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(57) Abstract

The present invention is directed to a two-step method for incorporating a partially soluble compound into a polymer matrix. The method of the invention comprises the steps of: (1) mixing a first portion of a partially soluble compound in its soluble phase into a polymer at a concentration near or equal to the compound's equilibrium solubility in the polymer to give a single homogeneous phase, followed by (2) mixing a second portion of the partially soluble compound in its solid phase into the polymer in a manner that the compound does not dissolve in the polymer but is dispersed throughout the polymer and the size or size distribution of the particles is controlled. The invention is further directed to compound/polymer compositions prepared by the above process, to delivery devices comprised of such compositions, and to a method of delivering to an environment of use a partially soluble active agent from a polymeric matrix, which method comprises placing an appropriately sized and shaped delivery device of the invention in the environment of use.

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POLYMER SYSTEM CONTAINING A PARTIALLY SOLUBLE COMPOUND

FIELD OF THE INVENTION

This invention pertains to a method for the incorporation of a partially soluble compound into a polymeric matrix and to the resulting compound/polymer matrix having advantageous physical and/or chemical properties.

BACKGROUND OF THE INVENTION

Crystalline and solid amorphous compounds are routinely mixed into polymers by several means for providing a plethora of compound-containing polymeric devices and products. Such mixing procedures are carried out in a single operation of adding the compound to the polymer. Depending upon the technique chosen, the compound may undergo a transition from a crystalline or solid state to a non-solid state. When, during the mixing procedure, the crystalline or solid compound goes through a non-solid phase (such as, for example, by melting or dissolution in a solvent), the compound will re-crystallize in the polymer matrix at a rate dependent upon many factors which influence the kinetics of recrystallization of that particular compound/polymer combination (such as, for example, solubility and mobility of the compound in the polymer, temperature, and the like) with equilibrium being reached when the dissolved compound reaches its limit of solubility in the polymer. The particle size of the resulting dispersion of solid compound in the polymer is difficult to control. On the other hand, if the compound remains in a crystalline or solid state during the mixing process, it will be dispersed throughout the polymer in the solid state with very little present in the polymer phase.

While the above resultant compound/polymer systems are useful in many instances, they can be less than desirable in certain applications. For example, the particle size of the compound can be critical to the characteristics of the final product, so that dispersed particles of uncontrolled size determined by the recrystallization process may give an unsatisfactory product for a particular desired use. Or, a particular portion of the compound may be required to be present incorporated into the polymer phase in

order to confer desired physical properties to the matrix. Also, if the compound is somewhat miscible in the polymer and is mixed in below its melting temperature, part of the mixed-in compound may, slowly and poorly controlled, dissolve in the polymer over time, resulting in a system containing less than the desired amount of solid material. Therefore, it would be desirable to provide a means for controlling the particle size of a crystalline or amorphous solid compound dispersed in a polymeric matrix and for controlling the distribution of compound in both soluble and solid phases in a polymer matrix.

SUMMARY OF THE INVENTION

The present invention is directed to a two-operation or two-step method for incorporating a partially soluble compound into a polymer matrix. The method of the invention comprises the steps of:

(1) mixing a first portion of a partially soluble compound in its soluble phase into a polymer at a concentration near or equal to the compound's equilibrium solubility in the polymer to form a single homogeneous phase, followed by

(2) mixing a second portion of the partially soluble compound in its solid phase into the polymer in a manner that the compound does not dissolve in the polymer but is dispersed throughout the polymer, so that the size of the solid particles is substantially controlled.

The invention is further directed to compound/polymer compositions prepared by the above process and which comprise a polymer containing a partially soluble compound in both dissolved and dispersed forms, wherein a first portion of the partially soluble compound is dissolved in its soluble phase within the polymer at a concentration near or equal to the compound's equilibrium solubility in the polymer to give a single homogeneous phase, and wherein a second portion of the partially soluble compound in its solid phase is dispersed throughout the polymer, the size of the particles of partially soluble compound in the solid phase being of a predetermined controlled size or size distribution.

The invention is also directed to delivery devices comprised of the above compound/polymer compositions, and to a method of

delivering to an environment of use a partially soluble active agent from a polymeric matrix, which method comprises placing an appropriately sized and shaped delivery device of the invention into the environment of use.

DESCRIPTION OF THE DRAWINGS

FIG. 1 shows graphically the fractional release of bupivacaine from a poly(orthoester) polymer matrix prepared according to the method of the present invention.

