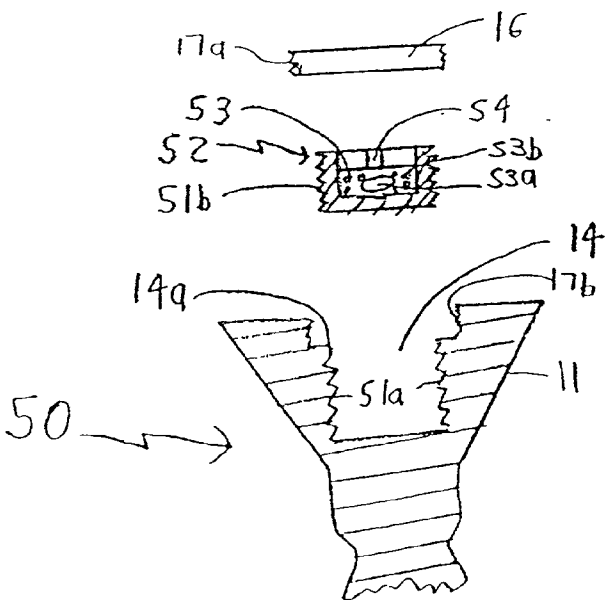


FIG. 5

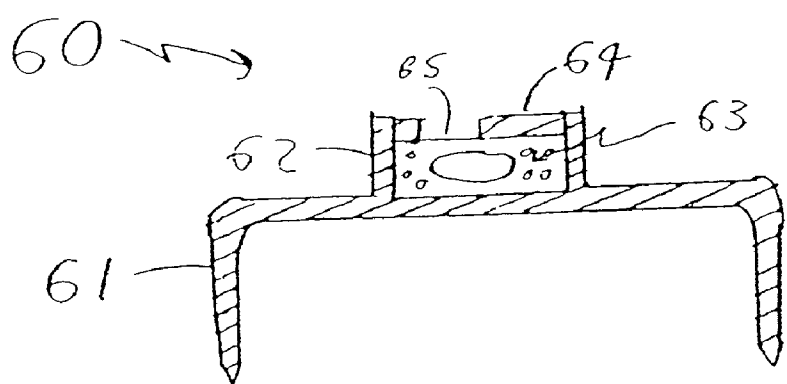


FIG. 6

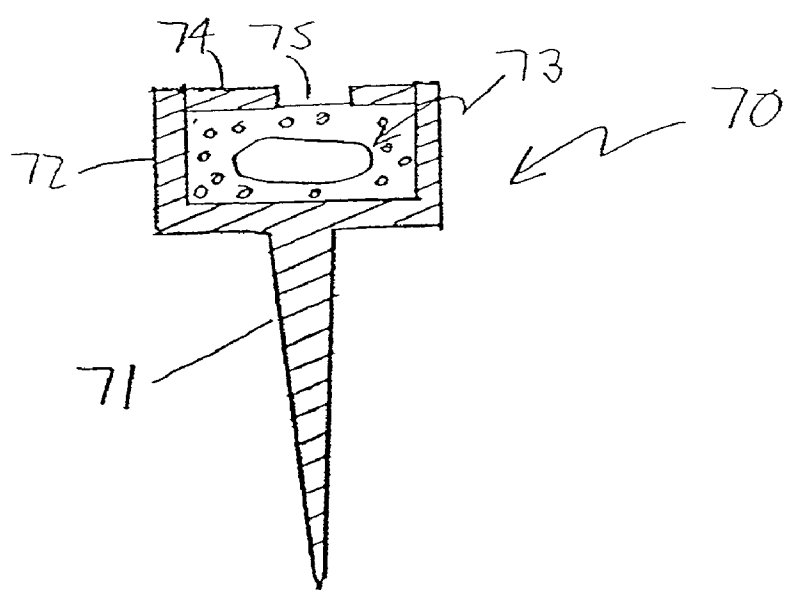


FIG. 7

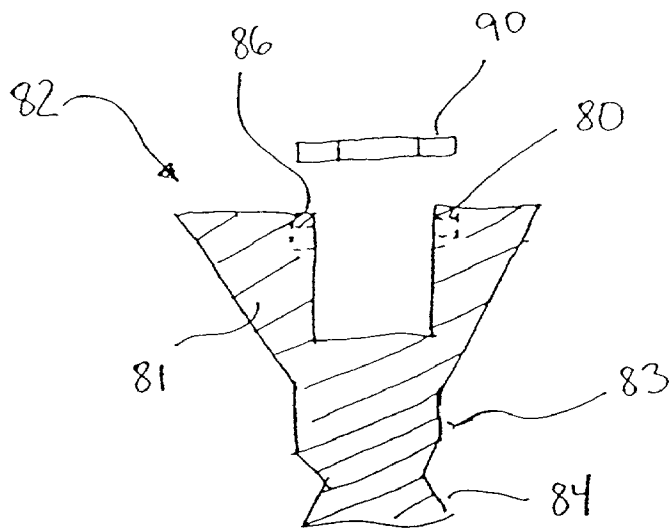


FIG. 8

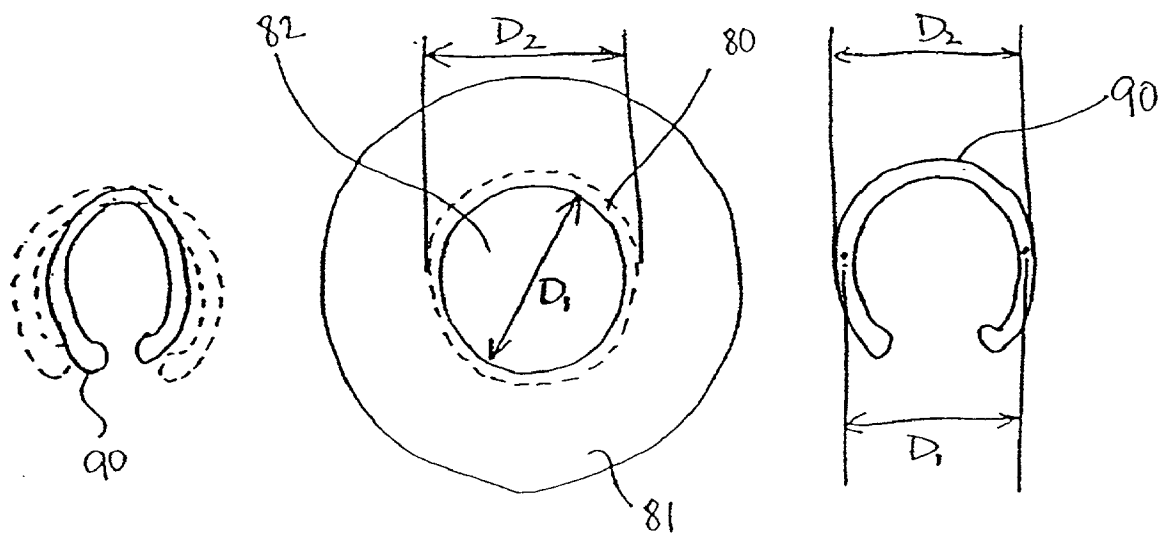


FIG. 9B

FIG. 9A

FIG. 9C

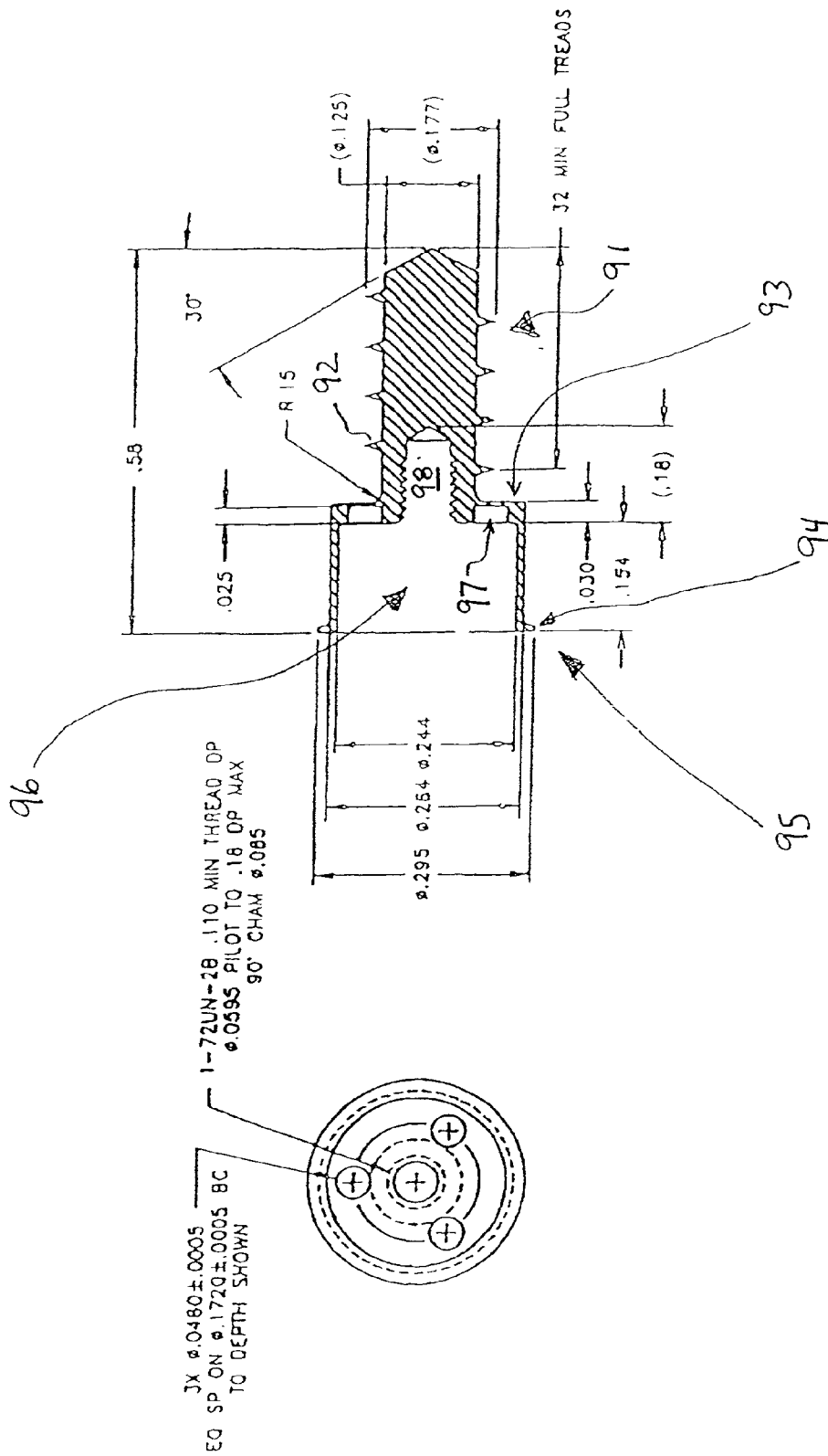


Figure 10A

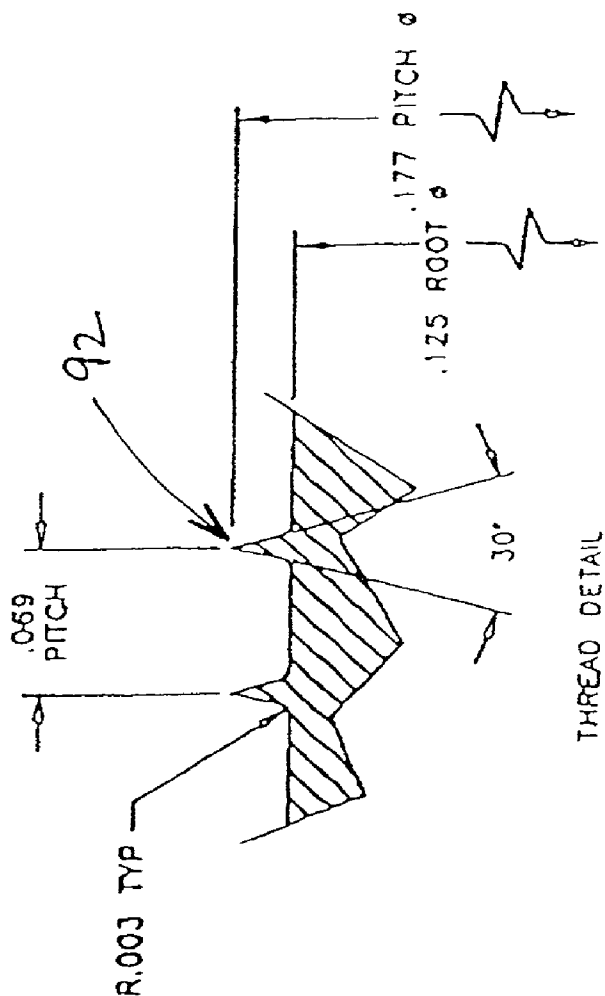


Figure 10B

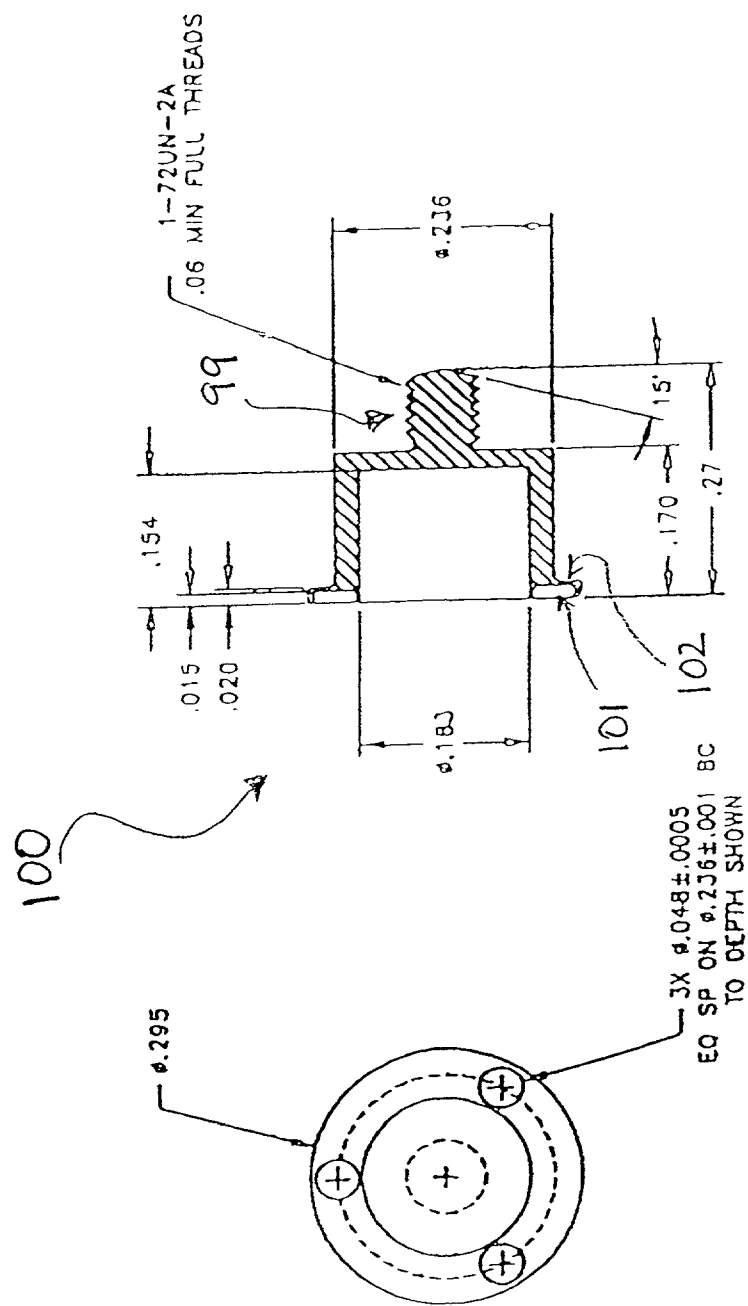


Figure 10C

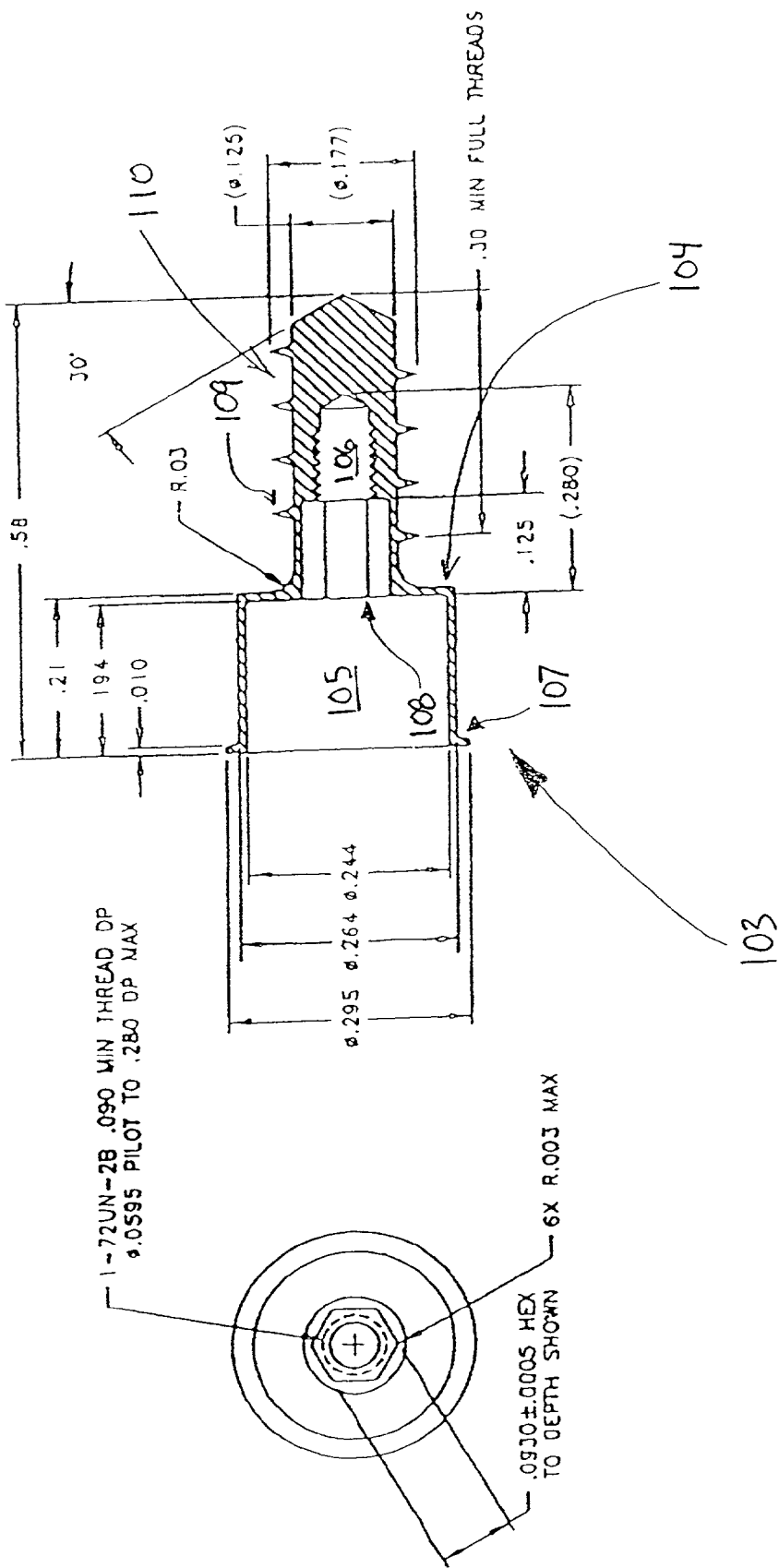


Figure 11A

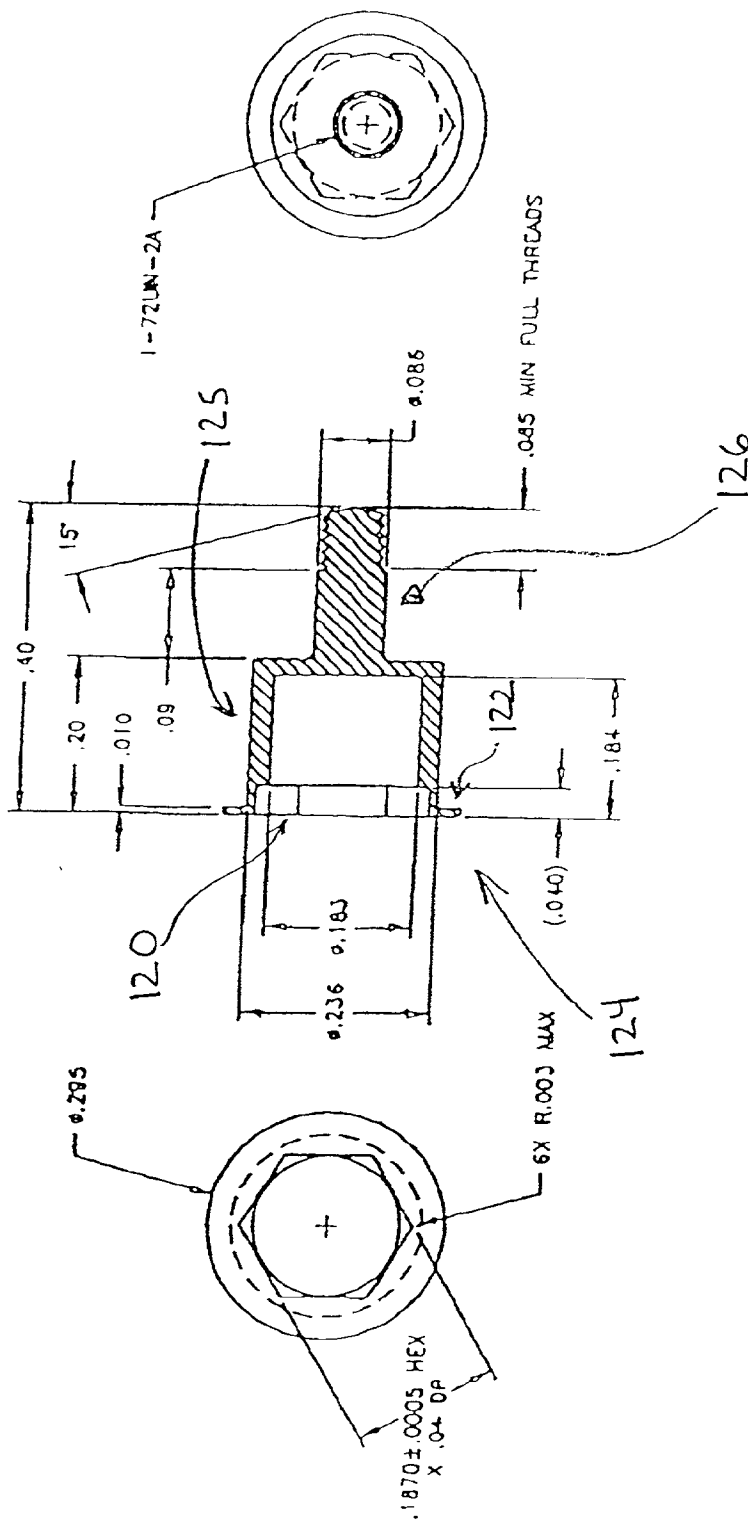


Figure 11B

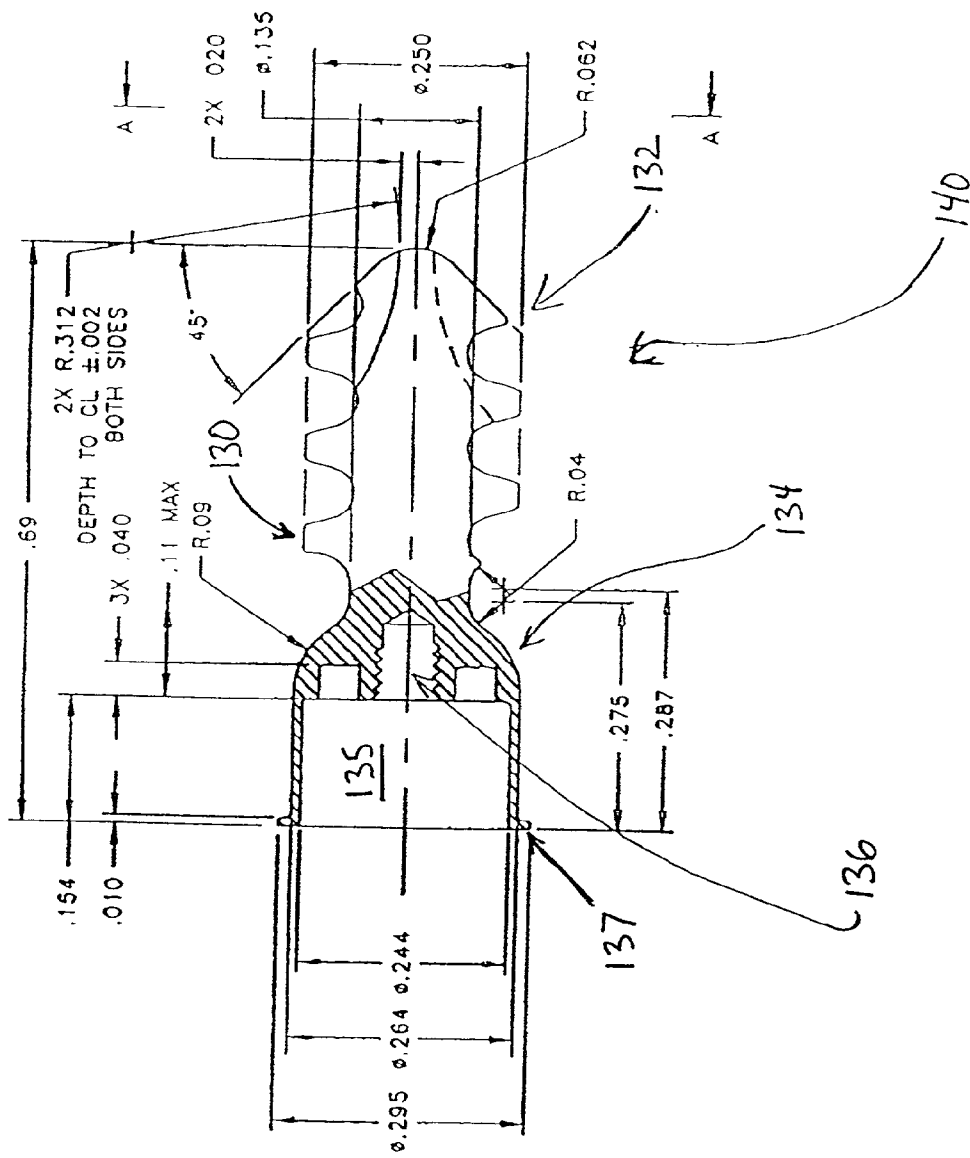


Figure 12A

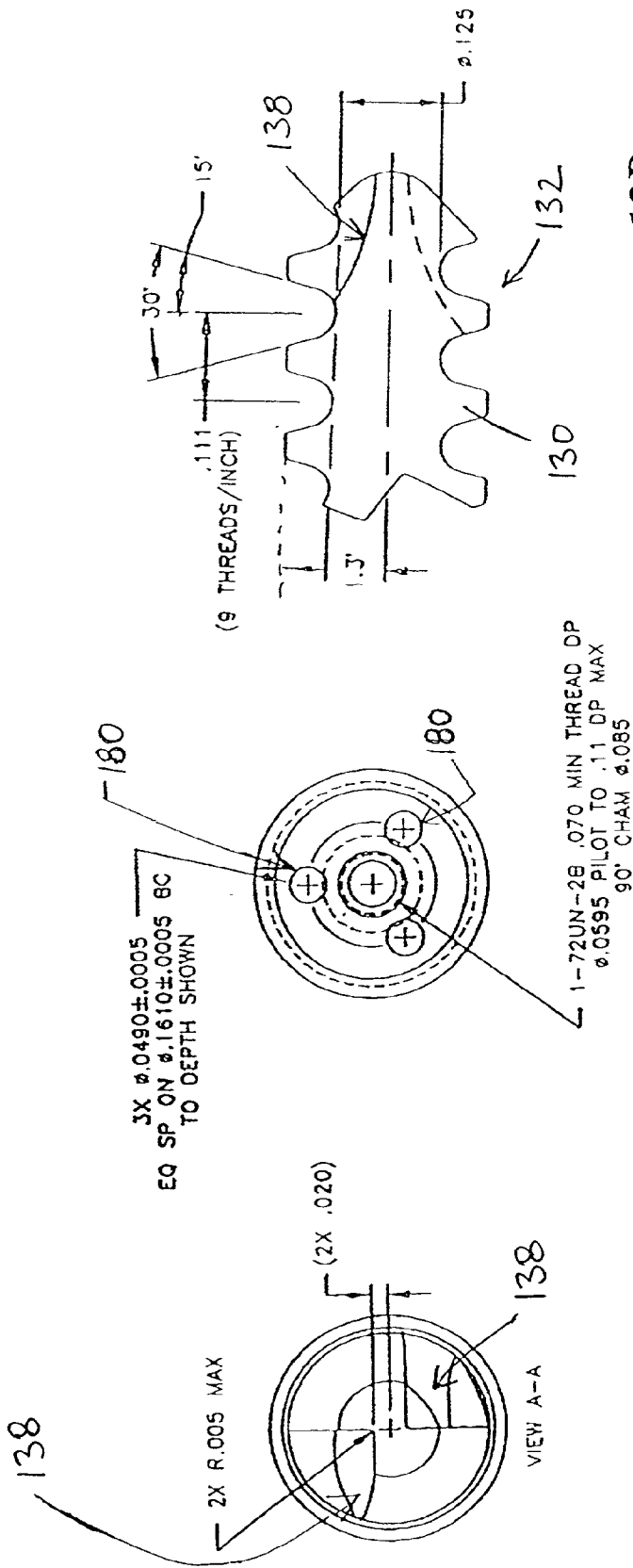


Figure 12D

Figure 12C

Figure 12B

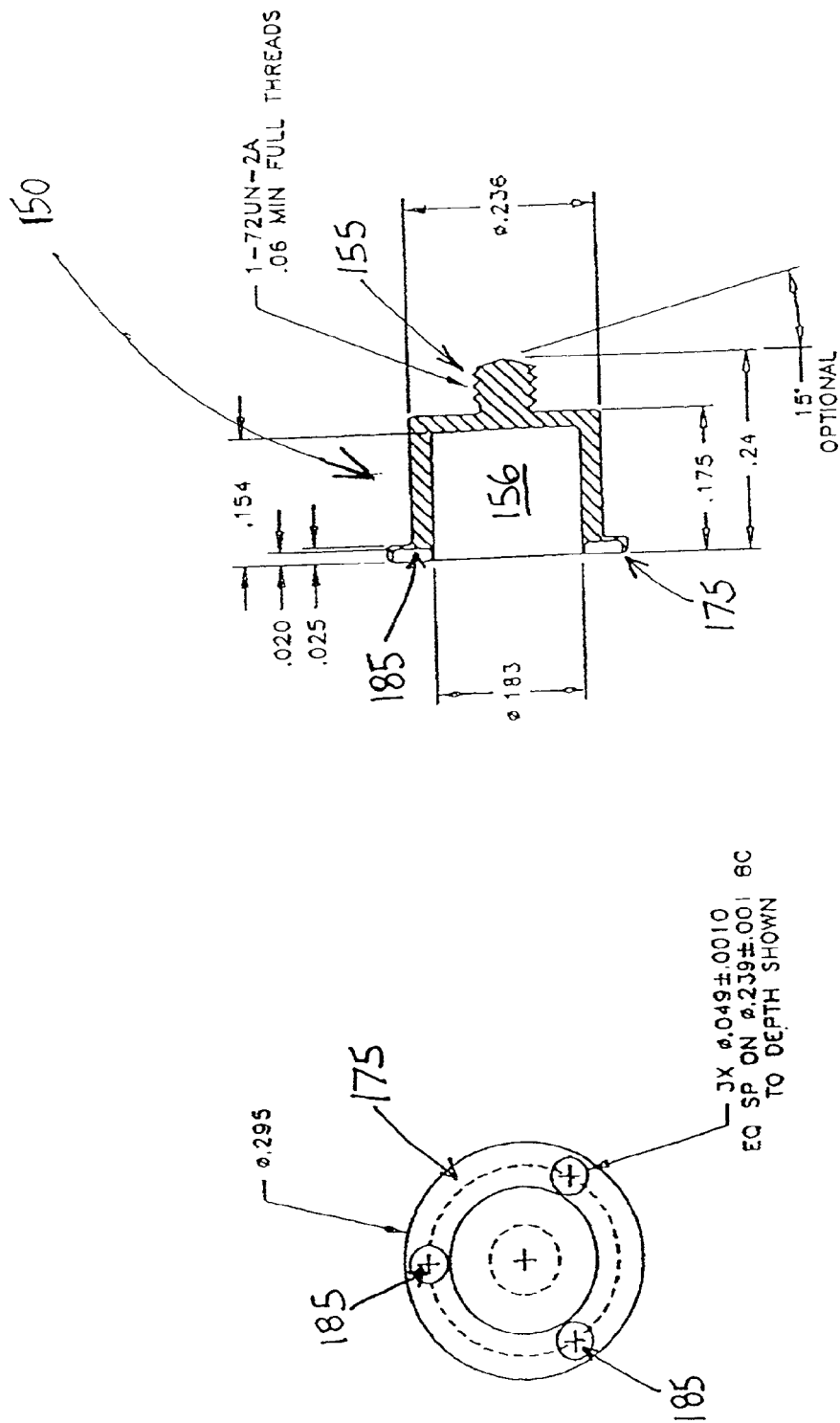


Figure 12F

Figure 12E

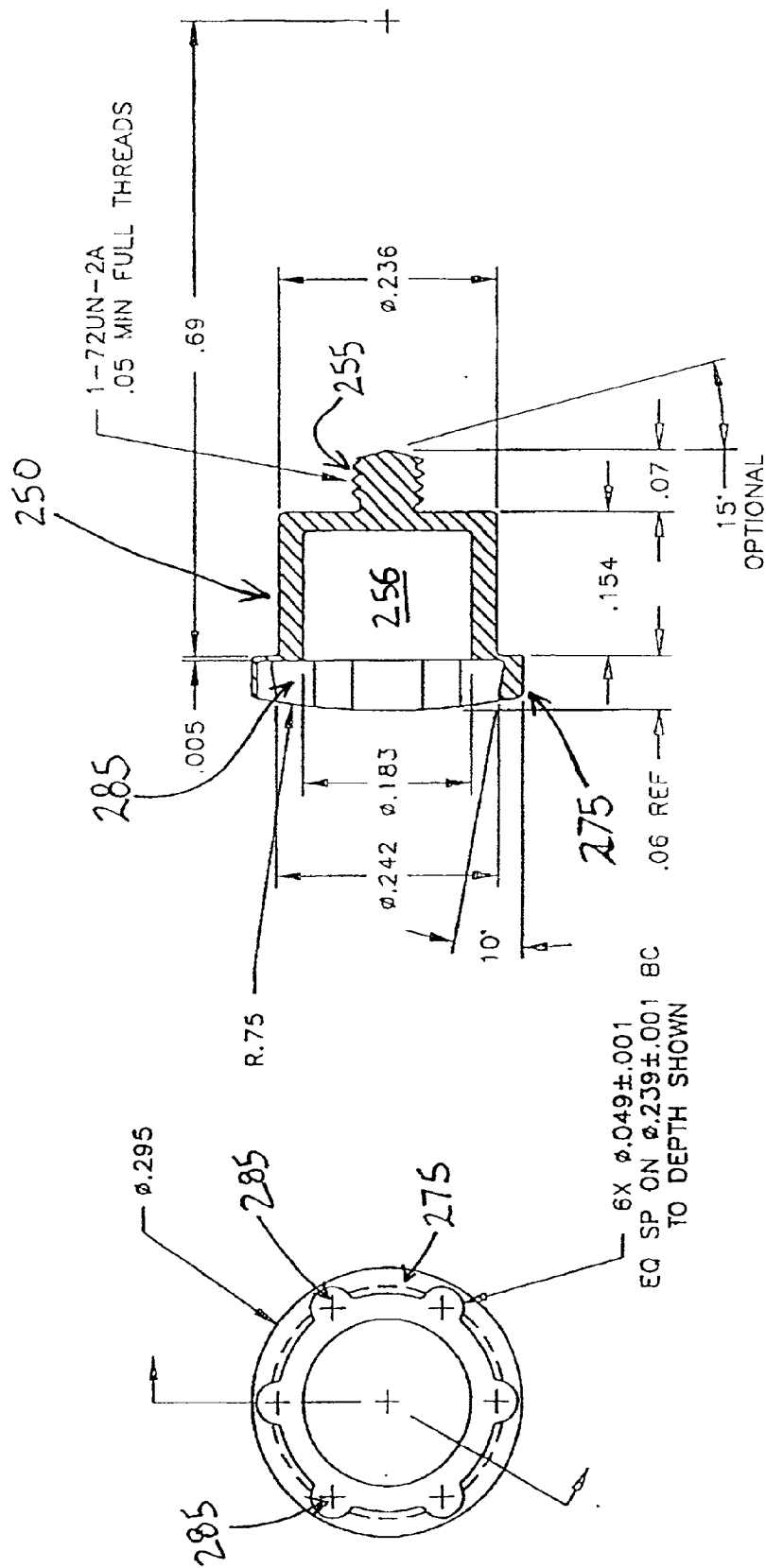


Figure 13A

Figure 13B

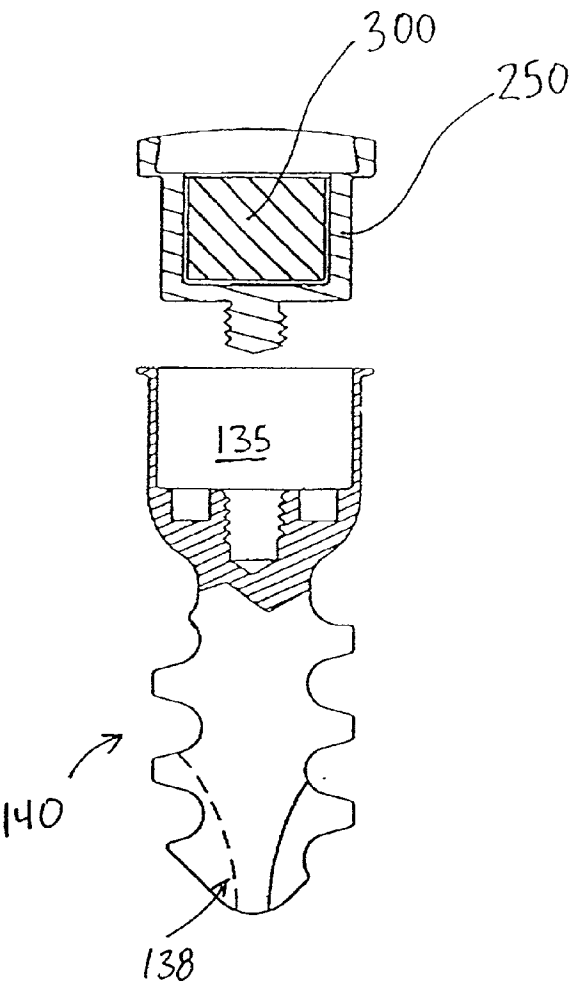


Figure 14A

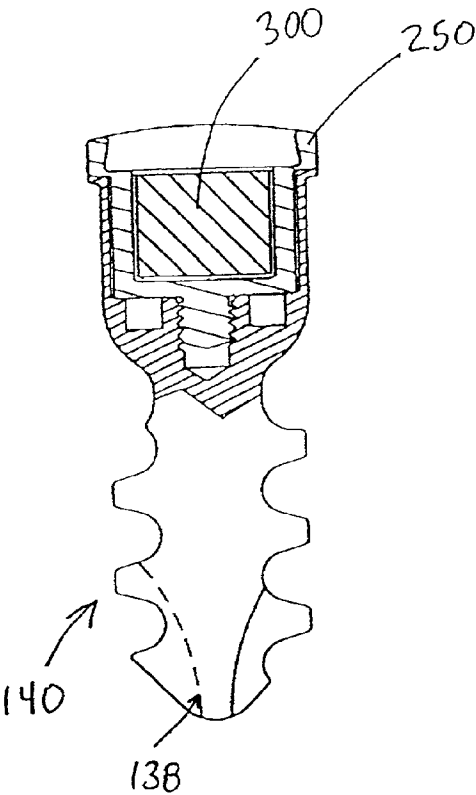


Figure 14B

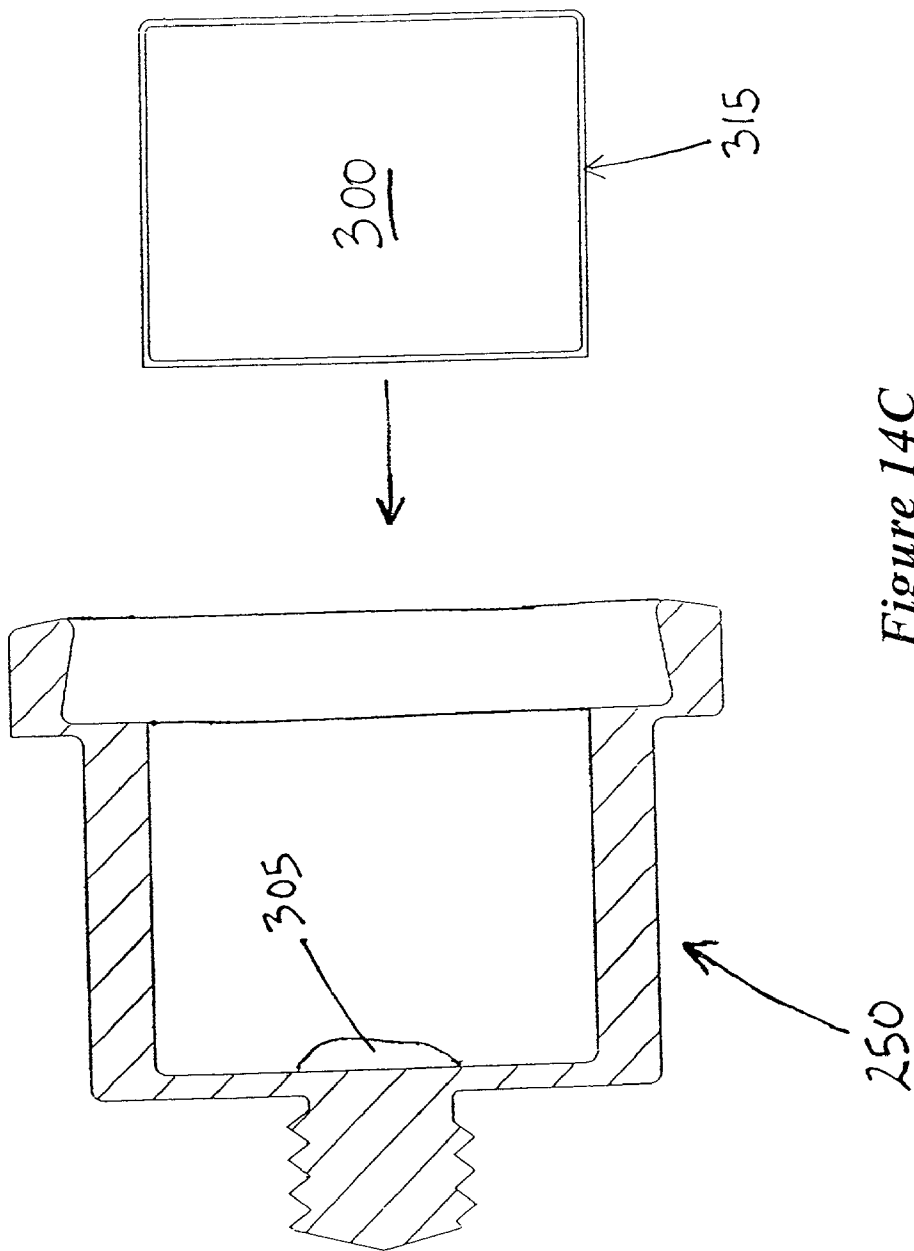


Figure 14C

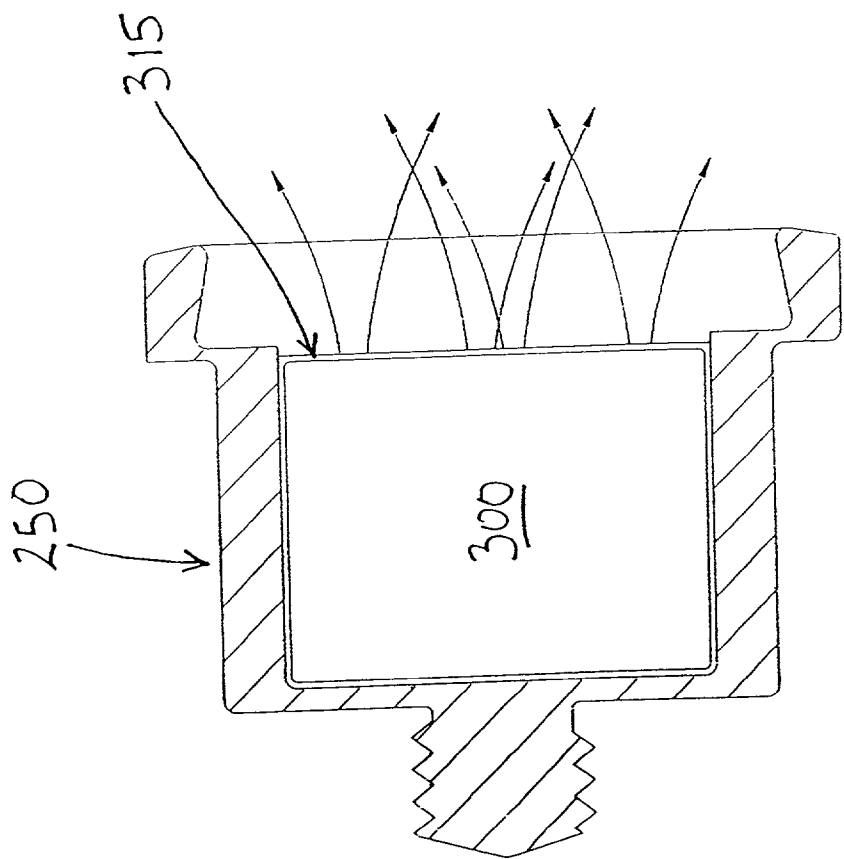


Figure 14D

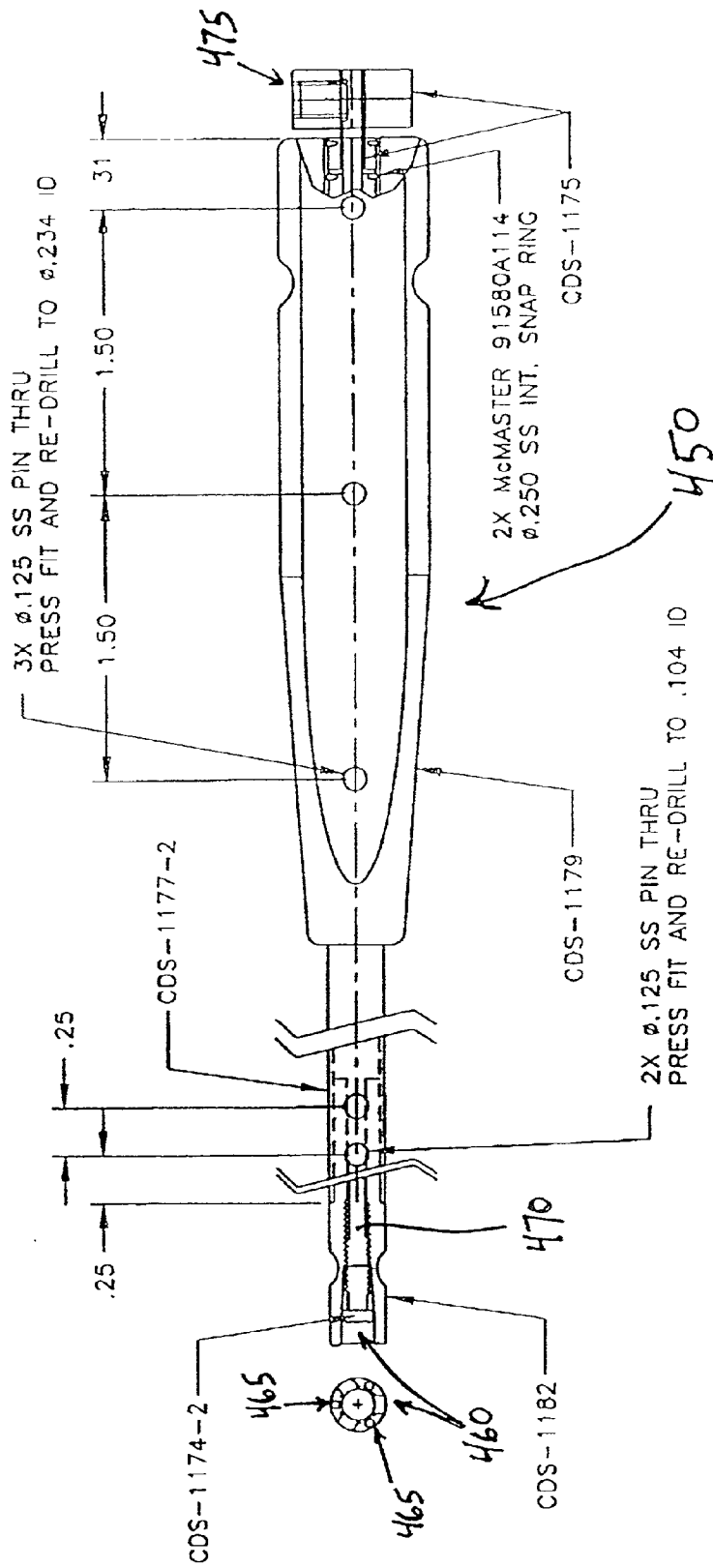


Figure 15A

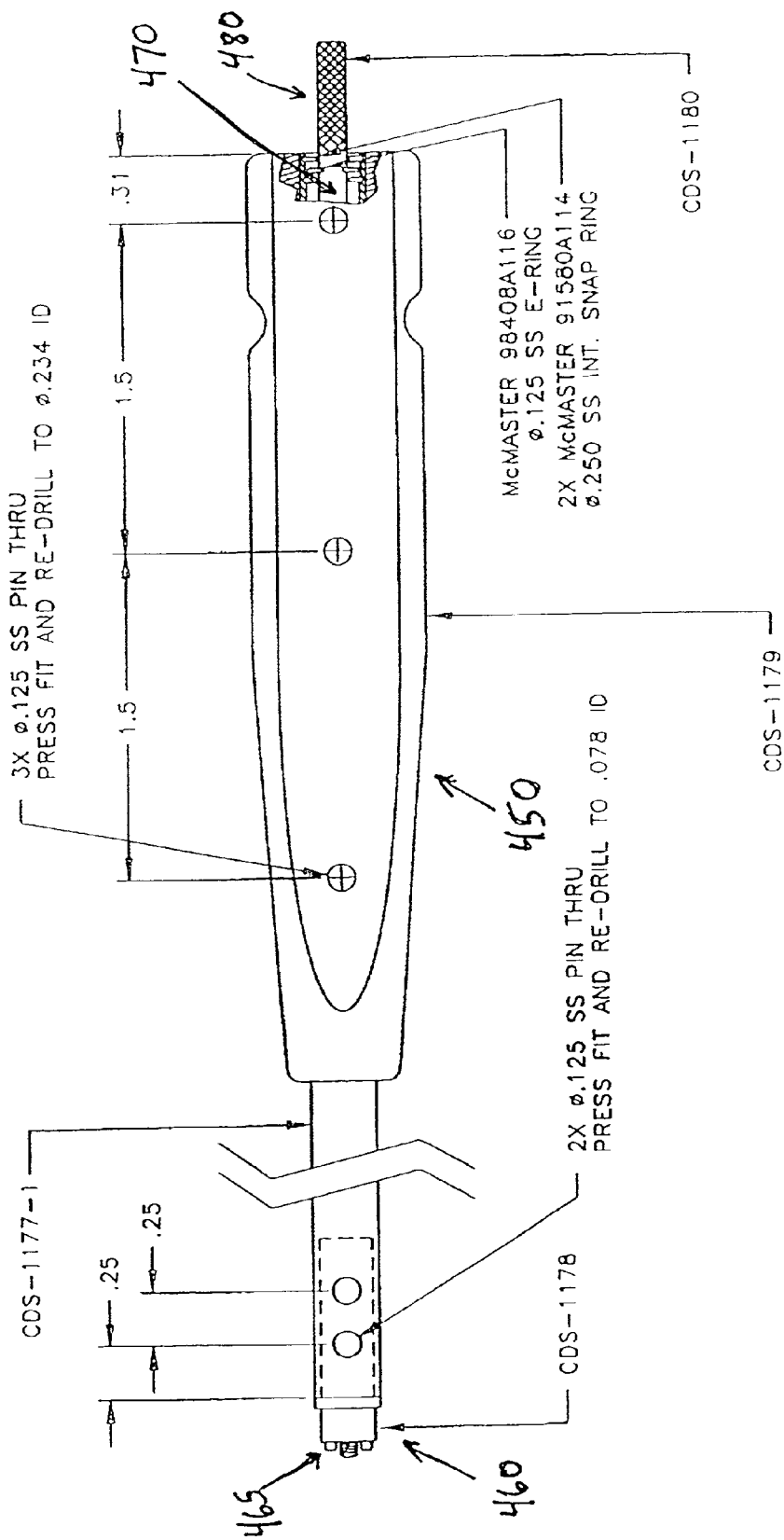


Figure 15B

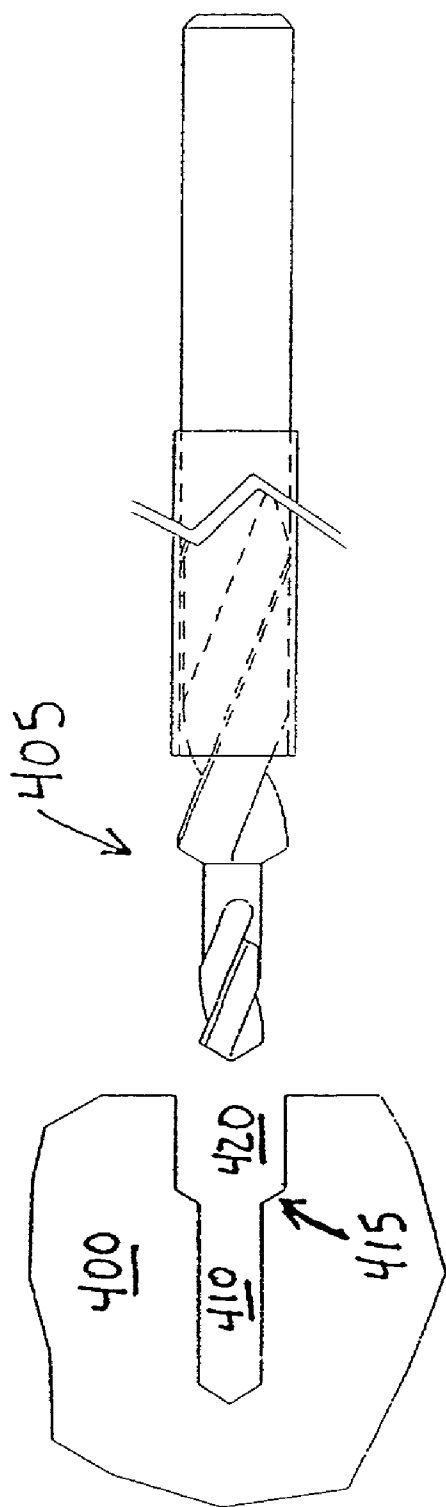


Figure 16A

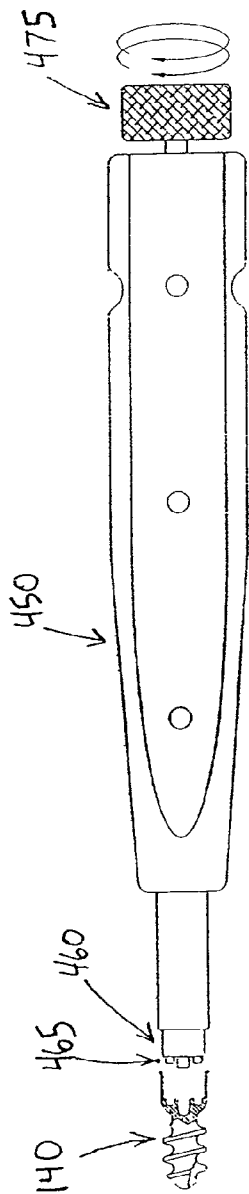


Figure 16B

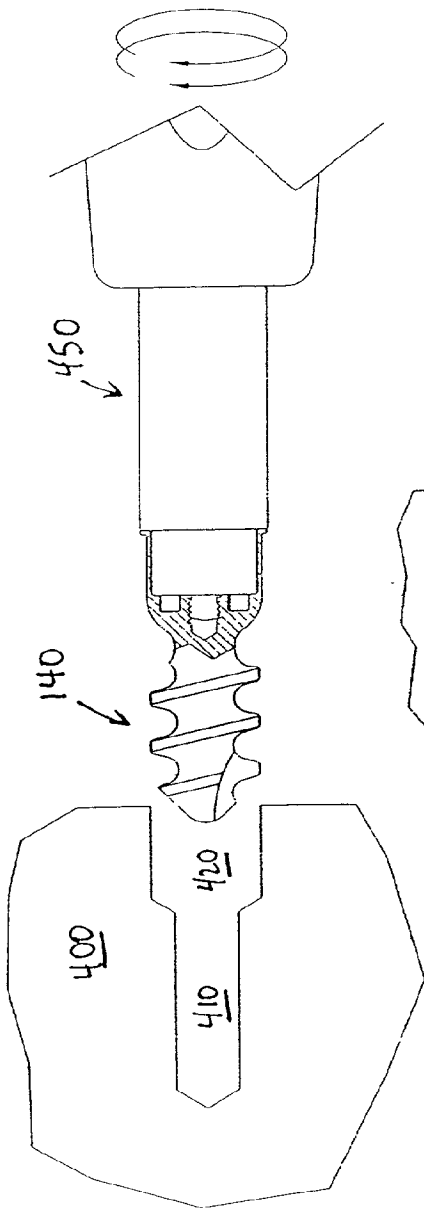


Figure 16C

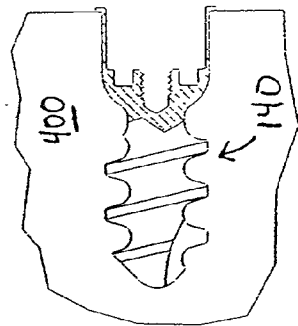


Figure 16D

DEVICE AND METHOD FOR TREATING CONDITIONS OF A JOINT

FIELD OF THE INVENTION

[0001] The present invention relates to the delivery of therapeutic compounds to joints, particularly to the sustained delivery of anti-inflammatory compounds to joints to treat arthritis.

