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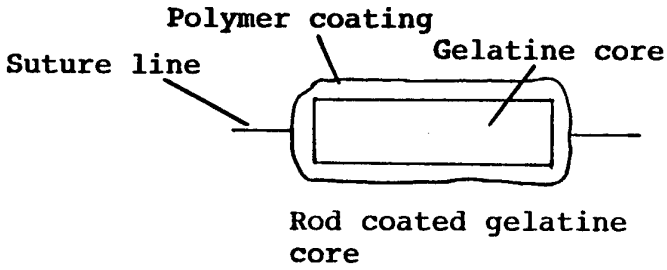

(57) Abstract

A pulse release implant comprising: an axial biodegradable core; a first concentric layer comprising dehydrated hydrogel containing an active ingredient; and an outer coating, said outer coating being removable by the environment in which the implant will reside after administration. A process of preparing a pulse release implant including the steps of: coating an axially disposed biodegradable core material with a hydrogel containing an active ingredient to form a concentric coating; separating the coating into discrete segments disposed along the core material; dehydrating the hydrogel; coating the discrete segments with an outer coating, said outer coating being removable by the environment in which the implant will reside after administration; and removing the exposed core material to obtain the pulse release implants.

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CONTROLLED RELEASE IMPLANTS

FIELD OF THE INVENTION

This invention relates to implants containing active ingredients, especially drugs or veterinary products suitable for administration to humans and animals in which the active ingredient is required to be administered in a pulsatile release profile.

Prior art implants are typically of the reservoir type and usually contain a single active ingredient and provide the continuous release of the active in a zero or first order mode of release kinetics.

Present methods of making these prior art implants use basically two approaches, viz, (i) tabletting; and (ii) melt processing. Representatives of these approaches are described as follows:

(i) Tabletting (International Patent Application No. PCT/AU87/00139)

A water insoluble excipient (eg, calcium phosphate) is thoroughly mixed with a bioactive agent such as a protein or peptide in an amount sufficient to give the required dosage unit of active ingredient in the final product. The bioactive agent is usually in the form of a solution or dispersion or powder to facilitate mixing. A water soluble excipient (eg, lactose), if used, is then added, together with the other desired additives, eg, a lubricating agent such as magnesium stearate, and mixed to form a homogeneous dry powder. The powder is then compressed into a tablet of the desired size and shape. The compressed tablet is then coated in a pan coater by spraying with a solution or dispersion of the coating material in an amount sufficient to give implants with the required coating thickness.

In an alternative coating method known as Wurster coating, the tablet is coated in a fluidized bed system.

(ii) Melt Processing ("A sustained release Ivermectin implant for livestock pest control" by J Allan Miller, R O Drummond, D D Oehler in "Controlled Release Delivery Systems" ed. Theodore J Roseman and S Z Mansdorf, 1983, Marcel-Dekker; Chapter 15, pp 223-236)

An implant containing 20% Ivermectin was formulated by dissolving technical Ivermectin in a melt of polyethylene glycol (PEG) (MW 15,000 - 20,000). The solution was then drawn by vacuum into a 3 mm internal diameter Teflon tube and allowed to cool. Upon cooling the resultant solid rod (3mm diameter) was removed and trimmed to the desired weight of 400 mg.

Implant products of this type are solid cylindrical rods of varying length and diameter and can have shapes ranging from flat discs to fine needles. This type of implant is useful where a prolonged continuous supply of the drug is required.

The pan coating and Wurster coating methods involve substantial contact between the implants being coated. During the drying process, the coating gets sticky resulting in implants sticking together or "twinning". It has been attempted to overcome this problem by the addition of additives and modifiers in the coating. When the implants are to be used for administration to humans or animals, the additives which may be used are limited to those substances cleared for regulatory use. Polyester coatings, for example, have been cleared for regulatory use however these present a particular problem in the pan coating method due to adhesion of the particles during the drying process. In addition pinholes and other discontinuities can form in the outer coat during the drying process.

It would be desirable to avoid mutual contact of the implants during the drying process and to be able to control the drying process to avoid the formation of pinholes and discontinuities.

There are frequent circumstances where implants are required to provide a pulsatile release of an active ingredient. An example of such circumstances is the so-called

"one shot vaccine" concept. Vaccination has been used to protect humans and animals against bacterial and viral infectious diseases. In the case of vaccines prepared in the form of killed suspensions of bacteria or viruses, or in the form of conjugated toxoids, repeated injections at specific time intervals are required in order for the vaccination to effect adequate levels of immunological response. These intervals may typically range from a few weeks to several months. Due to prevailing epidemiological, social, economic accessibility, human temperamental, or simply convenience reasons, it is highly desirable that effective protection against diseases can be obtained with single injections. In order to make this possible the one shot vaccines have to release the actives at the required intervals, i.e. in a pulsatile mode, in the required profile, i.e. a "dump". A further application of the "one shot vaccine" approach is a 6 month or 12 month contraceptive implant or vaginal suppository which delivers the contraceptive hormones in a succession of pulses, the active ingredient in this application not being a vaccine.

A further non-vaccine example relates to the need for delivery of reaction mixtures to sites of action, specifically the delivery of the lactoperoxidase thiocyanate enzyme substrate reaction system to the hindguts of piglets in the control of diarrhoea. Lactoperoxidase, coupled with a peroxide generating oxidase (eg, xanthine and xanthine oxidase) converts SCN to SCNO, a very reactive and lethal ion for micro-organisms. Pulse release technology can be used to address the problem of reinfection.

Constructing a delivery vehicle to meet these sorts of functional requirements demands a technology of making compartmentalised structures. The manufacturing process should preferably be simple, versatile, and amenable to mechanisation and automation.

Although the most important attribute of a controlled release drug delivery device is its capability to maintain a therapeutically effective level of drug in an animal body over a scheduled period of time, its adoption ultimately depends on the cost, convenience, and ease of its fabrication and administration (1).

In terms of the ease and convenience of administering these devices as implants, shapes like sheets, films or hemispheres are generally impractical. However rods, needles or cylinders are readily adapted for parenteral implantation using a conventional hypodermic needle.

Producing eccentric shapes such as rods, needles or cylinders with the above described prior art methods, is also problematic. The pan coating and Wurster coating methods are most amenable to implants of a generally rounded shape.

The applicant's copending Application PCT/AU93/00083 discloses a method of making implants which are suitable for continuous release of an active ingredient over a period of time which consist of a body member comprising a membrane forming a wall around a core matrix and comprising material which is substantially impervious to the active ingredient contained within the core matrix. The cylinder is generally open ended, the active ingredient being released directly through the open ends of the cylinder. In order to make an implant suitable for pulsatile release using this technique, it is necessary to separately coat the open ends of the implant. This separate coating step is expensive, clumsy, and time-consuming.

A need accordingly exists for a simple and economical manufacturing process for implants which can release bioactive materials and which can be readily adapted for complex, in particular, pulsatile release of these materials.

Accordingly, one aspect of the present invention contemplates a pulse release implant comprising:

an axial biodegradable core;

a first concentric layer comprising dehydrated hydrogel containing an active ingredient; and

an outer coating, said outer coating being removable by the environment in which the implant will reside after administration.

In a further embodiment of the present invention there is provided a process of preparing a pulse-release implant including the steps of:

coating an axially disposed biodegradable core material with a hydrogel containing an active ingredient to form a concentric coating;

separating the coating into discrete segments disposed along the core material;

dehydrating the hydrogel;

coating the discrete segments with an outer coating, said outer coating being removable by the environment in which the implant will reside after administration; and

removing the exposed core material to obtain the pulse release implants.

The biodegradable core may be formed from any suitable material. Preferably the core is biocompatible. The core may be formed from a string, suture or rod.

The term hydrogel is used in its ordinary art recognised meaning of a water-based three dimensional nonflowable amorphous structure. The gel may be created by ionic or hydrogen bond interactions. Hydrogels of particular interest consist of a solution of a polymer in water which under controllable conditions can be made to adopt either a fluid or semi-solid configuration. This allows the hydrogel to be applied as a fluid to the core member and retain its shape as a semi-solid form. Methods to induce the transition include temperature control or the use of cross-linking agents such as calcium ions. The temperature control method is suitable for gels such as agar and gelatine and the cross-linking method is suitable for hydrogels formed from substances such as alginate polymers.