FIG. 2 shows graphically the fractional release of bupivacaine from a poly(orthoester) polymer matrix prepared by a prior art one-step method.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

By utilizing a two-step mixing process according to the invention, the soluble fraction of the partially soluble compound can be mixed into the polymer first, allowing the compound to become dissolved in the polymer, such as by melting or dissolution in a solvent, to form a solid or semi-solid solution, thereby forming a single phase with molecules of the partially soluble compound dispersed substantially uniformly and randomly throughout the continuum of the polymer, as opposed to a two-phase solid or semi-solid in which granules or globules of one are dispersed through, or suspended in, the other. The soluble fraction of the compound is mixed into the polymer in an amount near or equal to the compound's equilibrium solubility in that particular polymer in order to obtain a polymer close to or at saturation with dissolved partially soluble compound. In the second step of the method of the invention, the solid fraction of the partially soluble compound that is to be dispersed throughout the polymer matrix is then mixed in, in such a way that the solid fraction does not dissolve in the polymer and the size of the particles remains substantially unchanged or changed in a controlled manner. By "substantially unchanged or changed in a controlled manner", as the term is used herein, is meant that the particles will not become smaller as a result of some of the particulate drug dissolving into the polymer, nor will they become

larger as a result of some of the drug precipitating out of the polymer. In other words, the size of the particles is predominantly determined by the initial preparation of the particles before mixing into the polymer and by the dispersive action during mixing and is influenced at the most to only a minor degree by recrystallization and dissolution processes or forces after the mixing. Initial preparation of the particles and dispersive forces during mixing are highly controllable, resulting in particle size that is highly controllable as well.

The method of this invention provides several important advantages over previously known methods.

The method provides a means of controlling the particle size of partially soluble compound in its solid phase mixed or dispersed into a polymeric matrix. The size can be chosen prior to incorporation and will not change substantially as a result of the incorporation process or will change in a known manner that can be controlled. This is important in giving a compound/polymer composition with advantageous or other desired properties, since it has been found that the particle size can be critical to the resulting characteristics of the composition and is therefore an important variable in polymeric drug delivery systems. It is extremely useful to be able to control such a variable. See, *Handbook of Fillers for Plastics*, H. Katz and J. Milewski, Eds. (Van Nostrand Reinhold Co., New York), for a discussion.

Also, the method of the invention provides a means of controlling the distribution of partially soluble compound in both soluble and solid phases in a polymer matrix. This is important in those instances where it is required to have a portion of the partially soluble compound incorporated into the polymer in order to confer certain desirable physical properties to the system, such as, for example, rheological properties in the case where the solubilized compound influences the glass transition temperature of the polymer, or polymer stability properties in the case where the solubilized compound acts as a stabilizer for the erosion of a bioerodible polymer.

Thus, the incorporation of a partially soluble compound into a polymer matrix by means of the two-step process of the present

invention achieves physical and/or chemical properties of the resulting compound/polymer matrix system which cannot be achieved by a one-step incorporation.

What is meant by the term "partially soluble compound", as used herein, is any compound that, when mixed together with a polymer, is present in the polymer in two phases, partly dissolved and partly solid, at equilibrium at the temperature of use. Any compound which meets this criterium may be used in the present invention. One class of suitable compounds are non-active additives which may be added to a polymer to alter or otherwise affect the physical and/or chemical properties of the polymer. Another class of suitable compounds are those which provide a therapeutic or other beneficial effect, such as drugs, and which are to be delivered or dispersed from the polymer matrix into an environment of use.

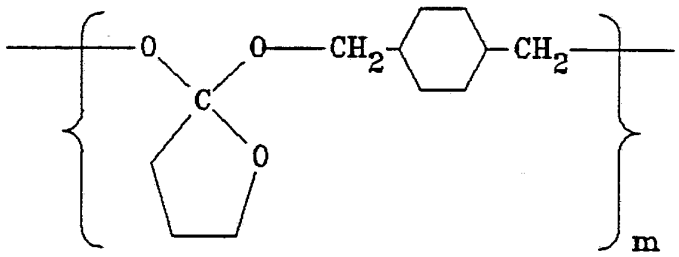
The term "matrix", as used herein, denotes a solid or semi-solid solution polymeric carrier having a partially soluble compound incorporated in its soluble phase. The term "system" of the invention, as used herein, denotes a solid or semi-solid polymeric carrier or matrix having a partially soluble compound incorporated in its soluble phase and dispersed in its solid phase. The carrier or matrix can be any desired shape, such as sphere, spheroid, cylinder, rod, sheet, and the like, or consistency, such as solid, malleable or deformable, flowable, and the like.