BACKGROUND OF THE INVENTION

[0002] Pain, in and of itself, constitutes a sufficient impetus for remedial action. Moreover, otherwise productive individuals lose more time due to pains, particularly in the joints, than to any other cause. Civilization and technological advances have ushered in a relatively sedentary existence, both as to work environment and leisure activities, which increases the likelihood of such pain-causing ailments. Although the term is applied to a wide variety of disorders, arthritis generally denotes the inflammation of a joint whether as a result of a disease, an infection, a genetic defect or some other cause. The long term effects of arthritis range from chronic pain to crippling disability.

[0003] Osteoarthritis is a disease that attacks cartilage. Surfaces of joint cartilage and underlying bone compress and become irregular, leading to pain, inflammation, bone spurs and limited movement. Osteoarthritis is one of the most common disabilities in the United States, affecting over 15% of the population. As osteoarthritis progresses, serious joint damage and chronic pain can result. Treatment alternatives are limited and, in many cases, ineffective. Aside from weight reduction and avoiding excessive stress on the joint cartilage, there is currently no specific treatment to halt cartilage degeneration or to repair damaged cartilage caused by osteoarthritis. The goal of treatment is to reduce joint pain and inflammation while improving and maintaining joint function. Current pharmacological treatments include oral anti-inflammatory