In the present invention, a hydrogel in a fluid form is applied to the axial biodegradable core, a transition to a semi-solid state is induced and the hydrogel is thereby immobilised. In this state, the hydrogel may be cut and otherwise manipulated. When water is removed from the semi-solid form, a dehydrated hydrogel is formed. The dehydrated hydrogel forms a rigid solid which is suitable for storage and handling.

Any suitable hydrogel may be used. Examples are gelatine, agar, alginates, carrageenan, gum gragacanth, acacia, or corn starch. It may also be desirable to include other components in the first concentric layer. Examples are disintegrating agents such as corn starch, potato starch, alginic acid and the like and/or a lubricant such as magnesium stearate. Osmotic modifiers such as sucrose and glucose may also be desirable. All such components, should be substantially pharmaceutically pure and non-toxic in the amounts employed and should be biocompatible and compatible with the active ingredient when used for human or animal use.

The active ingredient is typically a bioactive molecule and includes any native, synthetic or recombinant pharmaceutical agent or food additive or supplement including antigens, antibodies, cytokines, growth promotants, hormones, cancer cell inhibitory molecules or agents, immune stimulants or suppressants, anti-microbial agents including antibiotics, anti-viral agents, vitamins, minerals or inorganic or organic nutrients. The active ingredient may comprise one type of bioactive molecule or may be a mixture of different bioactive molecules. In a preferred embodiment the active ingredient includes antigens from the clostridial family.

The outer coating may be formed of any suitable biocompatible substance. The outer coating is generally membranous or polymeric and is substantially impervious to the active ingredient. The majority of the active material will be delivered or released as a result of the removal of the outer coating encasing the first concentric layer. Examples of suitable coating materials include modified starches, sugars, poly anhydrides, polyorthoesters, bioerodible polyesters and the polylactic/polyglycolic acid family of polymers. Polylactic/polyglycolic acids are particularly suitable as they are widely commercially available with various degradation profiles and have regulatory clearance.

The coating may have a thickness of from typically 10μm to 1,000μm depending on the application of the implant, and the permeability or degradability of the coating.

Sliding

The implant device may be in any suitable shape including elongate, oval, round, ball, capsule, rod, needle, or cylinder shape. Conveniently, the shape is an elongate cylindrical, rod or needle shape. In a most preferred embodiment, the implant device is elongate and generally cylindrical.

In the process of the present invention, an axially disposed biodegradable core material is coated with a hydrogel containing an active ingredient to form a concentric coating. Smaller discrete gel segments, which remain supported by the biodegradable core can be created by cutting the outer concentric hydrogel layer in such a way that the biodegradable core remains intact and sliding the cut segment along the axially disposed biodegradable core so as to form a space between the discrete gel segments. This operation will hereinafter be referred to as the "cut/slide operation".

The cut/slide operation may be performed after the hydrogel has been dried and prior to coating however it is generally easier to perform the cut/slide operation on wet hydrogel. Therefore in the process of the present invention the separation and dehydration steps may take place in either order. For example, the hydrogel may be dehydrated before separation into discrete segments although it is preferred that the hydrogel is separated before dehydration.

The outer coating may be applied in any suitable manner. For example, the outer coating may be applied by means of a mould, dipping, spraying or by application via a "rod" or "wick".

The above cut/slide operation overcomes certain deficiencies of known prior art coating methods in that the problems of the implants sticking together during the drying process is overcome and the problem of pinholes and discontinuities in the outer coat is alleviated as the drying process of the present invention may be better controlled.

Once the outer coating has been applied, the exposed core material may be cut away resulting in discrete pulse release implants.

The process of the present invention is readily adaptable for incorporation of heat labile active ingredients. It presents few constraints with respect to the choice of active ingredients; and it should be noted that by using a biodegradable structural support, such as surgical suture, the central core does not need to be removed from the final implant product.

The present device also provides the basis on which further refinement or sophistication of release can be effected. For instance, by using as the hydrogel layer bioerodible polyorthoester polymers prepared by the reaction between 3,9-bis(ethylidene-2,4,8,10-tetraoxaspiro-[5,5]-undecane) and various ratios of trans-cyclohexanedimethanol and 1,6-hexandiol (2), the production method can be readily adopted for mass production of needle injectable implants of antitumour agents such as 5-flurouracil for release in a time independent mode. Likewise, by using collagen poly (HEMA) hydrogel (1) as the incorporating matrix, needle injectable implants can be readily mass produced for a variety of hydrophilic or hydrophobic active substance with again a time independent release mode.

The recipient of the implant may be a human, livestock animal including a ruminant animal, e.g. a sheep, cow, horse, pig, goat or donkey, poultry, e.g. chicken, turkey, goose or game bird, a laboratory test animal, e.g. a rabbit, guinea pig or mouse, companion animal, e.g. dog or cat, or a wild animal in the captive or free state.

Administration of the implant may be by any convenient means but is generally by injection via the intravenous, intraperitoneal, intramuscular, sub-cutaneous or intradermal route. The device may also be surgically implanted or implanted by sub-surgical procedures such as during biopsy procedures. Devices such as these may also be administered by an oral route.

The amount of active ingredient used in a given implant will vary depending on the

type of bioactive molecule, condition in the animal being treated and the presence or absence of agonists to the active ingredient or antagonists to the condition being treated. In general, an effective amount of active ingredient is employed meaning an amount effective to induce, stimulate, promote or otherwise initiate the immediately intended result.

For example, if the active ingredient is an antigen, the effective amount is that required to stimulate an immune response to the antigen. Commonly, the active ingredient will be present in amounts ranging from a few micrograms to gram quantities per implant.

The invention will be further described by reference to the following non-limiting figures and examples. In the figures:

Figure 1 is a part sectional, part schematic, cross section of an apparatus suitable for preparing implant cores by chemically induced gelling.

Figure 2 is a part sectional, part schematic, cross section of an apparatus suitable for preparing implant cores by temperature induced gelling.

Figure 3 is a schematic illustration of spray coating of hydrogel implants.

Figure 4 is a schematic illustration of rod coating solvent based polymer coating application.

Figures 5 and 6 are graphs of dye release from 35% (pLa i.v. 1) tolulene rod coated gelatine core implants; in vitro at PBS at pH 7.2, 37 °C.

Implant Preparation

(1) Apparatus

Apparatus suitable for use in the method of the present invention varies depending whether the gel results from temperature or chemical effects. Figures 1 and 2 are part sectional, part schematic, cross sections of the apparatus for preparing implant cores. In one embodiment illustrated in Figure 1 for chemically induced gelling, the apparatus consists of a dialysis tube "1" fitted over an upper end portion "2" and a

lower end portion "3" and located in sealing engagement by waterproof rubber sealants "4" and "5". A supporting line formed of bioerodible core material "6" is maintained under tension by a spring steel bow "7". An inlet port "8" and bleeder hole "9" are provided respectively in the lower and upper end portions "2" and "3". An outer perforated mould "10" is provided to support the dialysis tube "1" and allow the ingress of gelling reagents to the dialysis tube. This outer perforated mould may be hinged to allow easy access to the dialysis tube.

In an alternative embodiment illustrated in Figure 2, suitable for temperature induced gelling, the dialysis tube "1" is replaced with a teflon tube "11" which may be in two longitudinal halves and the outer perforated mould "10" is replaced with a jacketed temperature control member "12".

For structural stability of the gel during subsequent processing the gel structure is held on the support "6". For symmetry and strength the support "6" is centred using the upper and lower end portions "2" and "3". The support line "6" is kept taut using a device "7" made of spring steel resembling a bow. This device serves also as a handle to transport the gel structure for the convenience and security of subsequent gel processing, e.g. drying and coating.

Referring to Figures 1 and 2, a central support which forms the bioerodible core "6", e.g. a surgical suture, is positioned at the radial centre in a cylindrical mould "1" or "11" using appropriate positioning guides. For water based polymeric matrices, the inner surface of the mould should be lined with material such as teflon to facilitate cast removal.