The polymeric material can be chosen from any polymer that is compatible with the partially soluble compound; that is, it does not interfere or react chemically, physically or therapeutically with the compound. The polymer may be erodible or degradable or it may be non-erodible. When the polymer matrix is to be used in a biological environment of use, the matrix material is also biocompatible (e.g., it should not be toxic or otherwise cause adverse tissue reactions), noncarcinogenic and causes no adverse immunological response. In a presently preferred embodiment of the invention, the polymer is bioerodible; that is, it is a material which is degradable or erodible in a human or other animal body, either enzymatically or non-enzymatically, to produce biocompatible or non-toxic by-products, such as innocuous low molecular weight species. The by-products can be further metabolized or excreted via normal physiologic pathways.

Representative natural bioerodible materials include naturally occurring polymers such as collagen, cross-linked collagen, agar-agar, gelatin, cross-linked gelatin, and polysaccharides, for example.

Examples of bioerodible synthetic polymers include, but are not limited to, poly(lactic acid) and poly(glycolic acid) or their derivatives; copolymers of lactic acid and glycolic acid; polyamides; polyesters; poly(orthoesters); poly(orthocarbonates); polycaprolactones; polyanhydrides; and polyvinylpyrrolidones. Mixtures and combinations of these may also be used.

Other examples of bioerodible polymers suitable for this invention are the poly(orthoesters) and the poly(orthocarbonates). These polymers are disclosed in U.S. Pat. Nos. 4,070,347, 4,093,709, 4,122,158, 4,131,648, 4,138,344, and 4,155,992, for example, all of which are incorporated herein by reference. A preferred embodiment is the poly(orthoesters). Suitable poly(orthoester) polymers can be selected from those under the trademark Alzamer®. In a presently preferred embodiment, the polymers as used in this invention are based upon the Alzamer® poly(orthoester) poly(2,2-dioxy-cis,trans-1,4-cyclohexane dimethylene tetrahydrofuran), which is normally a hard solid (glassy) polymer having the following structure (A):



(A)

where m equals a number such that the molecular weight of the polymer (A) is within the range of 1,000 to 100,000.

Other orthoester polymers with similar physical properties can be substituted for the polymers noted above, and are disclosed in, for example, U.S. Pat. No. 4,180,646, which is incorporated herein by reference.

The bioerodible polymers useful in the present invention may also be preferably chosen from the poly(lactic acids) or the poly(glycolic acids) or copolymers of lactic acid and glycolic acid. Such polymers and copolymers are well known in the art and are well documented in the literature.

Nonerodible polymers which may be used in the invention are well known in the art.

The polymer of the present invention may be selected from the group consisting of a homopolymer, physical mixtures of two or more polymers, and copolymers of two or more polymers. The term "polymer", as used herein, encompasses all of these. Methods for preparing these are known in the art or are described in the above-incorporated patents.

In the method of the present invention, an amount of partially soluble compound in its soluble phase, at a concentration near or equal to the compound's equilibrium solubility in a particular polymer at the temperature of use, is thoroughly mixed into the polymer until it has been completely incorporated. The term "at a concentration near or equal to the compound's equilibrium solubility", as used herein, means a concentration that is within about 5% above or below the equilibrium solubility, and is preferably within about 3% above or below the equilibrium solubility, more preferably substantially at the equilibrium solubility, of the partially soluble compound. The soluble phase of the compound may be obtained in a number of ways, such as, for example, by heating the compound to slightly above its melting temperature, or by dissolving the compound in a suitable solvent. This step produces a polymer close to or at saturation with dissolved partially soluble compound at the temperature of use to form a single homogeneous phase. After this incorporation step, a second portion of the partially soluble compound in its solid phase is mixed with the polymer previously saturated with solubilized compound. This second step is carried out in a manner such that the solid particles of partially soluble compound do not dissolve in the polymer. For example, when the soluble phase of the partially soluble compound is obtained by melting, the resulting saturated polymer is cooled to a temperature below the melting temperature of the partially soluble compound

before the solid portion of the compound is added. As another example, when the soluble phase of the partially soluble compound is obtained by dissolution, the solvent is evaporated off prior to addition of the solid portion of the compound. The resulting compound/polymer composition may then be formed into a beneficial agent delivery device or other desired article or system in ways known to the art.