and anti-pain medications. The effectiveness of these treatments decreases as the disease progresses. In severe osteoarthritis, joint replacement surgery is common. Sometimes surgery is forestalled with injections of steroids into the affected joint, but the delivery of drugs in this manner is painful, and the drugs themselves provide decreasing effectiveness and wear off after several weeks. In 1999, there were over 500,000 joint replacement surgeries funded by Medicare in the United States, which were likely mainly due to osteoarthritis.

[0004] Severe arthritis involves a serious auto-immune reaction for which steroids theoretically provide treatment but their efficacy is compromised by the systemic toxicity resulting from the dosage required to penetrate the natural barriers of the joints and the need for repeated treatments due to the chronic nature of the disease.

[0005] Steroids may be administered in many different ways. They can be given as tablets, or by injection into a muscle or into a vein.

[0006] Steroid injections are a common treatment for a variety of conditions in which inflammation causes pain, swelling and other problems. Joint pain due to osteoarthritis and rheumatoid arthritis are examples of conditions for which steroid injections may be helpful. Injections have the advantage of placing the steroids, often glucocorticoids, for

example, directly into a painful area. Because of this, steroid injections are able to reduce inflammation and pain relatively quickly. Unfortunately, steroid injections are a procedure that must be administered by a medical doctor, they are sometimes accompanied by an anesthetic to numb the area to be injected, and the effects of a steroid injection typically last for about only several months before a second injection is required. Furthermore, the injected area may become more painful over the first 24 hours after the local anesthetic wears off, requiring application of a cold compress or taking painkillers. In addition, it is usually suggested that the joint be rested for 24-48 hours after the injection, especially, for weight bearing joints such as the knee. Immediately after injection, the concentration of steroid within the joint is maximal. The injection becomes progressively less effective however as the steroid leaches out of the joint. For the above reasons, repeated injections to maintain therapeutic drug concentrations are not clinically acceptable and, consequently, high initial doses are sometimes given. This strategy, however, has the risk of producing toxicity if too much is given at one time.

[0007] Common side effects associated with steroid treatment include weight gain, thinning of the bones (osteoporosis), easy bruising, indigestion, mood changes, rises in blood sugar and blood pressure, and increased likelihood of developing infections. Because of their long-term side effects, it is recommended that corticosteroids should be given only after a careful and usually prolonged trial of less hazardous drugs. Furthermore, severe rebound follows the withdrawal of corticosteroids in active diseases, in part due to the down regulation of naturally occurring glucocorticoid steroids.