A temperature sensitive implant hydrogel layer or core matrix on the central support may be prepared in the following manner:

1 Insert the horizontally sectioned teflon tube "11" into the jacketed temperature control member "12" with approximately 1.0 cm of the teflon tube protruding from one end of the glass tube.

2 Run the support line "6" through the bottom end portion "3" and knot

on the external side of the end portion "3" to ensure the line does not pull through (see Step 9 below).

3 Pass the support line "6" through the mould (teflon tube "11" in the glass holder "12").

4 Insert the protruding section of the teflon tube "11" (from step 1) into the bottom end portion "3" (the analogy used was "like a condom").

5 Push the teflon/septum plug "11"/"3" into the glass tube "12" as far as possible (on the whole this remains 'outside' the glass tubing).

6 Seal the teflon/septum plug "11"/"3" by encasing the glass tube and septum end in the waterproof rubber sealant "4", e.g. wrap in parafilm™.

At this point either of two procedures may be followed. That is, either the mould is filled and the top end cap "2" put into position and the whole device sealed. Alternatively, the top end cap "2" is put into position and then the mould is filled and sealed.

7 Fill the mould with the required gelling solution using a syringe.

8 Run the top end portion "2" onto the support line and insert the top end portion "2" into the top of the teflon/glass tubing "11"/"12".

9 Hang the entire moulding unit from the support line to align the support line "6" along the centre of the mould.

10 When cured dismantle the mould and pull out the support line "6" with the core matrix attached.

(2) Implant Hydrogel Core Preparation

The matrix active ingredient and the hydrogel material in the gelling mix is compounded according to the individual formulations used. Usually the solutions of hydrogel and active materials are prepared separately and recombined in the proportion prescribed immediately prior to filling into the mould to minimise any possible denaturation or inactivation of the active

during the preparation of the hydrogel solution.

(i) Temperature induced gelling process

The assembled mould, the gelling mix and the filling device (eg a syringe) are separately equilibrated to the desired filling temperature. Thermal prefilling equilibration is desirable to prevent blockage during filling and deformities in the gel structure.

2a The preparation of the temperature induced gelling solution involves dissolution of a hydrogel, such as gelatine (270 mg), and, if required, an osmotic modifier such as sucrose (750 mg) in water (1.5 ml). The stock hydrogel solution is prepared by heating the suspended solutes in a water bath at 100 °C. Subsequent to dissolution, fluidity of the hydrogel solution is best maintained by holding at 37 - 45 °C.

2b A stock 'bioactive' solution is prepared by dissolution of the 'active' in water (0.5 ml). This solution is then held on ice.

2c If necessary, the requisite volume of the stock 'bioactive' solution is diluted to the requisite concentration by dissolution with water. This solution is also held on ice.

2d 0.5 ml of the stock 'bioactive' solution or diluted 'bioactive' solution is heated to 37 °C then combined with the stock hydrogel solution (1.5 ml) to give the gel solution. The combined hydrogel and active agent solutions are then mixed for 1 minute at 37 °C and dispensed into the moulds.

2e The gelling mix may be introduced to the mould by a syringe pump via the inlet "8" while the bleeding hole "9" provides an outflow for air and excess gel solution. Filling is preferably accomplished by one slow continuous action. By filling from bottom upward the process is made essentially trouble free and there is lesser likelihood of deformities in the gel structure due to occluded air bubbles especially in a clean teflon mould. Filling is completed when gelling mix appears to flow

from the outlet bleeding hole in the top positioning guide.

2f Following filling the complete assembly is maintained at the filling temperature for a short time and a check for proper filling is made.

2g Gelling of the matrix/active solution mix is accomplished by lowering the ambient temperature in the thermal jacket slowly. A slow transition is desirable to prevent deformities in the gel structure. To ensure good results, the complete assembly is kept at a temperature well below the critical gelling temperature for a period of time, for example, 30 minutes.

(ii) Chemically or ion induced gelling

For polymeric matrix materials which form a solid gel when in contact with a di- or trivalent cation or a catalytic agent, the supporting string, is centred by the positioning guides "2" and "3". The support line "6" is kept taut using a device "7" within an appropriate dialysis tubing "1" which in turn is enclosed within a rigid perforated support "10" for the convenience of filling and subsequent induction of gelling.

(3) Filling

3a Ion or chemically induced gelling is best achieved using the perforated mould assembly "10" with filled dialysis tube "1". This assembly is filled preferably by one slow continuous action. By filling from bottom upward the process is made essentially trouble free and there is lesser likelihood of deformities in the gel structure due to occluded air bubbles adhering to the dialysis tubing.

3b Filling is completed when gelling mix appears to flow from the outlet bleeding hole in the top positioning guide.

3c Following filling the complete assembly is maintained at the filling temperature for a short time and a check for proper filling is made.

3d The assembly is then transferred to a container of the inducer solution

which may be held at any preferred temperature, for example, at zero degrees Celsius if denaturation of an active is a concern. Equilibration of the inducer across the semi-permeable membrane affords the gelling of the matrix active solution mix.

3e Extra time should be allowed to ensure proper gel formation and possible hardening of the gel structure for example, 240 minutes.

(4) Removal of gel structure from mould

Depending on the gel structure strength, fresh gel structures on the support are usually very fragile and thus not readily lifted horizontally off the mould. Hence they are preferably kept in a vertical position and the two halves of the mould gently separated. To prevent damaging the gel structure, the top positioning guide should be removed before the removal of the mould halves but the bottom guide should remain in place.

(5) Segmentation of the Gel Structure

The moulded gel structure referred to above consists of an outer hydrogel layer which is supported by and concentric about an axial support line. Smaller discrete gel segments which remain supported by the axial support line can be created by cutting the outer concentric hydrogel layer in such a way that the axial line remains intact and sliding the cut segment along the axial line so as to form a space between the discrete small gel segments. The above cut/slide operation may be performed either before or after the concentric hydrogel layer has been dried and prior to coating. However, it is generally easier to perform the cut/slide operation on wet hydrogel.

(i) The "long section" may be segmented into lengths, e.g. 10 mm, maintained on the support line "6". The supported segments may then be dried and processed as required for specific applications.

(ii) In an alternate embodiment, the core matrix may be sectioned subsequent to drying but prior to coating.

(6) Drying

Depending on the molecular stability of the active compound and speed of drying, the water based gel structure may be air dried under ambient conditions or at low temperatures (e.g. at 2 °C) by flushing with dry nitrogen gas. For example, a gel structure containing about 10% total dry matter takes 8-10 hours to dry the gel to a constant weight at room temperature (21 °C). The drying time will be appreciably longer at lower temperatures. The drying times are gel composition dependent.

(7) Coating of the Gel Structure

(i) Once dried the gel structure mounted on the support may be reassembled with the 2 halves of the teflon mould of the same internal or different internal diameter to allow for the bioerodible outer coating to be applied to the core. Thus, after the cast is formed and dried, the dry cast may be coated with a water impermeable co-polymer such as polylactic acid (pLa)/polyglycolic acid (pGa) (85:15) co-polymer to form a coating.

(ii) Alternatively the dried gel structure on the support "6" may be coated by repeated dipping into a polymeric solution and drying to achieve a thin layer of a substantially water impermeable coating with specific transport characteristics (refer to Example 3).

(iii) Alternatively the dried gel structure on the support "6" may be coated by repeated spraying with a polymeric solution and drying to achieve a thin layer of a substantially water impermeable coating with specific transport characteristics (refer to Example 4).

(iv) Alternatively the dried gel structure on the support "6" may be coated by repeated application of a polymeric solution via a "rod" or "wick" and drying to achieve a thin layer of a substantially water impermeable coating with specific transport characteristics (refer to Example 5).

(8) Release Profile Control

For manipulating the release characteristics, the release mode of the present device can also be modified by the concentration and composition of the matrix materials. For example, when agar was used as the matrix material, the release was faster and the extent of release higher. This demonstrates the ability to affect the release rate by changes in matrix composition. Variations include replacement of the water based hydrogel matrix with hydrophobic materials such as glycerol monostearate.

EXAMPLE 1 - Fabrication of implant containing human serum albumin (HSA) and human IgG

This example is illustrative of temperature induced gelling and gives evidence of an immunological response to an incorporated antigen.