The particular reaction conditions of the present method will be dependent on the particular partially soluble compound to be incorporated, the chosen method of incorporation, and the particular polymer into which the compound is to be incorporated. These conditions are well known in the art for the particular compounds and polymers, or they can often be determined without undue experimentation. Whatever conditions are chosen, it is always necessary that the soluble portion of the partially soluble compound be mixed with the polymer in such a way that the partially soluble compound remains in its soluble phase until completely incorporated into the polymer. It is also always necessary that the solid phase of the partially soluble compound be mixed into the polymer in a manner that the particles of compound do not dissolve in the polymer.

The resulting composition of the invention comprises (a) a matrix of a polymer saturated or nearly saturated at the temperature of use with a partially soluble compound in its soluble phase, and (b) the partially soluble compound in its solid phase dispersed within the matrix. In other words, it is a system of polymer containing a partially soluble compound present in both dissolved and dispersed forms. This composition or system can be utilized in a variety of ways.

In a presently preferred embodiment, delivery devices for delivering an active, beneficial or therapeutic agent, where the agent is a partially soluble compound, can be prepared which comprise (a) a body formed of a polymer saturated or nearly saturated at the temperature of use with the partially soluble active agent in its soluble phase, and (b) the partially soluble active agent in its solid phase dispersed within the body. The agent is released from the device at a controlled rate and in a therapeutically or beneficially effective amount. The rate of release of the active

agent from the polymeric compositions of the present invention is significantly different from the rate of release from the polymer matrix without the dissolved agent incorporated therein.

Exemplary partially soluble active agents that can be delivered according to this invention are those that are compatible with the polymeric matrix and include, among others, biocides, sterilization agents, food supplements, nutrients, vitamins, sex sterilants, fertility inhibitors, and fertility promoters. They can include drugs that act on the peripheral nerves, adrenergic receptors, cholinergic receptors, nervous system, skeletal muscles, cardiovascular system, smooth muscles, blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, immunological system, reproductive system, skeletal system, autocoid systems, alimentary and excretory systems, histamine system, and central nervous system. Suitable agents may be selected from, for example, polysaccharides, steroids, analgesics, local anesthetics, antibiotic agents, anti-inflammatory corticosteroids, opiates, ocular drugs, and synthetic analogs of these molecules. Presently preferred are the steroids, local anesthetics and opiates.

The active agent can be present in the invention in the various chemical and physical forms such as uncharged molecules, molecular complexes, and pharmacologically acceptable acid addition and base addition salts such as hydrochlorides, hydrobromides, sulfate, laurylate, palmitate, phosphate, nitrate, borate, acetate, maleate, tartrate, oleate and salicylate. For acidic compounds, salts of metals, amines or organic cations can be used. Derivatives of agents such as esters, ethers and amides can be used. An active agent can be used alone or mixed with other active agents.

The lists of active agents recited above are given only to illustrate the types of active agents which are suitable for use in practicing the invention, and are not intended to be exhaustive.

The amount of partially soluble compound in its soluble phase to be added to the polymer will typically be that amount near or equal to the compound's equilibrium solubility in the particular polymer. An amount greater than 5% above the equilibrium solubility is not contemplated by this invention, since the excess portion of

compound that recrystallizes out will have resultant uncontrolled particle sizes.

When the partially soluble compound is an active agent for delivery to an environment of use, particularly when the polymer is bioerodible, the amount of active agent employed in both its soluble and its solid phases in the delivery device will be that amount necessary to deliver a therapeutically effective amount of the agent to achieve the desired result at the site of application. This is due to the fact that as the polymer erodes, it releases into the environment that portion of the partially soluble active agent that was previously dissolved within the polymer. This portion of the partially soluble active agent is then available for therapeutic activity. In practice, the amount of partially soluble active agent in the device will vary depending upon the particular agent, the severity of the condition, and the desired effect, as well as the desired rate and duration of release.

In addition to the polymer and the active agent, the devices of this invention may also include, if desired, one or more diluents; vehicles; stabilizers such as potassium phosphate, sodium phosphate, sodium carbonate or magnesium hydroxide; dyes; inert fillers; pigments; and other components of polymeric matrix systems as are known in the art.

In certain cases, a hydrophilic pore-forming excipient is used during the formation of the polymer to form the polymer into a porous structure. In such cases, the excipient will generally be included in the liquid mixture during the first step of the process. Pore-forming excipients and their use in forming porous polymer structures are well known in the art. When a pore-forming excipient of this nature is used, the soluble phase of the partially crystalline compound preferably has a greater solubility in the polymer than in the pore-forming excipient.