[0008] Intraarticular injections of corticosteroids may temporarily help control local synovitis in one or two particularly painful joints. Triamcinolone hexacetonide may suppress inflammation for the longest time; other depot corticosteroids, including prednisolone tertiary-butylacetate, also are effective. The soluble 21-phosphate preparations of prednisolone or dexamethasone are not recommended because of rapid clearance from the joint and very short duration of action. Side effects may not be as pronounced when steroids are given by injection to the knee. However, the effects of a steroid injection to the knee typically is limited to several months before another injection is required. Also, injections provide an initial level of steroid that is greater than therapeutically required and which rapidly declines beneath therapeutic levels.

[0009] Cytotoxic/immunosuppressive compound (e.g., methotrexate, cyclosporine) are increasingly used for severe, active rheumatoid arthritis. They can suppress inflammation and may allow reduction of corticosteroid doses. Yet, major side effects can occur, including liver disease, pneumonitis, and bone marrow suppression. Thus, patients require careful supervision by a specialist.

[0010] Broadly, there exists a need for an improved implantable sustained release drug delivery device and method and apparatus for implantation of said device. In particular, there exists a need for an improved device and method for treating conditions of joint or bones, such as arthritis, without undesirable systemic side effects and a need for repeated injections.

SUMMARY OF THE INVENTION

[0011] An advantage of the present invention is a method for treating conditions of the joint without undesirable systemic side effects.

[0012] An additional advantage of the present invention is a method for treating conditions of the joint without the need for repeated injections.

[0013] An advantage of the present invention is a method for long-term drug treatment without the need for frequent injections of a drug or drugs.

[0014] Another advantage of the present invention is a sustained release, implantable drug delivery device that is useful for treating medical conditions, such as but not limited to inflammatory or degenerative conditions.

[0015] Additional advantages and other features of the invention will be set forth in the description which follows and in part will become apparent to those having ordinary skill in the art upon examination of the following or may be learned from the practice of the invention. The advantages of the invention may be realized and obtained as particularly pointed out in the appended claims.

[0016] According to the present invention, the foregoing and other advantages are achieved, in part, by a method for locally administering a therapeutically effective compound to a joint of a mammal that comprises the step of: intraarticularly implanting a sustained release device to deliver the therapeutically effective compound within a synovial capsule of the joint, such that synovial fluid concentration of the compound is greater than plasma concentration of the compound.

[0017] In accord with aspects of the present invention, the foregoing and other advantages are also achieved in part by an implantable sustained release device for locally administering a therapeutically effective compound to a joint. The device contains a therapeutically effective compound and is configured to provide sustained release of the compound to synovial fluid such that the synovial fluid concentration remains greater than plasma concentration.

[0018] In another aspect of an implantable sustained release drug delivery device in accord with the invention, there is provided a mechanical member attachable to a portion of a body, a first chamber having an opening configured to receive a sustained release device, and a removably attachable retainer for retaining the sustained release device in the first chamber.

[0019] In still another aspect of an implantable sustained release drug delivery device in accord with the invention, there is provided a system comprising a mechanical member attachable to a portion of a body, a chamber disposed within the mechanical member configured to receive a sustained release device bearing at least one drug, and an opening in the chamber to permit release of the at least one drug borne by the sustained release device.

[0020] Another aspect of the present invention provides a method for administering a drug to a joint, the method comprising the step positioning a drug delivery system in a bone, the system configured to hold a sustained release drug delivery device.

[0021] Yet another aspect of the present invention provides a method for administering a drug to a joint, the method comprising the steps of positioning a mechanical member in or adjacent a bone, said mechanical member configured to hold a sustained release drug delivery device bearing at least one drug, and outputting said at least one drug from said sustained release drug delivery device at a substantially controlled rate.

[0022] Still another aspect of the invention is envisaged in an implantable sustained release device for locally administering a drug, comprising a bone screw including a hollow portion configured to receive a sustained release holding device, the sustained release holding device itself configured to receive a drug payload. In an aspect thereof, a drug payload including one or more drugs is included, as is a rate-limiting barrier configured to limit a release rate of a drug from the drug payload to thereby provide sustained release of the drug. The rate-limiting barrier may itself be configured to provide a steady-state release rate of a drug from the drug payload substantially equal to a steady-state rate of elimination of the drug from a treatment site and to provide a predetermined therapeutic concentration of the drug in the treatment site, said predetermined therapeutic concentration of the drug being greater than a plasma concentration of the drug until substantially all of the drug in the drug payload is depleted.

[0023] Additional advantages of the invention will become readily apparent to those skilled in the art from the following detailed description, wherein various embodiments of the invention are described simply by way of illustrating of the best mode contemplated in carrying out the invention. As will be realized, the invention is capable of other and different embodiments, and its details are capable of modifications in various obvious respects, all without departing from the invention. For example, the aspects of the invention presented herein are similarly applicable to other medical applications, including but not limited to bone fixation and localized treatments adjacent bone masses. Accordingly, the description is to be regarded as illustrative and not as restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] By way of example only, embodiments of the present invention will be described with reference to the accompanying drawings, in which:

[0025] **FIG. 1** shows a graph of fluocinolone acetonide (FA) in plasma versus synovial fluid in sheep in accord to one aspect of the invention.

[0026] **FIGS. 2A and 2B** respectively show an exploded cross-sectional view of a drug delivery system according to an embodiment of the present invention and a top view of a removable attachable retainer according to an embodiment of the present invention.

[0027] **FIG. 3** shows an exploded cross-sectional view of a drug delivery system according to a further embodiment of the present invention.

[0028] **FIG. 4** shows a top view of a removable attachable retainer according to the embodiment of the present invention shown in **FIG. 3**.

[0029] **FIG. 5** shows an exploded cross-sectional view of a drug delivery system according to a further embodiment of the present invention.

[0030] FIG. 6 shows a cross-sectional view of a drug delivery system according to a further embodiment of the present invention.

[0031] FIG. 7 shows a cross-sectional view of a drug delivery system according to a further embodiment of the present invention.

[0032] FIG. 8 shows a cross-sectional view of a drug delivery system according to yet another embodiment of the present invention.

[0033] FIGS. 9A-9C depict top views of the drug delivery system depicted in FIG. 8.

[0034] FIGS. 10A-10C depict cross-sectional views of a drug delivery system according to an embodiment of the present invention.

[0035] FIGS. 11A-11B depict cross-sectional views of another drug delivery system according to an embodiment of the present invention.

[0036] FIGS. 12A-12F depict cross-sectional views of a drug delivery system according to another embodiment of the present invention.

[0037] FIGS. 13A-13B depict cross-sectional views of an aspect of a drug delivery system according to another embodiment of the present invention.

[0038] FIGS. 14A-14D illustrate various cross-sectional views of aspects of a drug delivery system according to the embodiments of the present invention represented in FIGS. 12A-12D and/or 13A-13B.

[0039] FIGS. 15A-15B illustrate an apparatus used to insert a drug delivery device in accord with the invention.

[0040] FIGS. 16A-16G illustrate a method of inserting a drug delivery device in accord with the invention.

DESCRIPTION OF THE INVENTION

[0041] The present invention provides a method for administering a therapeutically effective compound to the synovial fluid of a joint. The method comprises the step of implanting a sustained release device within the joint such that the therapeutically effective compound is released within the synovial capsule. The synovial fluid concentration of the compound remains greater than plasma concentration for the lifetime of the sustained release device. In one aspect of the invention, the synovial fluid concentration of the compound remains at least one order of magnitude greater than the plasma concentration. In a preferred aspect of the invention, the synovial fluid concentration of the compound remains several orders of magnitude greater than the plasma concentration.

[0042] The present invention is particularly effective in treating joint diseases, such as inflammatory joint diseases, e.g., various forms of arthritis. Examples of inflammatory joint diseases which can be effectively treated in accordance with embodiments of the present invention include arthritis associated with spondylitis, diffuse connective tissue diseases such as rheumatoid arthritis, infectious arthritis and osteoarthritis.

[0043] Various therapeutically effective compounds can be effectively employed in implementing embodiments of the present invention include, for example, glucocorticoids,

anti-inflammatories such as dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof; as well as, non-steroidal anti-inflammatory drugs and cyclosporines.

[0044] As employed throughout this disclosure, the expression, "sustained release device" is intended to mean a device that is capable of releasing a drug(s) or compound over an extended period of time in a controlled fashion. The drug(s) or compound may advantageously include, but are not limited to, a steroid, an anti-inflammatory drug, antibiotic, anti-viral agent, cancer-fighting drug, or a pain relieving drug. Examples of sustained release devices useful in the present invention may be found in, for example, U.S. Pat. Nos. 6,051,576, 5,773,019, 6,001,386, 5,902,598, and 5,378,475 (incorporated herein by reference, in their entireties). Suitable sustained release devices could comprise an inner core bearing an effective amount of at least one low solubility agent and at least one non-bioerodible polymer coating layer which is permeable to low solubility agent(s). Suitable low solubility agents may include and are not limited to corticosteroids such as dexamethasone and triamcinolone acetonide, angiostatic steroids such as trihydroxy steroid, antibiotics including ciprofloxacin, and non-steroidal anti-inflammatory agents such as indomethacin and flurbiprofen, co-drugs including low solubility co-drugs of salts or conjugates of synergistic pharmacological agents such as suramin/amiloride or 5-FU/THS, and combinations thereof. Standard pharmaceutical textbooks provide procedures to obtain a low solubility form of a drug. By "low solubility", it is meant a solubility less than about 10 μg of compound per 1 ml (of water at a temperature of 25° C. as measured by procedures set forth in the 1995 USP). This includes compounds which are slightly soluble (about 0.01 $\mu\text{g}/\text{ml}$ -about 0.001 $\mu\text{g}/\text{ml}$), very slightly insoluble (about 0.001 $\mu\text{g}/\text{ml}$ -about 0.0001 $\mu\text{g}/\text{ml}$) and practically insoluble or insoluble compounds (less than about 0.0001 $\mu\text{g}/\text{ml}$).

[0045] Embodiments of the present invention include the sustained release of two or more drugs simultaneously. The sustained release device is configured, in one aspect of the invention, to provide release of a compound to synovial fluid such that the synovial fluid concentration remains greater than plasma concentration. The sustained release device is designed to maintain an optimal dosage level at the target site over the entire duration of treatment without substantial variability in dosing over time.

[0046] The sustained release device may be surgically implanted intraarticularly, i.e., within the synovial joint. In embodiments of the present invention, the sustained release device may be configured for attachment to a bone, as in co-pending U.S. Provisional Patent Application Serial Nos. 60/245,184 and 60/291,606, the entire disclosures of which are incorporated by reference herein. In other embodiments, the sustained release device may be configured for attachment to a ligament with suturing.

[0047] The concentration of the compound in the synovial fluid remains greater than the plasma concentration of the compound during the lifetime of the device. As the compound is released from the device, it enters the synovial fluid. Over time a steady state condition is established where the rate of compound entering the synovial fluid is substantially equivalent to the rate of compound eliminated from the joint. The compound that is eliminated from the joint is then

distributed throughout the rest of the body and is eliminated via excretion. This redistribution and excretion establishes the differential levels between the synovial fluid and the plasma. In embodiments of the present invention, the plasma concentration of the compound remains at or below 5 ng/mL. At such low concentrations, adverse systemic side effects are unlikely to develop. In contrast, the synovial fluid concentrations remain substantially therapeutic, during release of the compound from the sustained release device. The exact concentration depends on the condition and therapeutic index of the compound.

[0048] The present invention provides sustained release of the therapeutically effective compound for a duration of about 3 months to about 10 years, such as from about 6 months to about 5 years. In embodiments of the present invention, sustained release of the therapeutically effective compound is provided for about 3 years. As such, the need for frequent, repeated administrations, such as with injections is avoided.

[0049] The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become more apparent to those skilled in the art in light of the present disclosure.

[0050] Twelve Month Single Dose Toxicity Study in Beagle Dogs

[0051] Animals

- [0052] Species: *Canis familiaris*
- [0053] Strain: Beagle
- [0054] Source: Covance
- [0055] Age at Initiation: 5-9 months
- [0056] Weight at Initiation: 10-12 kg, to be documented in the study file
- [0057] Number of Males (including spares): 6+1 spare

[0058] Experimental Methodology

STUDY DESIGN				
Group Number	Number of Animals	Device	Dosing Regimen	Euthanasia
1	3	Fluocinolone acetoneide implant	1 implant in each hindlimb joint	1/group at Day 29, 91,
2	3	Fluocinolone acetoneide implant	4 implants in each hindlimb joint	and 365

[0059] Frequency and Duration of Administration

[0060] Devices were administered once via bilateral intraarticular implants. The day of surgical implantation was Day 1.

[0061] Implants

[0062] The devices were made as follows. Fluocinolone acetoneide, USP, was compressed into 1.5 mm diameter tablets using standard pharmaceutical methods. The tablets were placed into preformed cups made from silicone elas-

tomer. Cup size was dependent on dosage form. These cups were attached to polyvinyl acetate (PVA) suture tabs. For the 2 mg implants, the surface of the tablet not coated with silicone was attached to a suture tab with PVA solution. For the 6 mg implant, a side of the silicone cup was attached perpendicular to the suture tab. Finally, the assemblies are dip coated with PVA.

[0063] The implants were then cured at 135° C. for 5 hours and placed within the primary package. The product in the primary package was placed in a self-adhesive pouch and sterilized using gamma irradiation.

[0064] Preoperative Procedures

[0065] Anesthesia and Antibiotic Therapy

[0066] The animals were preanesthetized with atropine (0.4 mg/kg IM) and acepromazine (0.1 mg/kg IM). After about 10-30 minutes, the animals were initially anesthetized with methohexital 1 Na at 10-15 mg/kg IV, to effect. The animals were immediately intubated and maintained in anesthesia with isoflurane inhalant anesthetic delivered through a volume regulated respirator. The ETCO₂ was maintained within individual physiological ranges. An intravenous drip of lactated Ringer's solution was begun at a rate of approximately 10 mL/kg/hr. Procaine/Benzathine penicillin (40,000 IU/kg, IM) was also given.

[0067] Surgical Preparation

[0068] Hair was removed from the entire leg. Any excess hair was removed by vacuum. The surgical site was prepared for aseptic surgery by first washing the leg with povidone-iodine scrub solution followed by an application of 70% isopropyl alcohol, which was allowed to dry. Dura-Prep™ or similar solution was then applied to the entire leg and also allowed to dry. The entire leg, including the foot, was appropriately draped for strict aseptic surgery.

[0069] Surgical Procedures

[0070] Surgery was performed on both knee joints of all animals. A lateral skin incision was made to expose the fascia lata overlying the vastus lateralis cranially and the biceps femoris caudally. The joint was exposed through an incision in the lateral intermuscular septum to expose the femur by anterior retraction of the vastus lateralis and posterior retraction of the biceps femoris. Care was taken not to disrupt the tendon of origin of the long digital extensor as it originates from the lateral femoral condyle. The joint capsule was opened, the patella luxated medially, and the joint was held in full flexion. 2 mg devices were placed in the right leg and 18 mg implants were placed in the left leg. The implants were placed within the anterior intercondyloid fossa, immediately lateral to the origin of the posterior cruciate ligament. The bone may be slightly deepened at this location with a curette to accept the implant. The implant was sutured in place to the posterior cruciate ligament. The joint capsule was closed with 3/0 PDS in a simple interrupted fashion. The retinaculum and intermuscular septum were closed with 2/0 Vicryl in a continuous pattern. The fascia lata were closed with 2/0 PDS, and the subcutaneous tissues with 3/0 PDS, both in a simple continuous pattern. The skin was closed with 3/0 Vicryl in a subcuticular pattern.

[0071] Blood Collection

[0072] Blood was collected from a peripheral vessel. Blood volumes represent whole blood and are approximate amounts.

Timepoint	Clinical Pathology				BAC	
	Hema- tology	Clinical Chemistry	Coagulation	Cortisol	Blood	Synovial Fluid
Days 3, 7, 21, 29, 91, and 365	X	X	X	X	X	X
Volume of Whole Blood/Timepoint	1.3 mL	1.8 mL	1.8 mL	1.8 mL	5.0 mL	0.3–0.5 mL
Anticoagulant	EDTA	None	Sodium Citrate	None	EDTA	EDTA

[0073] The blood samples were processed for plasma, the plasma was extracted, and the plasma will be placed immediately in a $\leq -70^{\circ}$ C. freezer until transferred for analysis.