Preparation of Implant

0.9 ml of HSA/human IgG solution (9.5 and 5.8 mg/ml respectively in 0.1 M NaCl) were mixed with 0.5 ml of 1% NaCl solution and the mixture equilibrated to 43 °C. It was then mixed with 4.6 ml of gelatine/agar matrix solution (13% and 1.3% w/v respectively; gelatine, cell culture reagent from Porcine stein, approx 300 bloom, Sigma catalogue no. G1890) also equilibrated at 43 °C. The resultant mixture was transferred to the mould assembly equilibrated at 43 °C with a 7 mm internal diameter x 20 mm long teflon mould and a 0.45 mm diameter support line as the centre support. The inlets to the moulds were then stoppered and the moulds were allowed to equilibrate at 43 °C for 10-15 minutes before the temperature of the

thermal jacket was slowly lowered to that of running cold tap water at about 20 °C over 20 minutes. The gel was then solidified by cooling the mould assembly to 0 °C and maintaining it at that temperature for half an hour. After the mixture solidified the moulds were dismantled and the gel structure on a string stretched in a bow was removed carefully in a vertical orientation to avoid horizontal splitting of the gel structure by the stretched support while the gel structure was still fragile. The gel structure supported by the string support in a bow were cut and separated in the cut/slide operation and air dried at room temperature overnight (about 18 hours). The dried gel structures were then coated with a water based polyacrylic resin Eudragit E 30D by five repeated cycles of dipping in an Eudragit suspension for 30 seconds and drying for 60 minutes. Eudragit E 30D is an aqueous dispersion of poly(meth)acrylic acid esters supplied by Rohm Pharma GmbH Weiterstadt Darmstadt, West Germany. When dry, the gel structures were dismounted from the bow and trimmed to segments of 1 cm length (diameter 3 mm). Each segment was estimated to contain 0.05 ml of the original HSA/human IgG antigen solution.

Placebo implants were made in exactly the same way as the antigen implants except that the HSA/human IgG solution was replaced by 0.9 ml of 0.1 M NaCl.

Evaluation of Implant

Sheep previously immunised with human serum were implanted subcutaneously on the inside surface of hindlegs using a mechanical implanter fitted with a 2.8 mm internal diameter needle. Two implant segments containing antigen or placebo were given to each sheep.

To determine the antibody response, blood samples were taken from the sheep prior to receiving implants and on days 9, 15 and 23 following implantation. Sera were obtained from blood samples by standard serological practice and assayed for qualitative and quantitative antibody titres using double immuno diffusion and ELISA (Enzyme Linked Immuno Sorbent Assay) techniques respectively.

Results

Results of double immuno diffusion assay showed that there was an increase of antibody titre in recipients of the HSA/human IgG implants but not in those of the placebo. The increase in antibody titre was comparable to that obtained when normal immunisation protocol with adjuvanted antigen suspension was used. As shown in Table 1, the response in general was maximal at day 9 of the four scheduled sampling days for both the specific anti-IgG and anti-HSA responses. Maximal increases at day 9 ranged from four to thirteen fold for anti-IgG response and seven to twenty-five fold for anti-HSA. Titres were notably high relative to those in sheep receiving adjuvanted antigen suspensions, with amounts of specific antibodies approaching the highest that has yet been obtained from a few select sheep (that is in the order of 32 units of antibody in the sheep serum to either the HSA or human IgG). For three weeks following implantation, antibody titres remained significantly high but decreased with time in the antigen implanted animals.

In addition to the at least equivalent responses obtained, immunisation using antigen implants can afford a number of other advantages. Immunisation with implants was very simple to perform and compared with the routine method far less time consuming. Apart from the puncture mark caused by the implanter needle, no ulceration or swelling was evident at the implant site. This is in sharp contrast to the situation of routine practices when antigen suspensions, especially those using Freund's adjuvant, are used for immunisation.

TABLE 1 - Quantitative Antibody Response by ELISA Method of Determination

Sheep No.	Implant	Day 0	Day 9	Day 15	Day 23
Anti-IgG Response					
7	Antigen	3.3	19.9 (6.0X)	15.2 (4.6X)	9.6 (2.9 X)
9	Antigen	1.7	17.8 (10.5X)	14.0 (8.2X)	9.9 (5.8X)
3	Antigen	0.9	11.7 (13.0X)	8.9 (9.9X)	6.4 (7.1X)
0	Antigen	7.0	24.9 (3.6X)	28.3 (4.0X)	25.3 (3.6X)
8	Antigen	1.2	8.5 (7.1X)	6.9 (5.8X)	5.0 (4.2X)
5	Placebo	2.0	2.0 (1.0X)	2.2 (1.1X)	2.1 (1.1X)
6	Placebo	4.8	8.8 (1.8X)	8.2 (1.7X)	6.1 (1.3X)
4	Placebo	3.9	4.1 (1.1X)	nd -	nd -
Anti-HSA Response					
7	Antigen	1.6	15.7 (9.8X)	13.2 (8.3X)	8.0 (5.0X)
9	Antigen	1.0	21.1X (21.1X)	19.4 (19.4X)	14.5 (14.5X)
3	Antigen	0.9	22.3 (24.8X)	20.6 (22.9X)	14.2 (15.8X)
0	Antigen	3.5	23.8 (6.8X)	26.6 (7.6X)	18.9 (5.4X)
8	Antigen	1.5	13.3 (8.9X)	12.2 (8.1X)	9.8 (6.5X)
5	Placebo	1.0	0.9 (0.9X)	0.9 (0.9X)	0.9 (0.9X)
6	Placebo	4.9	6.4 (1.3X)	6.0 (1.2X)	5.8 (1.2X)
4	Placebo	1.7	1.5 (0.9X)	nd -	nd -

nd = not determined; figures in brackets represent the multiple increases over day 0

EXAMPLE 2

This example is illustrative of chemical induced gelling and is preferred for heat labile active material.

The ion induced gelling mould was assembled as described above (refer to Figure 1) and equilibrated at room temperature. 7 ml of 3% w/w aqueous sodium alginate [Sigma Co. cat No. A-2033, alginic acid sodium salt medium viscosity, from Macrocystis pyrifera (Kelp)] was mixed thoroughly with 7 ml of Clostridium novyi toxoid at room temperature. The active suspension was a concentrated solution of Clostridium novyi toxoid containing the toxoid produced by the bacteria and 5.3 mg/ml of hydrated aluminium hydroxide added as adjuvant. Although there is a slight increase in viscosity, the two suspensions may be held at lower temperatures (eg 4 °C) and mixed at lower temperatures. The resultant mixture was transferred with a syringe via the inlet port in the mould assembly to fill the dialysis tube inside to a slight overflow from the outlet bleeder hole with about 7 ml per mould. The two mould assemblies were transported into a bath of 500 ml aqueous $AlCl_3$ solution (0.5% w/w) at room temperature (or if desired at 1 °C) with continuous slow agitation using a magnetic stirrer. Gelling was usually effected within 2-3 hours of immersion but it is our normal practice to leave the gel structures to form for 4 hours. Following gel structure formation the moulds were removed from the gels in a vertical position. The resultant gel structures were allowed to dry at room temperature. When dry, the gels may be surface coated with Eudragit E 30D as previously described and/or reloaded with another layer of toxin alginate gel structure.

If desired sodium alginate may be directly substituted by K-carrageenan but the temperature during filling of the tube mould needs to be higher to prevent premature gelling of the K-carrageenan.

Also if rapid gelling of the matrix active solution is required, the gel inducing agent, $AlCl_3$, (e.g. 7 ml of 1.5% solution) can be added directly to the 14 ml of the alginate

C. novyi mix and the resultant solution mixed thoroughly and quickly.

EXAMPLE 3

This example illustrates the technique of dip coating of hydrogel implants and provides evidence of pulsatile release in vitro evaluation.

Polylactic acid (d,l-pLa) of inherent viscosity (i.v.) = 1.0 dl/g (supplied by Boehringer Ingelheim) of mass 12 g was dissolved in 120 ml of dichloromethane. Phosphate buffered saline (PBS), pH 7.2 was made according to the following recipe:

NaCl (80.00 g), KCl (2.00 g), $2HPO_4.12H_2O$ (15.36 g), KH_2PO_4 (2.00 g) dissolved in 1000 ml of distilled water.