Other excipients are optionally included. One class of such excipients are inert hydrophobic excipients that act to increase drug delivery and improve reproducibility from certain polymers. Examples of this type of excipient are calcium stearate, magnesium stearate, aluminum stearate, calcium phosphate, myciyl cerotate, β-carotene,

zeaxanthin, cholestane, 3-hydroxycholestane, cholesterol, 5,6-cholestene, 3-hydroxy-5,6-cholestene, and 3-amino-5,6-cholestene.

The devices of the invention can be manufactured by standard techniques. For example, the polymers with the agent mixed therewith can be extruded into filaments, spun into fibers, pressed into shaped articles, doctor-bladed into thin films, coated by solvent evaporation, coated by using a fluidized bed, compression molded, transfer molded, formed into microparticles by cryogrinding, and like methods of manufacture.

The devices can be a single matrix, a container with a reservoir therein, or a number of layers, for example. The devices can be made into various shapes such as flat, square, round, tubular, disc, ring, and the like. Presently preferred embodiments are films, rods, and particles. Also, the devices of the invention are sized, shaped and adapted for implantation, insertion, placement, depositing or spreading on the body, in the body, or in cavities and passageways of the body of an animal. Standard procedures for processing the polymer and the agent are known in the art or are described in *Plastic Encyclopedia*, Vol. 46, pp 62-70 (1969) and in the patents cited supra.

In the practice of the present invention, the device of the invention is placed in or on an environment of use. The environments in which the devices may be used include physiological environments within the body of a human or animal or aqueous environments such as pools, tanks, reservoirs, and the like serving recreational, industrial or residential purposes. The devices may also be utilized in the biotechnology area, such as to deliver nutrients or growth regulating compounds or other agents to cell cultures, for example. In the presently preferred embodiments, the environment of use is the body of an animal. Included in the term "animal" are humans, primates, mammals, domesticated or semi-domesticated animals (such as household, pet, and farm animals), laboratory animals (such as mice, rats and guinea pigs), birds, reptiles, fish, zoo animals, and the like. The devices may be placed on or in wounds, spread as a thin film, or injected as microparticles or placed subcutaneously or interperitoneally as an implant into the body, for example.

The following examples are set forth as representative and illustrative of the spirit of the present invention. These examples are not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1

A polymeric matrix according to the present invention where bupivacaine is the partially crystalline active agent is prepared as follows.

Bupivacaine, sodium carbonate, and cholesterol were each dried and milled. 83 Weight percent (wt%) of the polymer poly(2,2-dioxy-cis,trans-1,4-cyclohexane dimethylene tetrahydrofuran) ("polymer (A)" hereinabove) having a molecular weight of about 30,000 was mixed together with 5 wt% of cholesterol and 2 wt% of sodium carbonate at 115°C. Bupivacaine (5 wt%) was added, and mixing was continued at the elevated temperature until the bupivacaine was completed incorporated. This produces a polymer close to saturation with dissolved bupivacaine at room temperature. The mixture was then allowed to cool to 80°C, and 5 wt% of bupivacaine was added, with mixing. The mixture was then placed in a CSI miniextruder and mixing was continued at 80°C. It was then melt-pressed at 80°C into sheets which were die cut into 1x1 cm squares, 0.25 mm thick.

EXAMPLE 2

The release profiles of the drug bupivacaine from a matrix prepared according to Example 1 and from a matrix prepared by a prior art method were determined as follows.

Polymeric squares were prepared by a one-step process (the prior art method); that is, they were prepared in the same manner as described in Example 1 except that no bupivacaine was added to the mixture at elevated temperature, and all of the bupivacaine (10 wt%) was added to the polymer at one time at the lower temperature of 80°C.

The squares from either Example 1 or this Example were placed between two pieces of dialysis tubing and clamped with two concentric teflon rings. Three squares were tested from each composition. Each square device held by the teflon rings was immersed in release rate

media (phosphate buffer, pH 7.2), and the amount of bupivacaine released into the buffer was measured at selected intervals. After each measurement, the device was placed in fresh media.

The cumulative percent release of the bupivacaine from each of the two formulations is presented in **FIG. 1** (matrix of the invention) and **FIG. 2** (prior art matrix) and shows a steady, continuous release of the local anesthetic from the matrix prepared by the method of the present invention over a period of about 20 days, with the polymer remaining intact during that period. In contrast, release of the drug from the matrix prepared by the prior art method accelerated rapidly after about 7 days, corresponding to erosion of the polymer.