[0074] Synovial Fluid

[0075] After anesthesia (acepromazine, 0.2 mg/kg, IM followed by sodium pentobarbital, 22 mg/kg, IV, to effect) an attempt was made to obtain synovial fluid. Synovial fluid samples were immediately stored at $\leq -70^{\circ}$ C. in polypropylene tubes until transferred.

TABLE 1

Assayed Concentrations (ng/mL) of Fluocinolone Acetonide in Dog Plasma Samples						
Time (Days)	Dog 1001	Dog 1002	Dog 2001	Dog 2002	Dog 3001	Dog 3002
3	1.89	BQL	BQL	BQL	BQL	BQL
7	BQL	BQL	BQL	BQL	16.9	BQL
21	0.57	BQL	BQL	BQL	4.92	BQL
29	BQL	BQL	BQL	BQL	BQL	BQL

BQL = Below Quantition Limit, 0.5 ng/mL

[0076]

TABLE 2

Assayed Concentrations (ng/mL) of Fluocinolone Acetonide in Dog Synovial Fluid Samples (Left Leg)						
Time (Days)	Dog 1001	Dog 1002	Dog 2001	Dog 2002	Dog 3001	Dog 3002
3	656	357	89.0	193	788	207
7	290	405	194	279	35300	251
21	1070	373	X	393	5180	276
29	457	379	57.8	956	X	210
56	202071	541	X	X	36.9	X

BQL = Below Quantition Limit, 5 ng/mL

X = No sample collected for this timepoint

[0077]

TABLE 3

Assayed Concentrations (ng/mL) of Fluocinolone Acetonide in Dog Synovial Fluid Samples (Right Leg)						
Time (Days)	Dog 1001	Dog 1002	Dog 2001	Dog 2002	Dog 3001	Dog 3002
3	52.0	36.6	600	24.4	57.9	40.7
7	62.4	BQL	98.4	47.7	171	8.30
21	7.27	BQL	BQL	144	51.5	BQL
29	BQL	BQL	BQL	BQL	16.4	7.86
56	19.3	BQL	X	X	X	BQL

BQL = Below Quantition Limit, 5 ng/mL

X = No sample collected for this timepoint

[0078] The results shown in Tables 1-3 demonstrate the effectiveness of the present invention.

[0079] Pharmacokinetic Study of a Fluocinolone Acetonide Implant in the Stifle Joint of Sheep

[0080] Animals

Species:	<i>Ovis aries</i> (Sheep)
Strain:	Rambouillet
Source:	K Bar Livestock
Age at Initiation:	Adult
Weight at time of surgery/treatment:	35–75 kg.
Number and Sex:	12 males + 1 spare 12 females (nonpregnant) + 1 spare

[0081] Experimental Methodology

[0082] The objective of this study was to determine both the local and systemic pharmacokinetic profile of an intra-articular fluocinolone acetonide (FA screw) implant in the stifle joint of sheep. This study group consisted of 24 animals randomized into 2 groups of 6 males and 6 females per group, as shown in Table 4. The animals underwent surgical implantation of the FA Screw test device in the stifle joint on Day 1. Following a recovery period, blood and synovial fluid were collected periodically for pharmacokinetic determination. Following completion of a 24 month observation period, the animals will be euthanized and subjected to necropsy.

TABLE 4

Study Design						
Group	Number of Animals		Test	Dosage		Euthanasia/ Necropsy
Number	Males	Females	Device	Level*	Dosing Regimen	Day
1	6	6	FA Screw	1 implant	Surgical implantation of test device in one stifle joint	24 months after implantation
2	6	6	"	3 implants		

*Each implant nominally delivers approximately 60 micrograms/day of fluocinolone acetonide

[0083] Frequency and Duration of Administration

[0084] Devices were administered once via surgical implantation on Day 1.

[0085] Implants

[0086] The implant is a polymer-coated, sustained-release delivery system for Fluocinolone Acetonide (FA). The implant contains 55 mg of FA and is designed to deliver the drug for approximately 3 years. The tablet core contains approximately 55 mg of FA granulated with 10% PVA. The tablet core is positioned and adhered via an adhesive, such as a silicone adhesive, in the interchangeable head of the bone screw. The overall device geometry is that of a cancellous bone screw (i.e. the base) in which the head of the screw has been hollowed out to accept a removable cup (i.e. the payload) containing the drug tablet. In this embodiment, the screw is approximately 11/16" in length and is no more than 1/4" at its widest point (i.e. the screw head). The payload is sized to fit into the screw and to accommodate the tablet.

[0087] Preoperative Procedures

[0088] Anesthesia and Antibiotic Therapy

[0089] ProBios® or the equivalent (15 grams per os) was administered prior to surgery and on Day 2. The animals were premedicated with glycopyrrolate (0.02 mg/kg, intramuscularly [IM]), butorphanol (0.05 mg/kg, intravenously [IV]), and diazepam (0.2 mg/kg IV). Intravenous indwelling catheters were placed in peripheral veins as needed. Anesthesia was induced with methohexital (~10 mg/kg, IV). The animal was intubated and maintained in anesthesia with Halothane® inhalant anesthetic delivered through a volume regulated respirator, started as soon as possible after intubation. An esophageal tube was also be placed into the rumen to aid in keeping it decompressed. Lactated Ringer's solution was administered intravenously at a rate of ~10 mL/kg/hour. The total volume of crystalloid fluids administered did not exceed 2 L. Antibiotic prophylaxis began prior to surgery with the use of Cefotaxime (50 mg/kg, IV or IM).

[0090] Surgical Preparation

[0091] Eye ointment was applied to the eyes and all fleece was clipped from the entire leg, with any excess fleece removed by vacuum. The animal was positioned in lateral recumbency and the surgical site prepared for aseptic surgery by first washing the area with povidone-iodine scrub solution and 70% isopropyl alcohol, which was allowed to dry. Then, Dura-Prep™ or a similar solution was applied to the area and also allowed to dry. The area was then appropriately draped for strict aseptic surgery.

[0092] Surgical Procedures

[0093] A lateral skin incision was made to expose the fascia lata overlying the vastus lateralis cranially and the biceps femoris caudally. The joint was exposed through an incision in the lateral intermuscular septum to expose the femur by anterior retraction of the vastus lateralis and posterior retraction of the biceps femoris. Care was taken not to disrupt the tendon of origin of the long digital extensor as it originates from the lateral femoral condyle. The lateral geniculate vessels may be cauterized during this procedure. The joint capsule was opened, the patella luxated medially, and the joint held in full flexion. The appropriate number of implants (1 for Group 1; 3 for Group 2) were placed either within the anterior intercondyloid fossa (immediately lateral to the origin of the posterior cruciate ligament), the suprapatellar fossa, or the medial femoral condyle. The joint capsule was closed with 2/0 PDS in a simple interrupted fashion. The retinaculum, intermuscular septum, and fascia lata were closed with #2 PDS or Prolene® in a continuous pattern. The subcutaneous tissues were closed with 2/0 PDS and the skin closed with staples.

[0094] Blood Collection

[0095] Blood was collected from a peripheral vessel. Blood volumes represent whole blood and are approximate amounts.

Sample Collection Schedule				
Timepoint	Clinical Pathology			
	Serum		Bioanalytical Chemistry	
	Hematology	Chemistry	Blood	Synovial Fluid
Prior to surgery	X	X		
On Day 7			X	X
Once monthly for Months 1-12			X	X
Once quarterly for Months 13-24			X	X
Prior to necropsy	X	X	X	X
Volume of Whole Blood/ Timepoint	0.5 mL	1.8 mL	5.0 mL	0.3-0.5 mL
Anticoagulant	EDTA	None	EDTA	EDTA

[0096] The bioanalytical chemistry (BAC) blood samples were processed for plasma, the plasma was extracted and stored at ≤-70° C. until transferred for analysis.

[0097] Synovial Fluid

[0098] After anesthesia, an attempt was made to obtain synovial fluid. Synovial fluid samples were stored at $\leq -70^{\circ}\text{C}$. until transferred. Anesthesia for synovial fluid collection began after a minimum 12 hour fast (maximum 24 hours). An IM injection of diazepam (0.5 mg/kg) was given and then an IV catheter placed, followed by IV injections of 0.035 mg/kg xylazine and 3.0 mg/kg ketamine (combined in a syringe and injected slowly). Additional ketamine may be given as needed in increments of approximately 1 mg/kg. Anesthesia may be reversed with IV injections of yohimbine (0.125 mg/kg) or atipamezole (10 $\mu\text{g/kg}$).

[0099] FIG. 1 depicts the measured plasma versus synovial fluid concentrations in sheep and illustrates both the local and systemic pharmacokinetic profiles of intra-articular fluocinolone acetonide implants in the stifle joint of sheep. FIG. 1 represents a three-fold increase in FA concentrations in the synovial fluid of sheep at three and eight weeks. Plasma levels are between 0-0.35 ng/ml reflecting that drug delivered within the joint capsule is maintained at a high level over long periods of time. This differential in plasma and synovial fluid demonstrate the value of local therapy in treating joint disease. These results are illustrative of the general efficacy of the method and apparatus of the invention, but are not to be construed as limiting the scope of the invention in any way.

[0100] In an aspect of the invention, the fluocinolone acetonide, USP, are compressed into tablets using standard pharmaceutical methods and are dip coated with PVA, as discussed above, although other conventional processing means for applying the PVA (or other type of polymer coating or rate-limiting diffusion membrane) are acceptable in accord with the invention. Instead of placing the tablets into preformed silicone elastomer cups, however, the tablets are disposed within a bone screw 10 or other type of implantable device, as illustrated for example, in FIG. 2A and other figures appended hereto, which are described in greater detail below.

[0101] A drug delivery system 10 according to one aspect of the present invention is depicted in FIGS. 2A and 2B. The drug delivery system 10 (hereinafter "system 10") is generally in the form of a hollow-headed screw for attaching a sustained release device to a bone. System 10 comprises a hollow head 11, a neck 12, and a threaded shank 13 for threading system 10 into a hole in a bone. Head 11 is configured to allow system 10 to be screwed into a bone with head 11 substantially flush with the bone; for example, it can be chamfered and include slots S as shown in FIG. 2B to accommodate a (wrench). Device 10 is made of a material suitable for long-term insertion in the body, such as conventional surgical stainless steel. System 10 further comprises a chamber 14, such as a cylindrical chamber, formed inside head 11, for holding a sustained release device 15.

[0102] Sustained release device 15 includes an inner core 15a comprising an effective amount of a low solubility agent and a non-bioerodible polymer coating layer 15b that is permeable to the low solubility agent, wherein polymer coating layer 15b covers inner core 15a and is essentially non-release rate limiting. The polymer coating layer preferably covers the inner core and is essentially non-release rate limiting. In another aspect, the inner core may be substantially covered by the non-bioerodible polymer coating layer

15b that is not permeable to the low solubility agent, but instead defines and provides a plurality of small openings therein to permit sustained interaction between the inner core 15a and an external environment.

[0103] In still another aspect of the invention, the sustained release device 15 may be formed from a bioerodible material bearing a drug or a plurality of drugs. Bioerodible, as used herein, includes bioresorbable and bioabsorbable materials, as well as strictly bioerodible materials. Technically, bioabsorbable or bioresorbable materials are completely metabolized and eliminated from the body, whereas bioerodible materials are not necessary completely broken down and eliminated. Suitable bioerodible (and/or resorbable) polymeric materials include linear aliphatic polyesters (poly-glycolide, lactide, caprolactone, hydroxybutyrate) and their copolymers (poly-[glycolide-lactide], [glycolide-caprolactone], [glycolide-trimethylene carbonate], [lactic acid-lysine], [lactide-urethane], [ester-amide]), polyanhydrides, poly(orthoesters), polyphosphazenes, orthoesters, and poly(orthoester)/poly(ethylene glycol) block copolymers, to name a few. The bioerodible material may comprise combinations of materials or layers to achieve a desired result of bioeroding or bioabsorbing at a known, controlled rate.

[0104] Referring to FIGS. 2A and 2B, system 10 further comprises a removably attachable retainer 16, as of stainless steel, for retaining sustained release device 15 in chamber 14. Retainer 16 is generally cylindrical and comprises threads 17a in its outer wall for threadingly engaging threads 17b in an inner wall of chamber 14. Retainer 16 further comprises holes 18 for mating with torque transmitting pins of a screwdriver to remove and attach retainer 16 to system 10, and one or more openings 19 for allowing the drug from inner core 15a of sustained release device 15 to escape system 10. Those skilled in the art will understand that retainer 16 can be removably attached to system 10 by methods other than threads 17a, 17b.

[0105] In another embodiment of the present invention, shown in FIG. 5, a system 50 identical to that shown in FIGS. 2A and 2B is provided, except that an inner surface 14a of chamber 14 has threads 51a, and a second chamber 52 is removably attachable inside chamber 14. Second chamber 52 carries a sustained release device 53 comprising an inner core 53a and a polymer coating layer 53b, functionally similar to sustained release device 15 described in detail above. Second chamber 52 has threads 51b that threadingly engage threads 51a in the inner wall of chamber 14 to attach second chamber 52 to first chamber 14, and a pair of slots 54 for engaging a tool, such as a screwdriver, to screw second chamber 52 in and out of first chamber 14. After second chamber 52 is attached to chamber 14, retainer 16 is installed as described above.

[0106] In another embodiment of the present invention, shown in FIG. 3, system 30 comprises a hollow head 31, neck 32, threaded shank 33 for threading system 30 into a hole in a bone, and a first chamber 34 in head 31, similar to system 10 described above. However, in this embodiment of the present invention, a second chamber 35 is removably attachable inside first chamber 34, and carries a sustained release device 36 comprising an inner core 36a and a polymer coating layer 36b, functionally similar to sustained release device 15 described in detail above. Second chamber

35 has threads **37a** that threadedly engage threads **37b** in the inner wall of first chamber **34** to attach second chamber **35** to first chamber **34**, and a pair of slots **38** for engaging a tool, such as a screwdriver, to screw second chamber **35** in and out of first chamber **34**.

[0107] Referring now to **FIGS. 3 and 4**, system **30** further comprises a removably attachable retainer **39**, as of stainless steel, for retaining sustained release device **36** in second chamber **35**. Retainer **39** is generally cylindrical and comprises threads **40a** in its outer wall for threadingly engaging threads **40b** in an inner wall of second chamber **35**. Retainer **39** further comprises holes **41** for mating with a screwdriver to remove and attach it to second chamber **35**, and one or more openings **42** for allowing the drug from inner core **36a** of sustained release device **36** to escape system **30**. Those skilled in the art will understand that retainer **39** can be removably attached to second chamber **35** by methods other than threads **40a**, **40b**.

[0108] To attach the system of the embodiments of the present invention shown in **FIGS. 2A-5** to a body, such as a human body, a hole, such as but not limited to a chamfered hole, may be first drilled into a bone. The assembled system **10**, **30**, **50** is then screwed into the hole such that the head of the device is flush with the bone. The sustained release device **15** or second chamber **35**, **52** containing the sustained release device can be easily replaced as necessary when the drug of the inner core **15a**, **36a**, **53a** has been completely released without removing the entire system from the body.

[0109] In other embodiments of the present invention, illustrated in **FIGS. 6 and 7**, the system **60**, **70** comprises a staple **61** or a nail **71** that is driven into the bone instead of a screw. Still further, the system **60** illustrated in **FIG. 6** may be configured to clasp around a body part, such as a bone, by deformation of the outwardly protruding portions of staple **61** until a suitable securement of the staple **61** to the body part is obtained. A chamber **62**, **72** holds a sustained release device **63**, **73**, which is retained in chamber **62**, **72** by a removably attachable retainer **64**, **74** having a hole **65**, **75** for allowing release of the drug. Of course, in the embodiments of **FIGS. 6 and 7**, the system **60**, **70** does not sit flush with the bone, but protrudes somewhat. To minimize irritation to surrounding soft tissue, the sharply angled edges may be chamfered or rounded.