The hydrogel cores containing red food dye or antigen were manufactured according to the methodology described above using the cut/slide method.

Referring to Figure 2, dried hydrogel cores on the support line "6" attached to the spring steel bow "7" were dipped into the solution of polylactic acid in dichloromethane. Immersion time was 30 seconds for each coat. Upon removal from the polymer solution the excess polymer solution was allowed to run down the implants and the hanger was then inverted to allow the polymer to run the other way: this aids in spreading the polymer evenly over the implants. As illustrated in Table 2, groups were dipped either four times, i.e. 4 coats or six times, i.e. 6 coats. At least one hour drying time was allowed between coats to ensure adequate drying under the ambient conditions. Individual cut implants were each placed in individual glass vials. PBS of volume 10 ml was added to each vial and they were placed in an incubator at 37 °C. Monitoring was carried out using U.V. visible spectroscopy to measure dye release into the solution.

TABLE 2

Experimental Conditions			
Number of Samples	Number of Coats	Temperature (°C)	pH
7	4	37	7.2
7	6	37	7.2

One sample commenced dye release early at day 4 and took 14 days to attain 100% release at day 18.

Of the remaining replicates mean release was at day 48. The same implants attained a 100% release profile in an average of 5.3 days +/- 2.7 days. All samples commenced dye release within a six day period between days 45 and 51. The total release time from when the first of the six implants commenced dye release (>10% release) to when the final implant reached 100% release was 14 days, i.e. from day 45 to day 59.

There appeared to be no statistically significant difference between samples with 4 coats and those with 6 coats. This is expected as the pLa polymers are, in general, bulk eroding thus are generally unaffected by sample thickness.

The results show a significant delay in the time of onset of release of die compared to uncoated samples which gave 100% release within 3 hours of immersion in PBS.

EXAMPLE 4

This example illustrates spray coating of hydrogel implants and provides evidence of pulsatile release from an in vitro examination.

Polylactic acid (d,l-pLa) of inherent viscosity (i.v.) = 1.0 dl/g (supplied by Boehringer Ingelheim) of mass 12 g was dissolved in 120 ml of dichloromethane.

Phosphate buffered saline (PBS), pH 7.2 was made according to the following recipe:

NaCl (80.00 g), KCl (2.00 g), $2HPO_4.12H_2O$ (15.36 g), KH_2PO_4 (2.00 g) dissolved in 1000 ml of distilled water.

The hydrogel cores containing red food dye or antigen were manufactured according to the methodology described above using the cut/slide method.

An atomising spray nozzle connected to a compressed air cylinder and to a 250 ml separating funnel which contained the different polymer solutions was used to apply the polymer to the gelatine cores being rotated about the support line using a "rotisserie" mechanism (refer to Figure 3). A polymer solution was sprayed onto the implant cores using air brush with a gas pressure of 200 kPa and a distance of 10-30 mm between the air brush outlet to the implant cores. The implant core string was hand rotated during spraying in order to obtain uniform coating. 65 ml of polymer solution was sprayed on a string of implant cores.

Referring to Figure 2, the position on the support line "6" of all implants was noted, seven of those were selected at random and their weights recorded. Implants were placed in glass vials. PBS of volume 10 ml was added to each vial and they were placed in an incubator at 37 °C and pH = 7.2. The d,l-PLA (iv = 0.1 dl/g) produced an opaque papery coating which had a granular appearance. Despite their appearance swelling without release was apparent from an early stage.

Results of the incubation work are given in Table 3. Seven implants were placed in individual sample vials containing 10 ml phosphate buffer pH = 7.2 and incubated at 37 °C. Monitoring was carried out using U.V. visible spectroscopy to measure dye release into the solution. One implant started to release on day 36, others started to release between days 73 and 79.

TABLE3

Spray Coating Results

	Absorbency/Time (days)																				
	0	3	7	11	20	25	27	32	36	38	42	45	55	60	71	73	74	77	78	79	80
Sample Position																					
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.041	0.597
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.234	0.626
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.044	0.63	0.63	0.631	
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.059	0.206	0.601	
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.096	0.384	0.629	0.629		
13	0	0	0	0	0	0	0	0	0.042	0.069	0.093	0.121	0.16	0.613	0.613	0.613					
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.612	0.612

EXAMPLE 5

This example illustrates "rod coated" solvent based polymer application and provides evidence of pulsatile release in in vitro evaluation.

A method of coating gelatine cores was investigated to try to overcome the difficulty of covering the ends and edges of the core when spray coating. A saturated viscous solution of polylactic acid (d,l-pLa) of inherent viscosity (i.v.) = 1.0 dl/g in dichloromethane (20% w/v) was made. Furthermore a connected series of gelatine cores supported on an axial support was made using the cut/slide operation as described above. It was found that if one large viscous drop of material was spread along a slowly rotating gelatine core (approximately 120 rpm), the drop remained evenly dispersed and seemed to successfully surround the sharp edges and the end of the core (Fig. 4A). Application of the solvent based polymer was with a glass rod. The rod is dipped into a viscous polymer solution to pick up a small amount of material (Fig. 4B). The material is then applied to one end of the gelatine core and drawn to the other (Fig. 4C).

Forty of these samples were placed in a PBS, pH = 7.2, twenty at 37 °C and twenty at 50 °C. Results of the 50 °C appear in Table 4 and in Figures 5 and 6. Monitoring was carried out using U.V. visible spectroscopy to measure dye release into the solution. The 37 °C samples had been in vitro for sixty days, the majority of which show no signs of release (Table 4).

TABLE 4

Rod Coating Results
In Vitro Data

	Absorbency/Time (days)																			
	0	12	14	17	18	19	20	27	28	31	35	38	39	40	41	42	45	46	47	49	52
Sample																					
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0.091	0.148	0.268	0.398	0.423	0.449	0.474	0.498	0.527	0.561	0.565	0.573	0.574	0.577	0.582	0.59	0.6	0.6	0.6	0.6
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0.6																			
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0.6																			
10	0	0	0	0	0	0	0	0	0	0	0.023	0.04	0.072	0.112	0.173	0.337	0.521	0.527	0.557	0.6	0.6
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.06	0.216	0.579	0.6
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0.06	0.245	0.274	0.291	0.335	0.362	0.405	0.421	0.447	0.465	0.473
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0.6																			
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0.039	0.091	0.159	0.196	0.228	0.26	0.292	0.305	0.35	0.461	0.535	0.572	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.29	0.171

EXAMPLE 6

This example shows the use of implants to obtain pulsatile release in animals.

An experiment was performed in which the delayed release from implants of tetanus toxoid was demonstrated by detecting by ELISA antibodies produced by the mice in response to the released antigen.

Implants were made as described in Example 4 except that 0.5 mg tetanus toxoid per implant was used as the active ingredient.

Antigens were used in implants with two coat compositions and the control group (3) received antigen in uncoated gelatine cores.

Mice were implanted subcutaneously on the inside surface of hind legs using a mechanical implanter fitted with a 2.8 mm internal diameter needle. One implant segment containing antigen or placebo was given to each mouse.

To determine the antibody response, blood samples were taken intra-ocularly from the mice prior to receiving implants and on days 14, 21, 36, 49, and 63 following implantation. Sera were obtained from blood samples by standard serological practice and assayed for qualitative and quantitative antibody titres using double immuno diffusion and ELISA (Enzyme Linked Immuno Sorbent Assay) techniques respectively.

ELISA method

Nunc Maxisorp microtitre plates were coated overnight at 4 °C with the antigen of choice. Test serum was serially diluted on the plate to final dilutions in the range 800 to 25,600, and incubated at room temperature for one hour. Plates were washed and rabbit antiserum to mouse immunoglobulin, conjugated with horse radish peroxidase, was added and incubated at room temperature for one hour. Peroxidase activity was

detected using 2,2'-azino-bis(s-ethylbenzthiazoline-6-sulphonic acid) (ABTS) substrate.

Evidence of seroconversion and thus of the release of antigen was any positive titre (800 to 25,600) obtained.