The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that the materials, proportions, operating conditions, and other parameters of the systems and methods described herein may be further modified or substituted in various ways without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A method for preparing a polymer system containing a partially soluble compound in both dissolved and dispersed forms, wherein the method comprises the steps of:

(1) mixing a first portion of a partially soluble compound in its soluble phase into a polymer at a concentration near or equal to the compound's equilibrium solubility in the polymer to give a single homogeneous phase, followed by

(2) mixing a second portion of the partially soluble compound in its solid phase into the polymer in a manner that the compound does not dissolve in the polymer but is dispersed throughout the polymer and the size or size distribution of the solid particles of the partially soluble compound is controlled.

2. A method for controlling the size of solid particles of a partially soluble compound dispersed in a polymer, wherein the method comprises the steps of:

(1) mixing a first portion of the partially soluble compound in its soluble phase into a polymer at a concentration near or equal to the compound's equilibrium solubility in the polymer to give a single homogeneous phase, followed by

(2) mixing a second portion of the partially soluble compound in its solid phase, the particles in the solid phase being of a predetermined size, into the polymer in a manner that the partially soluble compound does not dissolve in the polymer but is dispersed throughout the polymer, wherein the size of the particles in the solid phase remains substantially unchanged or is changed in a controlled manner.

3. A method according to claim 1 or 2 wherein the soluble phase is obtained by mixing the polymer and the partially soluble compound at a temperature above the melting temperature of the partially soluble compound, and the solid phase is mixed into the polymer at a temperature below the melting temperature of the partially soluble compound.

4. A method according to claim 1 or 2 wherein the soluble phase is obtained by dissolving the partially soluble compound in a solvent, and the solvent is then removed prior to mixing in the solid phase of the partially soluble compound.

5. A method for delivering a partially soluble compound to an environment of use at a controlled rate, which method comprises placing a delivery device in the environment of use, wherein the delivery device is comprised of:

(a) a shaped body, sized and adapted for delivering the partially soluble compound to the environment of use, the body formed of a release rate-controlling matrix material, where the matrix material is comprised of a polymer which has therein the partially soluble compound in its soluble phase at a concentration near or equal to the compound's equilibrium solubility in the polymer to give a single homogeneous phase, and

(b) solid particles of the partially soluble compound in its solid phase dispersed within the body, where the solid particles of the partially soluble compound are of a predetermined controlled size or size distribution.

6. A method for regulating the rate of release of a partially soluble compound to an environment of use from a polymeric matrix over time, which method comprises placing a delivery device in the environment of use, wherein the delivery device is comprised of:

(a) a shaped body, sized and adapted for delivering the partially soluble compound to the environment of use, the body formed of a release rate-controlling matrix material, where the matrix material is comprised of a polymer which has therein the partially soluble compound in its soluble phase at a concentration near or equal to the compound's equilibrium solubility in the polymer to give a single homogeneous phase, and

(b) solid particles of the partially soluble compound in its solid phase dispersed within the body, where the solid particles of partially soluble compound are of a predetermined controlled size or size distribution.

7. A method according to claim 1, 2, 5 or 6 wherein the polymer is a bioerodible polymer.

8. A method according to claim 1, 2, 5 or 6 wherein the polymer is a bioerodible polymer selected from the group consisting of a poly(orthoester) polymer, a poly(lactic acid) polymer, a poly(glycolic acid) polymer, and a copolymer of lactic acid and glycolic acid.

9. A method according to claim 1, 2, 5 or 6 wherein the partially soluble compound is a therapeutic agent and is present in a therapeutically effective amount.

10. A method according to claim 1, 2, 5 or 6 wherein the solid particles of the partially soluble compound in its solid phase are of a predetermined uniform size.

11. A method according to claim 1, 2, 5 or 6 wherein the polymer is the bioerodible polymer poly(2,2-dioxy-cis,trans-1,4-cyclohexane dimethylene tetrahydrofuran), and the partially soluble compound is bupivacaine.

12. A composition comprising a polymer containing a partially soluble compound in both dissolved and dispersed forms, wherein a first portion of the partially soluble compound is dissolved in its soluble phase within the polymer at a concentration near or equal to the compound's equilibrium solubility in the polymer to give a single homogeneous phase, and wherein a second portion of the partially soluble compound in its solid phase is dispersed throughout the polymer, the size of the particles in the solid phase being of a predetermined controlled size or size distribution.