[0110] In still another embodiment of the invention, as shown in **FIG. 8**, a groove **80** is provided in a head **81** of system **85**. As depicted, the system comprises a head **81** having a chamber **82**, a neck **83**, and a threaded shank **84** for threading device **85** into a bone or into a hole formed in a bone. Groove **80** is formed within the head **81** to have an outer diameter D_2 greater than the diameter D_1 of the chamber and is set apart from the top surface of the head **81** so as to be bounded by a retaining ledge **86** on an upper portion thereof. A retaining member **88** is removably insertable within groove **80**, as shown in **FIGS. 9A-9C**. **FIG. 9A** shows another aspect of the relation between groove **80** and chamber **82**. In this embodiment, it is preferred that the retaining member **88** possess a curvilinear shape, such as a c-shape, as shown in **FIG. 9A**, wherein at least a portion of the member has a diameter substantially equal to D_2 and at least a portion having an inner diameter less than D_1 . Further, it is desired that this retaining member **88** be at least

sufficiently resilient to permit elastic deformation of at least a portion thereof to permit insertion of the retaining member into groove **80**.

[0111] In an equilibrium state, shown in **FIG. 9C**, the curvilinear member could not be inserted into the groove as it would be blocked by the retaining ledge **86** disposed on an upper side of the groove, retaining ledge possessing a diameter substantially similar to that of chamber **82**. By appropriately disposed tensile or compressive forces, however, curvilinear member **88** may be sufficiently elastically deformed from the equilibrium position, depicted by dashed lines in **FIG. 9A**, to permit insertion into groove **80**. In the inserted position, the retaining member **88** resumes its equilibrium position and an outer edge thereof abuts or conforms to the groove outer diameter. Moreover, at least a portion of an inner diameter of the retaining member possesses a diameter less than the diameter D_1 of the chamber **82**, thus at least partially occluding the opening to the chamber. In this way, an object in the chamber, such as a sustained release device **53**, may be retained within the chamber **82** by the portion of the retaining member **88** at least partially occluding the chamber. This occluding portion may comprise, as shown in **FIG. 9C**, a curvilinear portion which bounds an inner diameter D_1 of the chamber along an arc substantially equal to a length of the retaining member **88** or may simply comprise one or more projecting portions. Additionally, the degree of occlusion, or blocking of the chamber opening, may be varied in accord with the application by corresponding variation of the inner diameter of the occluding portion or projection portions of the retaining ring **88**.

[0112] Still another embodiment of the invention is shown in **FIGS. 10A-10C**. **FIG. 10A** depicts a top view and a cross-sectional view of a screw **95** having a screw head defining a hollow head **96** therein. A sustained release holding device **100** (see **FIG. 10C**) is detachably insertable into the hollow-head **96** portion of screw **95** to retain and locally deliver a drug provided therein. Screw **95** includes a threaded shank **91** for threading the screw comprising the drug delivery system into a hole in a bone (not shown). It is generally preferred to position a top surface of the screw **95** substantially flush with the bone, by means of an appropriate screw configuration or by provision of appropriate burr holes. In this embodiment, an inside diameter of the hollow head **96** is 0.244 inches and an outer diameter of the hollow head is 0.264 inches. A lip **94** formed at a top portion of the hollow head **96** has an outer diameter of 0.295 inches.

[0113] The depth of the hollow head **96** is 0.154 inches and a plurality of torque transmitting structures **97** are provided in a base portion **93** of the hollow head to facilitate mechanical securement of the screw into a receiving surface, such as a bone. These torque transmitting structures **97**, as illustrated in **FIG. 10A**, comprise three Phillips-head receiving portions disposed along a diameter of about 0.172 inches to a depth of less than about 0.025 inches. A diameter of the torque transmitting structures **97** may be about 0.048 inches. In accord with previous aspects of the invention, this torque transmitting structure may comprise one or more slots or may comprise other structures conventionally employed to transmit torques. The threaded shank **91** is at least 0.32 inches in length and possesses, in the illustrated embodiment, a thread **92** having a pitch of 0.69 inches, a root (or minor) diameter of 0.125 inches, and a major diameter of

0.177 inches, wherein the sides of the threads intersect one another at a 30° angle. A tip of the threaded shank 91 is angled, such as at a 30° angle to facilitate insertion.

[0114] Formed within an upper portion of the threaded shank 91 exposed to the hollow head 96 is a recessed threaded portion 98 having a depth of about 0.18 inches. As shown in FIG. 10A, the minimum thread depth is approximately 0.110 inches with a thread major diameter of about 0.0595 inches. FIG. 10C illustrates the corresponding threaded shank 99 of the sustained release holding device 100. The sustained release holding device 100 is configured for insertion into the hollow head 96 of screw 95. As such, the outer diameter of the sustained release holding device 100 is 0.236 inches and the depth is approximately 0.170 inches. The inner diameter of the sustained release holding device 100 is 0.183 inches. At an upper portion thereof is a lip 102 having an outer diameter of 0.295 inches configured to matingly engage the lip 94 of the hollow head 96 of screw 95.

[0115] A plurality of torque transmitting structures 101 are provided in lip 102 to facilitate mechanical securement of the sustained release holding device 100 into the hollow head 96 of screw 95. These torque transmitting structures 97, as illustrated in FIG. 10C, comprise three Phillips-head receiving portions disposed along a diameter of about 0.236 inches to a depth of between about 0.15 inches. A diameter of the torque transmitting structures 97 may be about 0.048 inches. In accord with previous aspects of the invention, this torque transmitting structure may comprise one or more slots or may comprise other structures conventionally employed to transmit torques. Projecting from a bottom portion of the sustained release holding device 100 is threaded shank 99, which is configured to matingly engage the recessed threaded portion 98 of the upper portion of the thread shank 91. In the illustrated embodiment, the threaded shank 99 has a length of about 0.10 inches and the threads extend along the shank about 0.06 inches.

[0116] Yet another embodiment of the present invention is shown in FIGS. 11A-11B. FIG. 11A depicts a top view and a cross-sectional view of a screw 103 having a screw head defining a hollow head therein (i.e., a hollow head) 105. A sustained release holding device 124 (see FIG. 11B) is detachably insertable within the hollow-head 105 to retain and locally deliver a drug provided therein. Screw 103 also includes a threaded shank 110 for threading the screw 103 comprising the drug delivery system into a bone (not shown). It is generally preferred to position a top surface of the screw 103 substantially flush with the bone, by means of an appropriate screw configuration or by provision of appropriate burr holes.

[0117] In this embodiment, similar to the embodiment depicted in FIGS. 10A-10C, an inside diameter of the hollow head 105 is 0.244 inches and an outer diameter of the hollow head is 0.264 inches. Lip 107 formed at a top portion of the hollow head 105 has an outer diameter of 0.295 inches. The threaded shank 110 is about 0.37 inches in length and possesses, in the illustrated embodiment, a thread 109 having a pitch of 0.69 inches, a root (or minor) diameter of 0.125 inches, and a major diameter of 0.177 inches, wherein the sides of the threads intersect one another at a 30° angle. A tip of the threaded shank 110 is angled, in the illustrated embodiment, at a 30° angle to facilitate insertion.

[0118] The interior depth of the hollow head 105 is 0.154 inches. Threaded shank 110 is provided on a bottom portion 104 of the hollow head 105. Formed within an upper portion of the threaded shank 110 and exposed to the hollow head 105 through a torque transmitting structure 108 is a recessed threaded portion 106 having a maximum depth of about 0.28 inches. As shown in FIG. 11A, the minimum thread depth of the threaded portion 106 is about 0.09 inches with a thread major diameter of about 0.0595 inches. Torque transmitting structure 108 is centrally provided in the base portion 110 of the hollow head 105 to facilitate mechanical securement of the screw 103 into a receiving surface, such as a bone. The torque transmitting structure 108 illustrated in FIG. 11A comprises a hexagonal key having a diameter of about 0.093 inches and a depth of about 0.125 inches.

[0119] FIG. 11B illustrates an embodiment of a sustained release holding device 124 configured for insertion into the hollow head 105 of screw 103. At a bottom portion of the sustained release holding device 124 is a threaded shank 126 corresponding substantially to the opening formed by the torque transmitting structure 108 and recessed threaded portion 106 of screw 103. The threaded shank 126 has a total axial length of about 0.20 inches, of which the threads comprise about 0.085 inches. The threads are configured to matingly engage those of the threaded portion 106 of screw 103 and are not provided in the portion of the threaded shank 126 corresponding to the screw 103 hexagonal key 108.

[0120] An outer diameter of the sustained release holding device 124 of FIG. 11B is 0.236 inches and the depth is approximately 0.184 inches. The inner diameter of the sustained release holding device 124 is 0.183 inches. At an upper portion thereof is a lip 122 having an outer diameter of 0.295 inches configured to matingly engage the lip 107 of the hollow head 105 of screw 103. A torque transmitting structure 120 is provided in lip 122 and/or hollow cylindrical body 125 of the sustained release holding device 124 to facilitate mechanical securement of the sustained release holding device 124 into the hollow head 105 of screw 103. The torque transmitting structure 120 illustrated in FIG. 11B comprises a hexagonal key having a diameter of about 0.1870 inches and a depth of about 0.040 inches.

[0121] FIG. 12A is a cross-sectional view of a self-tapping or self-drilling screw 140 in accord with the invention having a screw head defining a hollow head 135 therein. A sustained release holding device 150 (see FIG. 12F) is detachably insertable within the hollow head 135 to retain and locally deliver a drug provided therein. Screw 140 also includes a threaded shank 132 for threading the screw 140 comprising the drug delivery system into a bone. It is generally preferred to position a top surface of the screw 140 substantially flush with the bone, by means of an appropriate screw configuration or by provision of appropriate burr holes. It is preferred, but not necessary, to round or chamfer the transition between the hollow head 135 and the threaded shank 132 to form a shoulder 134. In one aspect thereof, the shoulder 134 is rounded with a radius of 0.09 inches in the transition from the hollow head 135 to a point of inflection in concavity toward a middle portion of the shoulder 134, at which point the shoulder is rounded with a radius of 0.04 inches.

[0122] It is preferred that the screw 140 is made of a cleaned and passivated 6AL-4V titanium alloy, although any

other surgical grade material of comparable strength, such as but not limited to stainless steel, composites, plastics, and/or ceramics exhibiting sufficient strength and/or hardness to permit insertion into and retention within the selected substrate (e.g., bone). To minimize stresses on the screw **140** and threaded shank **132**, a pilot hole may be drilled into the bone.

[0123] Corners of the threaded shank **132** are rounded, to about 0.005 inches, to remove sharp corners. Further, all burrs from manufacture are to be removed and all edges are rounded to a minimum of about 0.003-0.005 inches. This may be accomplished, for example, by micro bead blasting with S2 bead or by any other conventional surface treatment methods known to those skilled in the art. Further, it is to be understood that the dimensions described and depicted with respect to the illustrated embodiment are not limiting as to any other embodiments of the invention and do not represent, for simplicity of illustration, conventional manufacturing tolerances.

[0124] In this embodiment, an inside diameter of the hollow head **135** is 0.244 inches and an outer diameter of the hollow head is 0.264 inches. Lip **137** formed at a top portion of the hollow head **135** has an outer diameter of 0.295 inches. The threaded shank **132** is about 0.39 to 0.41 inches in length and possesses, in the illustrated embodiment, a thread **138** having a pitch of about 0.111 inches and a root (or minor) diameter of about 0.125 inches at the tip of the screw **140**, although the geometry of the tip may vary in a manner known to those skilled in the art in accord with the entry or initial drilling conditions expected for a particular application. In the embodiment depicted in **FIG. 12D**, the root diameter increases, from the initial root diameter of about 0.125 inches at the tip of the screw **140**, by about 0.005 inch per thread up to about 0.135 inches at a base of the thread **138** adjacent the head of the screw. The thread **138** has a major diameter of about 0.250 inches and possesses a thread angle of about 15° ($2\alpha=30^\circ$). As illustrated, the threaded shank **132** has 9 threads per inch. A tip of the threaded shank **132** is smoothly angled, in the illustrated embodiment, at a 45° angle and is radiused at about 0.062 inches.

[0125] With respect to the cutting faces or heels of the screw **140** corresponding to the flutes **138**, the flutes are radiused at 0.312 inches centered on a perpendicular to the tip of screw **140**. As known to those skilled in the art, flutes are longitudinal channels formed in a tap to create cutting edges on the thread profile and to provide chip spaces and cutting fluid passages. The cutting face of the flutes may possess positive, negative, or zero rake, in accord with a desired angular relationship between the cutting face with a radial line through the crest of the tooth at the cutting edge. In this aspect of the invention, two flutes **138** are formed opposite one another as shown in **FIG. 12B**.

[0126] As shown in **FIG. 12A**, The interior depth of the hollow head **135** is 0.154 inches. A recessed threaded portion **136**, having a maximum depth of about 0.11 inches, is provided at a central portion of a bottom of the hollow head **135**. In one aspect, recessed threaded portion **136**, as shown in **FIG. 12C**, has a thread depth of about 0.07 inches with a thread diameter of about 0.0595 inches. The overall depth of the threaded portion **136** is about 0.11 inches. The terminus of the recessed threaded portion **136** may comprise

a chamfered portion, as illustrated. Torque transmitting structures **180** are also provided at a bottom of the hollow head **135** to facilitate mechanical securement of the screw **140** into a receiving surface, such as a bone. The torque transmitting structures **180** illustrated in **FIG. 12C** comprise 0.040 inch deep holes having a diameter of about 0.049 inches (± 0.0005) spaced on a diameter of the screw hollow head **135** of 0.161 inches (± 0.0005).

[0127] **FIGS. 12E-12F** illustrate an embodiment of a sustained release holding device **150** configured for insertion into the hollow head **135** of screw **140**. A threaded shank **155** is disposed at a bottom portion of the sustained release holding device **150**. Threaded shank **155** is configured to matingly engage the opening formed by the recessed threaded portion **136** of screw **140**. As shown in **FIG. 12F**, the threaded shank **155** has a total axial length of about 0.065 inches, of which the threads comprise about 0.06 inches to engage a corresponding portion of threaded portion **136** of screw **140**.

[0128] An outer diameter of the sustained release holding device **150** of **FIGS. 12E-12F** is 0.236 inches and the depth of an interior cavity **156** defined thereby is approximately 0.175 inches. The inner diameter of the sustained release holding device **150** is 0.183 inches. At an upper portion thereof is a lip **175** having an outer diameter of 0.295 inches configured to matingly engage the lip **137** of the hollow head **135** of screw **140**. Torque transmitting structures **185** are provided in lip **175** of the sustained release holding device **150** to facilitate mechanical securement of the sustained release holding device **150** into the hollow head **135** of screw **140**. The torque transmitting structures **185** illustrated in **FIGS. 12E-12F** comprise 0.020 inch deep holes having a diameter of about 0.049 inches (± 0.001) spaced on a diameter of the sustained release holding device **150** lip **175** of 0.239 inches (± 0.001).

[0129] **FIGS. 13A-13B** illustrate another embodiment of a sustained release holding device **250** configured for insertion into the hollow head **135** of screw **140**. A threaded shank **255** is disposed at a bottom portion of the sustained release holding device **250**. Threaded shank **255** is configured to matingly engage the opening formed by the recessed threaded portion **136** of screw **140**. As shown in **FIG. 13B**, the threaded shank **255** has a total axial length of about 0.07 inches, of which the threads comprise at least about 0.05 inches to engage a corresponding portion of threaded portion **136** of screw **140**.