The results given in Table 5 indicate that the majority of animals given uncoated samples showed seroconversion having been achieved within 14 days whereas no seroconversion was observed with coated implants until 21 days. With implants coated with pLa homopolymer (i.v. = 1.0) seroconversion in all cases had not been achieved even after 63 days. That 100% seroconversion will result in all cases is indicated from the observed eventual seroconversion of all animals treated with implants coated with 50:50 pLa/pGa (i.v. = 1.0). Animals receiving placebo implants gave no antibody tire to Tetanus toxoid.

TABLE 5

Group	No. of Mice	Coat composition	Seroconversion number (days)				
			14	21	36	49	63
1	6	d,l-pLa (i.v. = 1.0)	0/6	0/6	3/6	3/6	3/6
2	6	d,l-pLa/pGa (50:50; i.v. = 1.0)	0/5	2/5	5/5	5/5	5/5
3	4	no coat	2/3	2/3	3/3	3/3	3/3
3	5	placebo - no coat	0/5	0/5	0/5	0/5	0/5

Since modifications within the spirit and scope of the invention may be readily effected by persons skilled in the art, it is to be understood that the invention is not limited to the particular embodiment described, by way of example, hereinabove.

REFERENCES:

1. R. Jeyanthi and K. Pandurange Rao, "Controlled Release of Anti-Cancer Drugs from Collagen-Poly (HEMA) Hydrogel Matrices", Journal of Controlled Release 13 (1990), 91-98.

2. Y.F. Maa and J. Heller, "Controlled Release of 5-Fluorouracil from Linear Poly (Orthoesters)", Journal of Controlled Release, 13 (1990), 11-19.

CLAIMS:-

1. A pulse release implant comprising:

an axial biodegradable core;

a first concentric layer comprising dehydrated hydrogel containing an active ingredient; and

an outer coating, said outer coating being removable by the environment in which the implant will reside after administration.

2. A pulse release implant according to claim 1 wherein the hydrogel is selected from gelatine, agar, alginates, carrageenan, gum gragacanth, acacia, and corn starch.

3. A pulse release implant according to claim 1 wherein the first concentric layer further includes one or more components selected from disintegrating agents, lubricants or osmotic modifiers.

4. A pulse release implant according to claim 1 wherein the active ingredient is a pharmaceutical substance.

5. A pulse release implant according to claim 1 wherein the pharmaceutical substance is an antibody, cytokine, growth promotant, hormones, cancer cell inhibitory molecule or agent, immune stimulant, and/or immune suppressant.

6. A pulse release implant according to claim 1 wherein the active ingredient is an antigen or an anti-microbial, anti-fungal or anti-viral agent.

7. A pulse release implant according to claim 1 wherein the active ingredient is a nutrient, vitamin or mineral.

8. A pulse release implant according to claim 6 wherein said antigen is an antigen from the clostridial family.

9. A pulse release implant according to claim 1 wherein the outer coating is formed from a material selected from modified starches, sugars, polyanhydrides, polyorthoesters, bioerodible polyesters and polylactic/polyglycolic acids.

10. A pulse release implant according to claim 9 wherein the outer coating is formed from polylactic/polyglycolic acids.

11. A process of preparing a pulse release implant including the steps of:

coating an axially disposed biodegradable core material with a hydrogel containing an active ingredient to form a concentric coating;

separating the coating into discrete segments disposed along the core material;

dehydrating the hydrogel;

coating the discrete segments with an outer coating, said outer coating being removable by the environment in which the implant will reside after administration; and

removing the exposed core material to obtain the pulse release implants.

12. A process according to claim 11 wherein the separation step takes place before the dehydration step prior to coating with the outer coating.

13. A process according to claim 11 wherein the separation step takes place after the dehydration step prior to coating with the outer coating.

14. A process according to claim 11 wherein the outer coating is applied by forming said coating in a mould and subsequently removing said mould.

15. A process according to claim 11 wherein said outer coating is formed by dipping the hydrogel coated biodegradable core into a coating solution.

16. A process according to claim 11 wherein said outer coating is formed by spraying said hydrogel coated biodegradable core.

17. A process according to claim 11 wherein said outer coating is formed by application of the coating material to the hydrogel coated biodegradable core via a rod or wick.