13. A composition comprising a partially soluble compound in both dissolved and dispersed forms in a polymer, the composition prepared according to the method of Claim 1.

14. A composition according to claim 12 or 13 wherein the particles of the partially soluble compound in its solid phase are of a predetermined uniform size.

15. A composition according to claim 12 or 13 wherein the polymer is a bioerodible polymer.

16. A composition according to claim 12 or 13 wherein the polymer is a bioerodible polymer selected from the group consisting of a poly(orthoester) polymer, a poly(lactic acid) polymer, a poly(glycolic acid) polymer, and a copolymer of lactic acid and glycolic acid.

17. A composition according to claim 12 or 13 wherein the partially soluble compound is a therapeutic agent and is present in a therapeutically effective amount.

18. A composition according to claim 12 or 13 wherein the polymer is the bioerodible polymer poly(2,2-dioxy-cis,trans-1,4-cyclohexane dimethylene tetrahydrofuran), and the partially soluble compound is bupivacaine.

19. A device for delivering a partially soluble compound to an environment of use at a controlled rate, wherein the device comprises:

(a) a shaped body, sized and adapted for delivering the partially soluble compound to the environment of use, the body formed of a release rate-controlling matrix material, where the matrix material is comprised of a polymer which has therein the partially soluble compound in its soluble phase at a concentration near or equal to the compound's equilibrium solubility in the polymer to give a single homogeneous phase, and

(b) solid particles of the partially soluble compound in its solid phase dispersed within the body, where the solid particles are of a predetermined controlled size or size distribution.

20. A device according to claim 19 wherein the particles of the partially soluble compound in its solid phase are of a predetermined uniform size.

21. A device according to claim 19 wherein the polymer is a bioerodible polymer.

22. A device according to claim 19 wherein the polymer is a bioerodible polymer selected from the group consisting of a poly(orthoester) polymer, a poly(lactic acid) polymer, a poly(glycolic acid) polymer, and a copolymer of lactic acid and glycolic acid.

23. A device according to claim 19 wherein the partially soluble compound is a therapeutic agent and is present in a therapeutically effective amount.

24. A device according to claim 19 wherein the polymer is the bioerodible polymer poly(2,2-dioxy-cis,trans-1,4-cyclohexane dimethylene tetrahydrofuran), and the partially soluble agent is bupivacaine.