[0130] An outer diameter of the sustained release holding device **250** of **FIGS. 13A-13B** is 0.236 inches and the depth of the interior cavity **256** defined thereby is approximately 0.154 inches. The inner diameter of the sustained release holding device **250** is 0.183 inches. At an upper portion thereof is a lip **275** having an outer diameter of 0.295 inches configured to matingly engage the lip **137** of the hollow head **135** of screw **140**. The upper surfaces of the sustained release holding device **250** are slightly rounded, having a radius of 0.75.

[0131] Torque transmitting structures **285** are provided in lip **275** of the sustained release holding device **250** to facilitate mechanical securement of the sustained release holding device **250** into the hollow head **135** of screw **140**. The torque transmitting structures **285** illustrated in **FIG. 13A** comprise recessed portions in the sidewall of the lip **275**

that are approximately 0.06 inches deep. As shown, these recessed portions are configured to extend slightly inwardly with increasing depth, at an angle of between approximately 8°-12°. The torque transmitting structures or recessed portions **285** are, as illustrated, generally semi-circular, possessing a diameter of about 0.049 inches (± 0.001) spaced on a diameter of the sustained release holding device **250** lip **275** of 0.239 inches (± 0.001). Spacing and geometry of the torque transmitting structures or recessed portions **285** may be freely varied to suit the tools and fittings available to produce the torque required to secure the sustained release holding device within the hollow head **135** of screw **140** and may comprise, for example, slots, keys or holes.

[0132] The assembled structure of sustained release holding device **250** and the hollow head **135** of screw **140** is depicted in FIGS. 14A-14B, wherein a drug payload **300** is shown within the sustained release holding device **250**. FIG. 14C shows one means of insertion and securement of the drug payload **300** within the sustained release holding device **250**. An adhesive **305** is provided along one or more inner surfaces of the sustained release holding device **250** prior to insertion of the drug payload **300**. Upon insertion of the drug payload **300**, the adhesive **305** sets and retains the drug payload in place. Although it is preferred that the adhesive **305** have a low enough viscosity to permit the adhesive to flow into gaps between the drug payload **300** and the inner surfaces of sustained release holding device **250**, this property is not required and any adhesive **305** compatible with the drug payload coating layer or rate-limiting barrier **315**, the drug itself, and/or the material of the sustained release holding device **250**, corresponding to various embodiments of the invention, is acceptable.

[0133] In accord with the invention, the adhesive **305** may be one that can be applied, at room temperature, by a physician, veterinarian, or medical worker, in accord with the application to facilitate flexibility of drug payload **300** selection and application. It is also possible, in accord with the invention, to pre-form frequently applied drug payloads **300** within the sustained release holding device **250** to simplify ease of end use by a physician, veterinarian, or medical worker. Such pre-formed combinations of drug payload **300** and screw **140** could permit additionally permit utilization of other means of adhesive affixation, including thermosetting resins or compounds. However, any adhesive process utilizing elevated temperatures would have to be selected so as not to materially degrade either the coating of the drug payload **300** or the drug contained therein, as the efficacy of various drugs have been shown to be adversely affected by elevated temperatures. Further, such pre-formed combinations of drug payloads **300** and screw **140** would require some adjustment to the structures and methods provided herein to permit the screw **140** to be inserted into the target substrate (e.g., bone) by application of torque directly to the head or upper portion of the screw or of an upper portion of the sustained release holding device (e.g., **250**). In other words, torque transmitting structures **285** can be disposed within or integrated into the head or upper portion of the screw **140** or sustained release holding device **250** in a manner known to those skilled in the art.

[0134] Once implanted, the drug payload **300** is released at a controlled rate over an extended period of time, in accord with the intended therapeutic result, into the area of the patient's body surrounding the insertion site as repre-

sented in FIG. 14D. The release rate may be controlled, for example, by appropriate variance of coating layer or rate-limiting barrier **315** properties and geometry. The coating layer **315**, such as but not limited to a polymer coating layer, may be selectively omitted, entirely or partially, from one or more portions of the surface area of the drug to be delivered, particularly from the drug surface adjacent the outlet of the sustained release holding device **250**. In one aspect thereof, the coating layer **315** may be applied only to a surface of the drug payload **300** adjacent the opening of the sustained release holding device **250**. In such an embodiment, adhesive **305** should be selected so as not to structurally or chemically degrade the drug(s) present in the drug payload **300**.

[0135] In still another aspect thereof, the coating layer **315** may be applied to a surface of the drug payload **300** adjacent the opening of the sustained release holding device **250** and to an opposing surface adjacent adhesive **305**, wherein the adhesive is selected by volume and/or viscosity to limit flow of the adhesive to adjoining surfaces of the drug payload not having a coating layer.

[0136] One device suitable for use in installing an embodiment of the drug delivery system of the invention is depicted in FIGS. 15A-15B. The drill imparting the torque to the screw may comprise essentially any automated, motorized, or manual drill considered acceptable by medical practitioners for medical applications. In one aspect of contemplated surgical procedures, the area of implantation is made accessible by movement of soft tissues away from the targeted area and a conventional hand held drill may be used. In other aspects thereof, to minimize trauma to the tissues, less invasive procedures are used and the drill bit **405** may be advantageously provided within a cannula or drill sleeve, such as those conventionally applied during arthroscopic or orthroscopic surgery, to prevent damage to soft tissue during drilling.

[0137] FIGS. 15A-15B illustrate different embodiments drivers **450** configured to drive screw **140** into the preformed pilot holes **410**, **420** as discussed later with respect to FIG. 16A. Each driver **450** has a head **460** configured to matingly engage torque transmitting structures **180** on the interior portion of hollow head **135**. As depicted in FIGS. 15A-15B, the head **460** comprises three drive members **465** approximately 0.040 inches in length having a diameter of about 0.049 inches spaced on a diameter of 0.161 inches to correspond with the screw **140** depicted in FIGS. 12A-12F. The drive members **465** can assume any shape, number or distribution corresponding to that of the torque transmitting structures **180** of the hollow head **135**. In operation, the drive shaft **470** of the driver **450** is rotated clockwise or counterclockwise, at a proximal end, to produce a corresponding clockwise or counterclockwise motion of the head **460** at a distal end. The proximal end of the driver **450** may, as shown in FIG. 15A have a knob **475** having a radius configured to permit generation of varying degrees of torque in accord with a moment arm applied by a medical provider's digital manipulation. Alternatively, as shown in FIG. 15B, the drive shaft itself may simply be provided with a high friction or grippable surface **480** having a diameter substantially equal to the diameter of the drive shaft **470** itself to permit less torque than the driver **450** depicted in FIG. 15A to thereby enable a finer degree of control and tactile sensitivity.

Although the drivers **450** depicted are manually operated, the drivers **450** may advantageously be motorized.

[0138] A method for implanting a drug delivery device in accord with FIGS. 14A-14D into a bone is depicted in FIGS. 16A-16G.

[0139] First, as shown in FIG. 16A, it is preferred to drill a pilot hole into the bone **400**. Alternatively, a self-tapping or self-drilling screw may be used. The drill bit **405** depicted in FIG. 16A produces a first pilot hole **410** having a first depth and first diameter D1 and a second pilot hole **420** having a second depth and a second diameter D2. The first diameter D1 is selected to be less than the outer diameter of the threaded shank **132** (i.e., less than 0.25 inches in the embodiment of FIG. 12A) and is preferably less than or equal to the root diameter of the threaded shank **132** (i.e., less than 0.135 inches in the embodiment of FIG. 12A) or of the tip of the screw **140** (i.e., less than the initial root diameter of about 0.125 inches in the embodiment of FIG. 12A) to permit effective securement of the threaded shank **132** into the bone **400**.

[0140] An intermediary portion **415** between the first diameter and the second diameter is preferably chamfered or angled to correspond to the shape of the shoulder **134** of the screw **140**. An abrupt step-change in diameter may, however, also be used in accord with a screw so configured in accord with the invention. Second diameter D2 of pilot hole **420** is configured to substantially correspond to an outer diameter of the hollow head **135** of the screw **140**. Although not shown, drill bit **405** may comprise a third section configured to drill a relatively shallow third hole having a thickness corresponding to a thickness of the lip **137** of the hollow head **135**. In this way, an upper edge of the lip and hollow head may be provided flush with the surface of the bone.

[0141] FIG. 16B illustrates a step of connecting the screw **140** of FIG. 12A and the driver **450** of FIG. 15A in accord with the invention. FIG. 16C illustrates insertion of the screw **140** into the pilot holes **410**, **420** drilled into the bone **400** by applying a torque to the driver **450** drive shaft **470** by means of the knob **475**. FIG. 16D depicts the screw **140** inserted into the bone **400**.

[0142] Following insertion of the screw **140**, the drug payload **300** is inserted in accord with the aspect of the invention depicted in FIG. 14C, wherein a health care provider first places an adhesive material **305** on at least one surface of the inner walls of the sustained release holding device (e.g., **250**) and, second, presses the drug payload against the adhesive to secure the drug payload within the sustained release holding device.

[0143] Once the drug payload **300** is secured within the sustained release holding device **250** and following lapse of a setting time for the adhesive, if necessary, the sustained release holding device **250** may be inserted into the hollow head **135** of screw **140**, as shown in FIGS. 16E-16G. FIG. 16E illustrates a step of connecting the sustained release holding device **250** of FIGS. 13A-13B and a driver **550** substantially similar to that of driver **450** of FIG. 15A. In this particular embodiment of driver **550**, the distal end **590** has a raised portion or boss **555** configured to engage the inside of lip **275** of the sustained release holding device **250**. This engagement is accomplished by rotating knob **575** clockwise

to retract the drive shaft **570** linearly away from distal end **590** using threads **580** to convert the rotary motion to a linear motion.

[0144] The inner diameter ID of distal end **590** between points A1 and A2, as depicted in FIG. 16F, is substantially constant and is greater than an outside diameter OD of the driver head **560**. The inner diameter ID of distal end **590** at point A2 is substantially equal to an outside diameter OD of the driver head **560**. The inner diameter ID of distal end **590** between points A2 and A3, as depicted in FIG. 16F, decreases with increasing distance from the front or leftmost of distal end, as shown, and is less than an outside diameter OD of the driver head **560**. Therefore, as the driver head **560** is withdrawn past point A2, the driver head exerts an outward force against the inner walls of the distal end **590**. The narrowed portion **585** adjacent the distal end **590** facilitates outward flexure of the distal end walls, including the raised portion or boss **555**.

[0145] Accordingly, when driver head **560** is retracted, boss **555** is splayed outwardly to engage the inside of lip **275** of the sustained release holding device **250** and secure the sustained release holding device to the driver **550** as shown in FIG. 16F. Once secured, the sustained release holding device **250** is placed within the hollow head so that the threaded shank **225** is adjacent to and in initial contact with the threaded portion **136**. Driver **550** is then itself rotated clockwise to screw the threaded shank **225** into the threaded portion **136** to secure the sustained release holding device **250** in the hollow head **135**.

[0146] Engagement between the boss **555** and the lip **275** of sustained release holding device **250** is then released by rotating knob **575** to linearly advance driver head **560** and return the outwardly splayed boss **555** to its original or equilibrium position, whereupon it does not contact the lip **275**. The driver **550** may then be removed, leaving the installed bone screw **140** bearing a drug payload **300** in sustained release holding device **250**, as shown in FIG. 16G.

[0147] The purpose of the above description and examples is to illustrate some embodiments of the present invention without implying any limitation. It will be apparent to those of skill in the art that various modifications and variations may be made to the method and device of the present invention without departing from the spirit or scope of the invention. All patents and publications cited herein are incorporated by reference in their entireties.

What is claimed is:

1. A method for locally administering a therapeutically effective compound to a joint of a mammal, the method comprising the step of:

intraarticularly implanting a sustained release device to deliver the therapeutically effective compound within a synovial capsule of the joint such that synovial fluid concentration of the compound is greater than plasma concentration of the compound during substantial lifetime of the device.

2. The method of claim 1, wherein the plasma concentration is substantially non-toxic.

3. The method according to claim 1, wherein the synovial fluid concentration is therapeutic.

4. The method according to claim 1, wherein the device releases the therapeutically effective compound for at least 8 weeks.

5. The method according to claim 1, wherein the device releases the therapeutically effective compound for at least 12 months.

6. The method according to claim 1, wherein the device releases the therapeutically effective compound for about 3 years.

7. The method according to claim 1, wherein the synovial fluid concentration of the compound remains several orders of magnitude greater than the plasma concentration over the lifetime of the device.

8. The method according to claim 1, wherein the therapeutically effective compound is fluocinolone acetonide.

9. The method according to claim 1, wherein the therapeutically effective compound is a cyclosporine.

10. A method for treating arthritis of joint, the method comprising the step of:

intraarticularly implanting a sustained release device into a joint to deliver a therapeutically effective compound within a synovial capsule of the joint such that synovial fluid concentration of the compound is greater than plasma concentration of the compound during substantial lifetime of the device.

11. An implantable sustained release device for locally administering a drug, the device comprising:

a bone screw including a hollow portion configured to receive a sustained release holding device, said sustained release holding device itself configured to receive a drug payload.

12. An implantable sustained release device in accord with claim 11, wherein the sustained release holding device is removably provided within said hollow portion.

13. An implantable sustained release device in accord with claim 12, further comprising:

a drug payload including one or more drugs;

a rate-limiting barrier configured to limit a release rate of a drug from the drug payload to thereby provide sustained release of the drug.

14. An implantable sustained release device in accord with claim 13,

wherein the rate-limiting barrier is configured to provide a steady-state release rate of a drug from the drug payload substantially equal to a steady-state rate of elimination of the drug from a treatment site, and

wherein the rate-limiting barrier is configured to provide a predetermined therapeutic concentration of the drug in the treatment site, said predetermined therapeutic concentration of the drug being greater than a plasma concentration of the drug until substantially all of the drug in the drug payload is depleted.

15. A system comprising:

a mechanical member attachable to a portion of a body;

a first chamber having an opening configured to receive a sustained release device;

a sustained release device; and

a removably attachable retainer for retaining the sustained release device in the first chamber.

16. The system according to claim 15, wherein the mechanical member is substantially rigid and is configured for at least partial insertion into a bone.

17. The system according to claim 16, wherein the mechanical member comprises a screw.

18. The system according to claim 17, wherein the first chamber is defined within a head of the screw.

19. The system according to claim 18, wherein the sustained release device comprises a drug-bearing insert attachable within said first chamber.

20. The system according to claim 19, wherein the drug-bearing insert is removably attachable within said first chamber by a mechanical fastener.

21. The system according to claim 15, wherein the sustained release device comprises an inner core comprising an effective amount of a low solubility agent; and

a non-bioerodible polymer coating layer, the polymer layer being permeable to the low solubility agent, wherein the polymer coating layer covers the inner core and is essentially non-release rate limiting.

22. The system according to claim 15, wherein said removably attachable retainer partially occludes the chamber opening.

23. A system comprising:

a mechanical member attachable to a portion of a body;

a chamber disposed within the mechanical member configured to receive a sustained release device bearing at least one drug; and

an opening in the chamber to permit release of the at least one drug borne by the sustained release device.

24. The system according to claim 23, further comprising a sustained release device configured for placement in said chamber of said mechanical member.

25. The system according to claim 24, wherein the sustained release device comprises an inner core comprising an effective amount of at least one low solubility agent; and

a non-bioerodible polymer coating layer, the polymer layer being permeable to the at least one low solubility agent, wherein the polymer coating layer covers the inner core and is essentially non-release rate limiting.

26. The system according to claim 25, wherein the mechanical member is substantially rigid and is configured for at least partial insertion into a bone.

27. The system according to claim 26, wherein the mechanical member comprises a screw.

28. The system according to claim 27, wherein the chamber is defined within a head of the screw.

29. A method for administering a drug to a joint, the method comprising the step of:

positioning a mechanical member in or adjacent a bone, said mechanical member configured to hold a sustained release drug delivery device bearing at least one drug; and

outputting said at least one drug from said sustained release drug delivery device at a substantially controlled rate.

30. The method of claim 29, wherein the drug comprises a steroid.

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