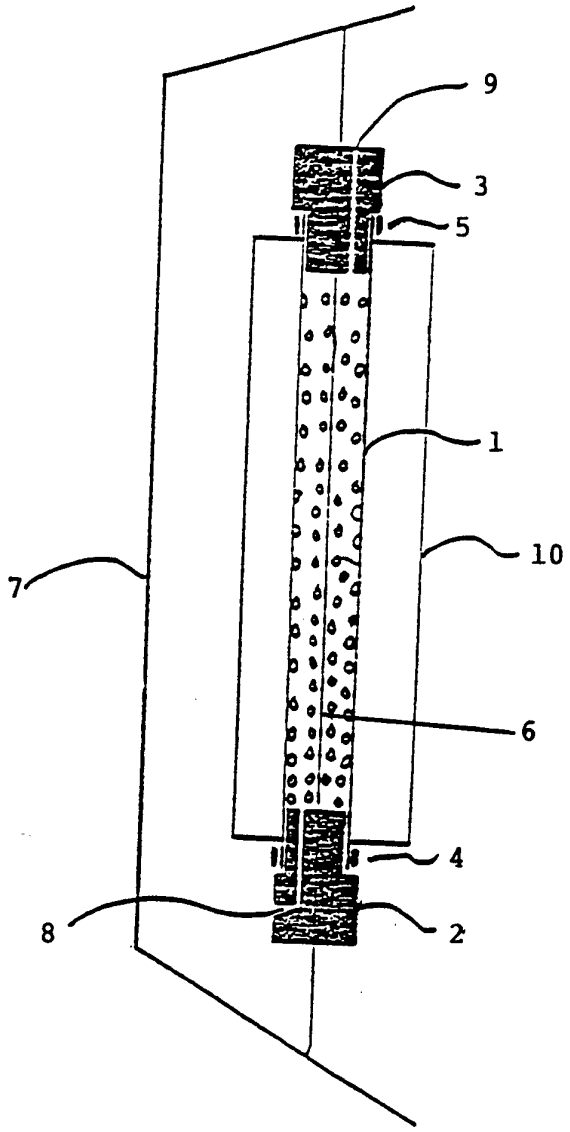

FIGURE 1

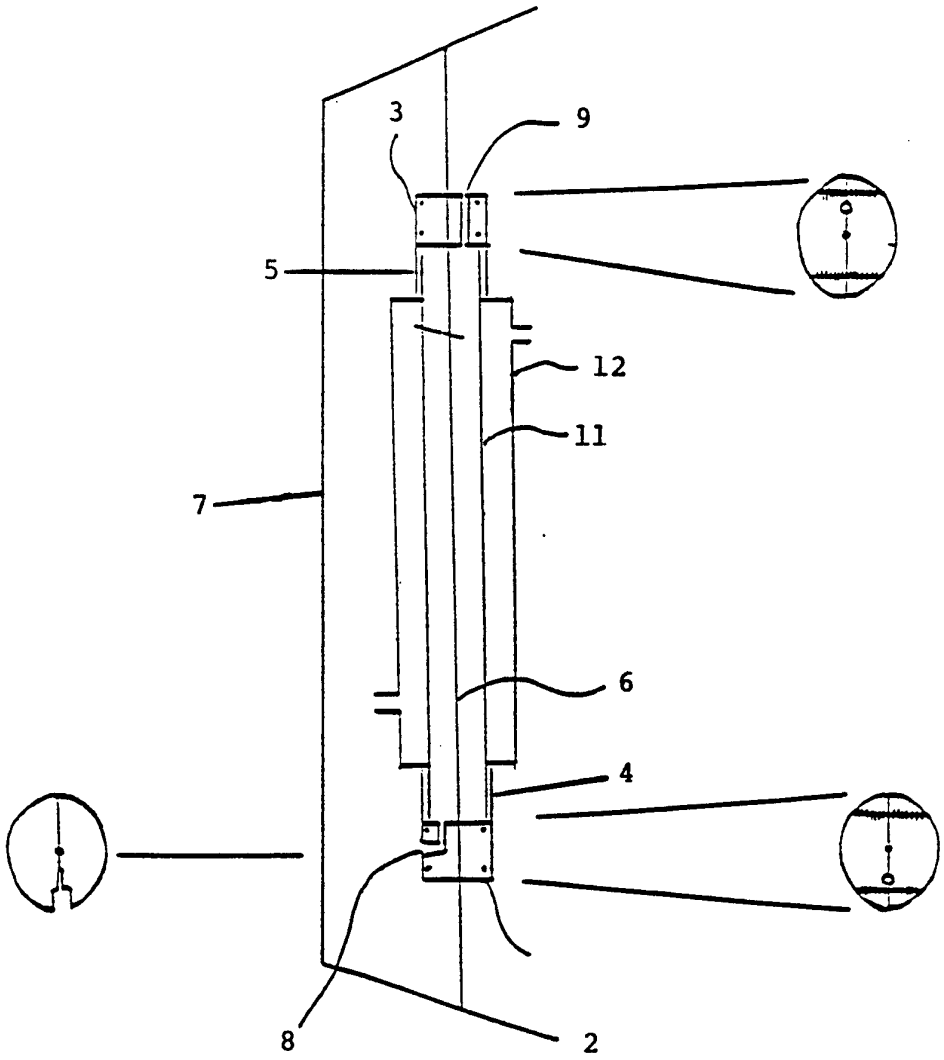

FIGURE 2

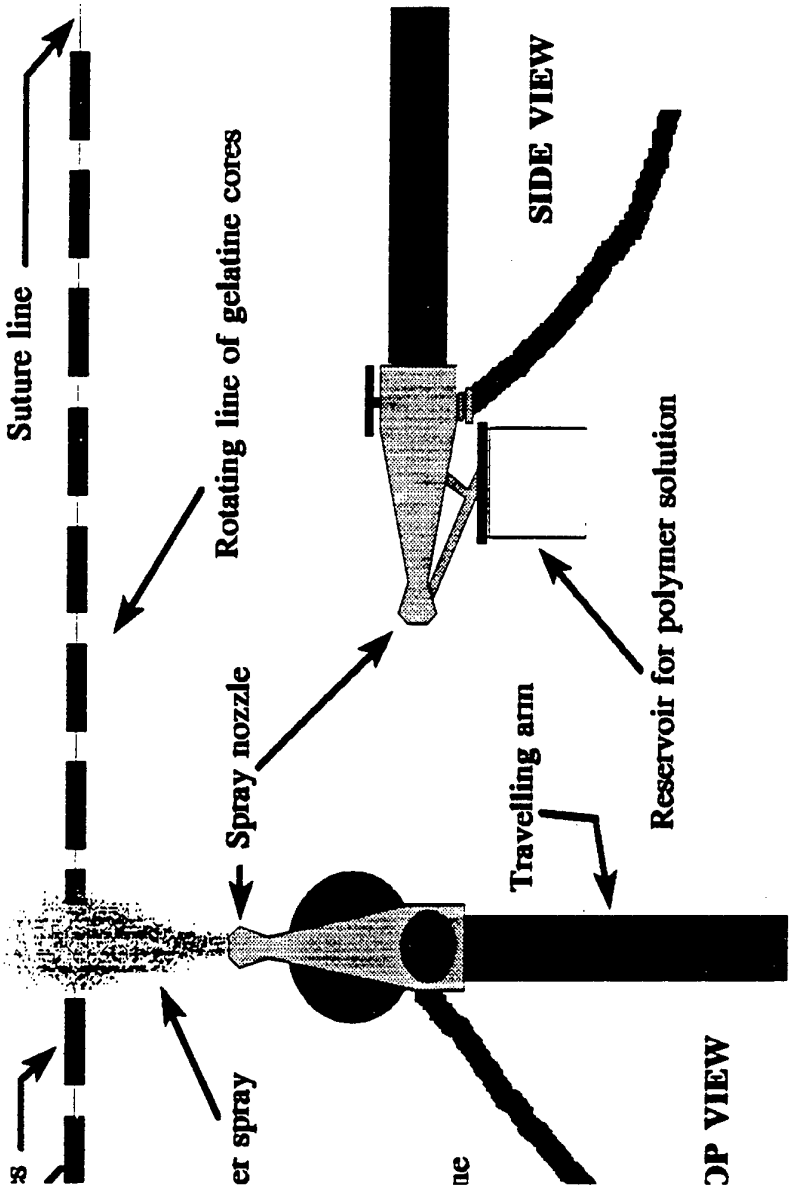
Suture line
Rotating line of gelatine cores
SIDE VIEW
Spray nozzle
Travelling arm
Reservoir for polymer solution
er spray
OP VIEW

FIGURE 3

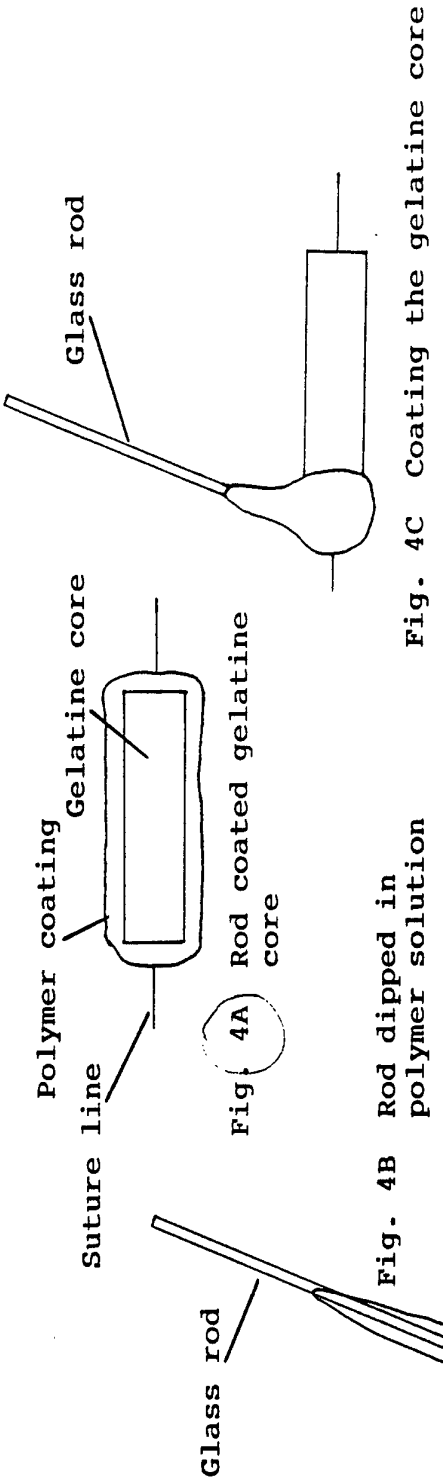
Glass rod
Fig. 4C Coating the gelatine core
Polymer coating
Gelatine core
Suture line
Rod coated gelatine core
Fig. 4A
Rod dipped in polymer solution
Fig. 4B
Glass rod