1/1 FIG. 1

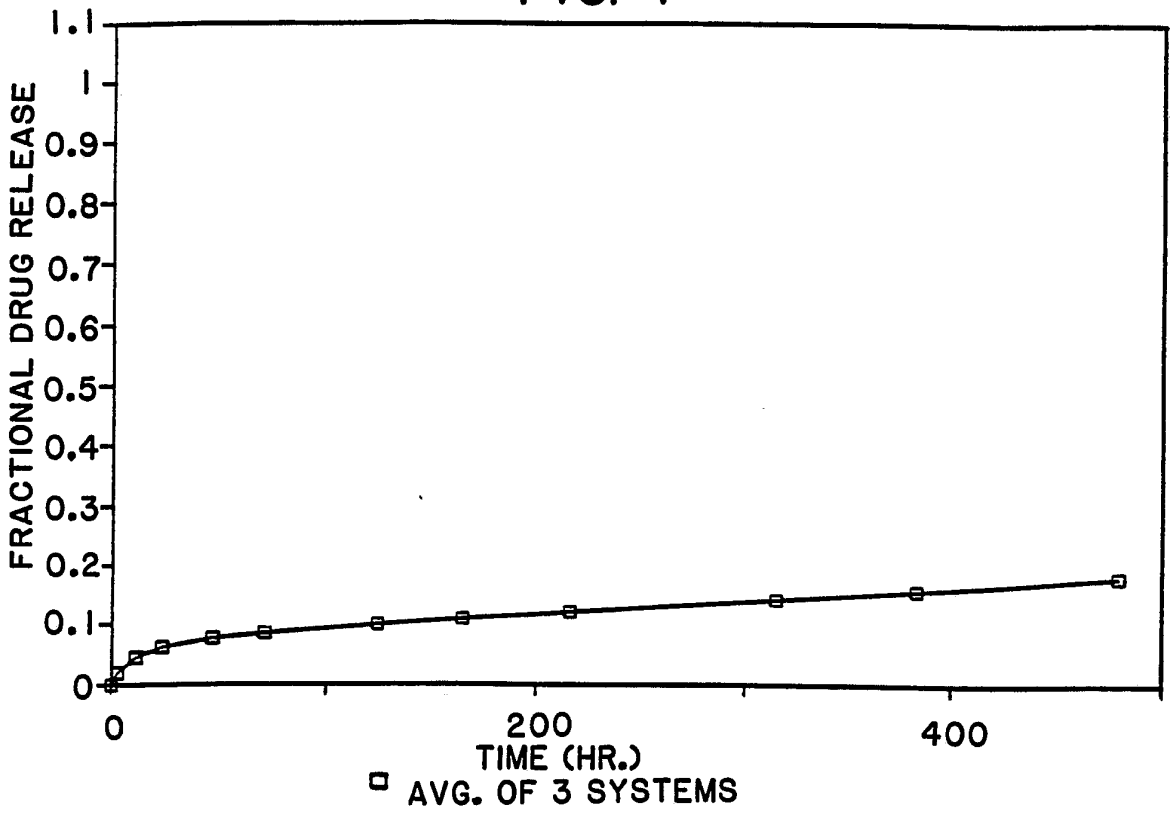
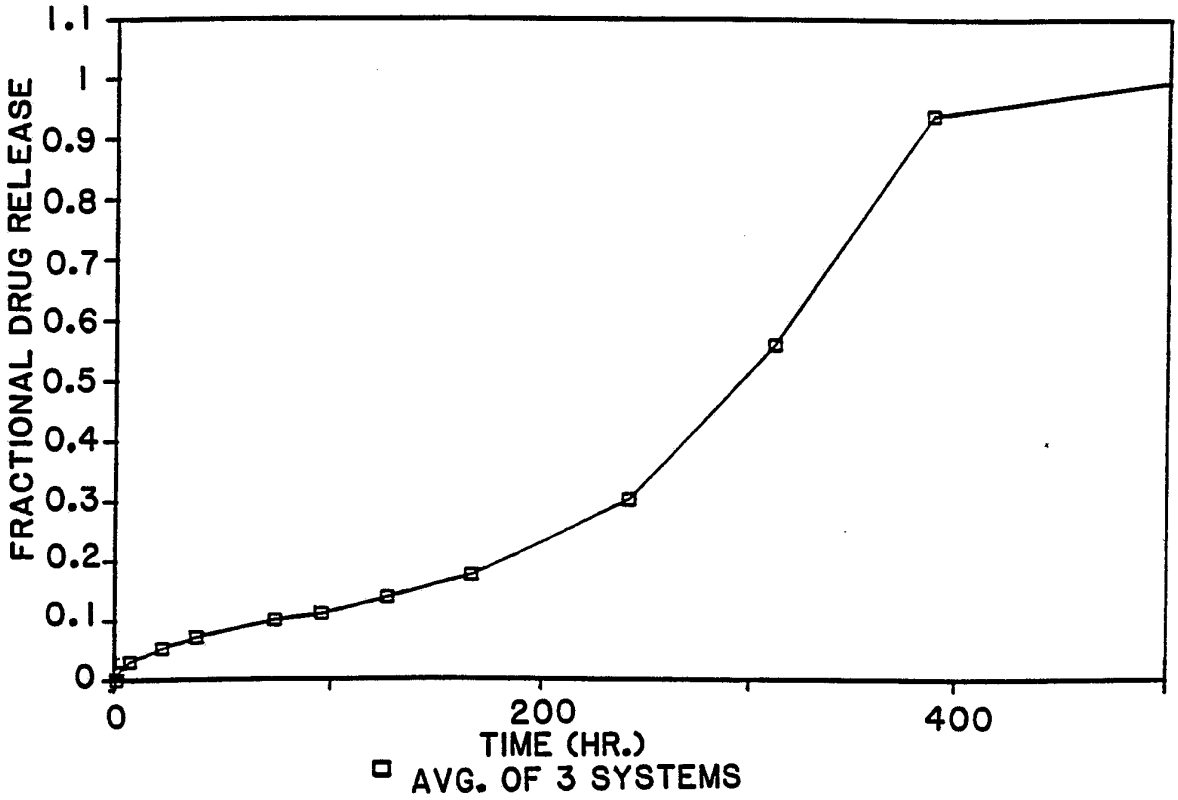

FRACTIONAL DRUG RELEASE
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
200
400
TIME (HR.)
AVG. OF 3 SYSTEMS

FIG. 2


FRACTIONAL DRUG RELEASE
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TIME (HR.)
AVG. OF 3 SYSTEMS