FIGURE 4

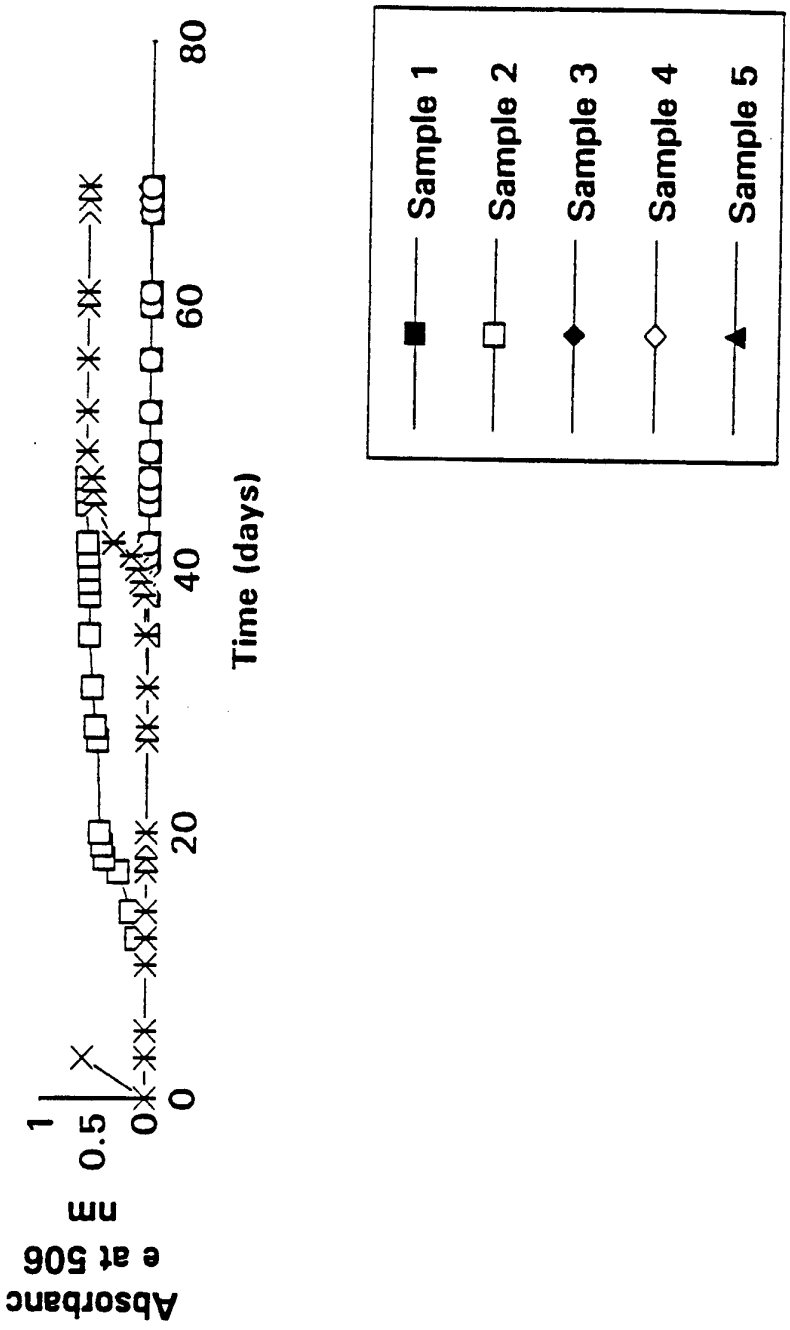
Absorbanc
e at 506
nm
1
0.5
0
0
20
40
60
80
Time (days)
Sample 1
Sample 2
Sample 3
Sample 4
Sample 5

FIGURE 5

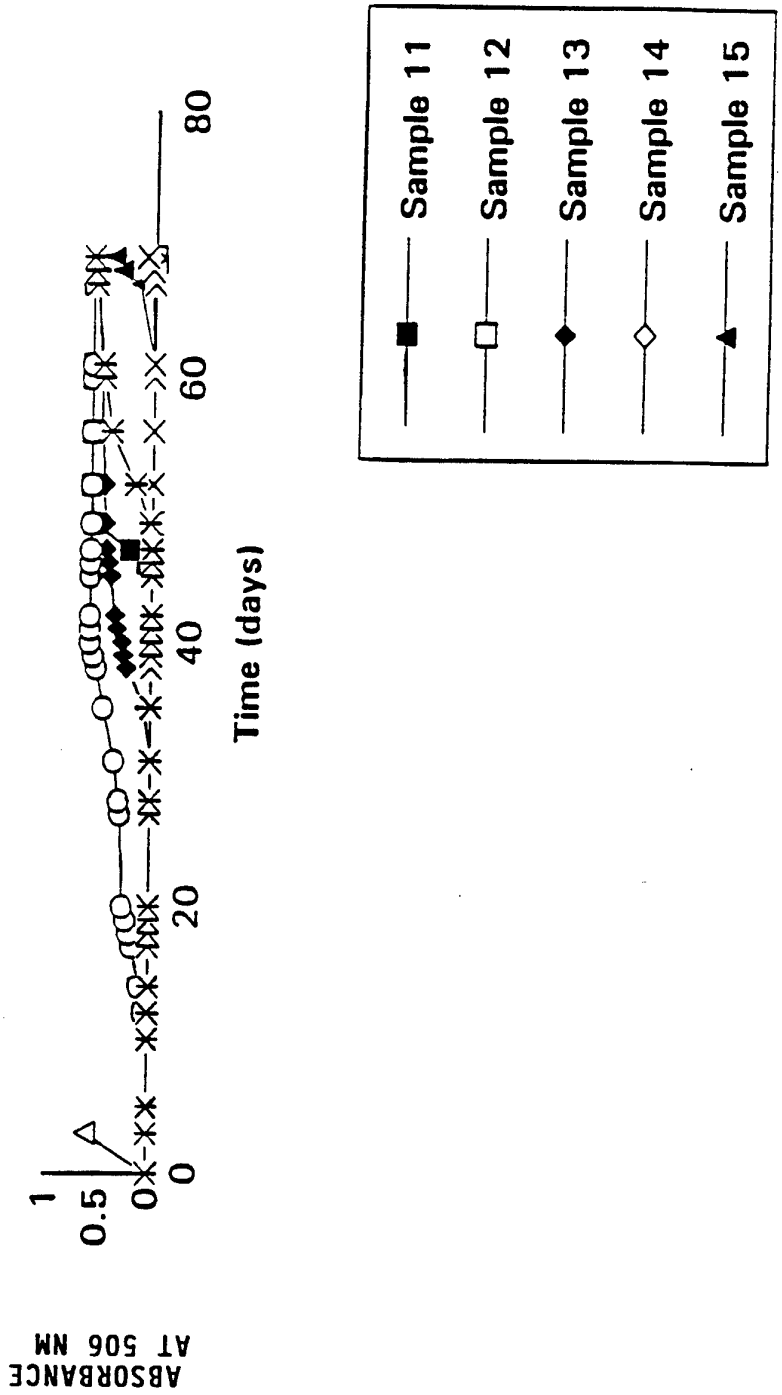
Sample 11
Sample 12
Sample 13
Sample 14
Sample 15
Time (days)
0
20
40
60
80
0.5
1
ABSORBANCE AT 506 NM

FIGURE 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 93/00392

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.[5] A61K 9/28, 9/00, 9/02

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int Cl[5] A61K 9/28, 9/00, 9/02

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

AU: IPC as above

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)

WPAT: HYDROGEL
JAPIO: HYDROGEL
JOPAL: HYDROGEL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A, 4961932 (THEEUWES) 9 October 1990 (09.10.90) Column 14 Example 11, Column 15 lines 42-65, Figure 14	1-7, 9-17
X	US,A, 4434153 (URQUHART et al.) 28 February 1984 Column 3 lines 30-38, 48-62, Column 4 lines 10-24, 46-57, Claims	1-7, 9-17
X	EP,A, 250374 (RECORDATI INDUSTRIA CHIMICA E FARMACEUTICA SPA) 23 December 1987 (23.12.87) Page 3 lines 4-20, 40-49, claims	1-7, 9-17

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 1993 (12.11.93)	19 NOV 1993 (19.11.93)

Name and mailing address of the ISA/AU	Authorized officer
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Facsimile No. 06 2853929	Telephone No. (06) 2832253

INTERNATIONAL SEARCH REPORT

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	**Citation of document, with indication, where appropriate of the relevant passages**	**Relevant to Claim No.**
A	AU,B, 47877/90 (615129) (PFIZER INC) 19 July 1990 (19.07.90) Page 1A lines 3-6, page 3 line 28-page 4 line 4, page 7 line 27-page 8 line 7, page 9 line 21-page 10 line 11, page 12 lines 10-24	1-7, 9-17
P,A	AU,A, 21073/92 (EUROCELTIQUE S.A.) 18 March 1993 (18.03.93) Page 4 lines 18-27, page 5 lines 22-32	1-7, 9-17
A	GB,A, 2189995 (ALZA CORPORATION) 11 November 1987 (11.11.87) Page 1 lines 4-9, page 2 line 60-page 3 line 104, Figure 3, claims	1-7, 9-17
A	AU,B, 71837/87 (621030) (ALZA CORPORATION) 12 November 1987 (12.11.87) Page 1A lines 4-8, page 6 line 7-page 10 line 22, Figure 3, claims	1-7, 9-17
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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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END OF ANNEX