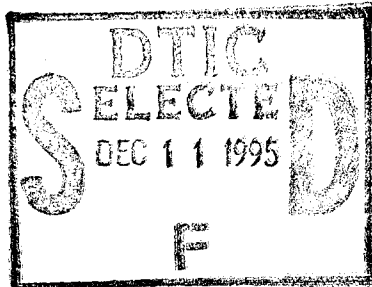


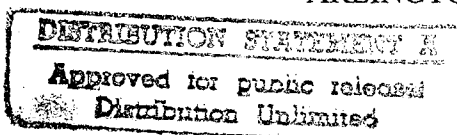
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Navy Case No. 76,652
Inventor(s): Ronald R. Price et al.

PATENT APPLICATION

1
2
3 **CONTROLLED RELEASE OF ACTIVE AGENTS**
4 **USING INORGANIC TUBULES**
5

6 **CROSS-REFERENCE TO RELATED APPLICATIONS**

7 This application is a continuation-in-part of co-pending U.S. Patent Application No.
8 08/206,149, filed March 7, 1994, by Ronald R. Price et al., which was a divisional of co-
9 pending U.S. Patent Application No. 08/077,503, filed June 17, 1993, by Ronald R. Price et
10 al. Both applications are incorporated herein by reference in their entireties for all
11 purposes.
12

13 **BACKGROUND OF THE INVENTION**
14

15 **1. Field of the Invention**

16 This invention relates to compositions and methods for releasing active agents at a
17 selected rate. More particularly, this invention relates to such methods and compositions
18 using inorganic microtubular ceramics, and especially naturally occurring microtubular
19 minerals for environmentally friendly controlled release.
20

1 **2. Description of the Related Art**

2 Active agents are chemicals that have some effect in some environment of use. For
3 almost any active agent, for use in almost any use environment, it is desired to modulate the
4 release of the active agent into the use environment, so that the active agent is released into
5 the use environment at a selected rate, and over a selected time. There are several,
6 frequently complementary, reasons for modulating active agent release.

7 Many active agents are preferably released at a desired concentration, or in a desired
8 concentration range. Drugs, for example, are preferably introduced into the body within a
9 therapeutic range. Below this range, there will not be enough of the drug in the body to
10 achieve the desired therapeutic effect. Above this range, no additional therapeutic effect
11 will be conferred, or adverse side effects of the drug will outweigh the therapeutic effect of
12 the drug.

13 Analogous dynamics are at work for most every active agent. As another example,
14 antifouling agents for use on ship hulls are typically environmentally unfriendly. Thus, it is
15 desired to control the release rate of these antifouling agents, to keep their release into the
16 environment at an acceptable level. At the same time, it is desired to release these
17 antifouling agents at effective levels. See generally U.S. Patent No. 5,049,382, issued
18 September 17, 1991 to Price et al.

19 Likewise, many active agents are preferably released at a sustained rate over a
20 desirable period. For example, many drugs (e.g., antibiotics) are preferably absorbed and
21 metabolized by the body over a prolonged therapeutic course of treatment. Traditionally,

1 this is done by administering repeated, regular doses (e.g., regular oral or injected doses),
2 or by a sustained administration, such as an intravenous drip. Other drugs (e.g., antihyper-
3 tensive drugs, birth control hormones) do not have a finite course of treatment. For these
4 drugs, sustained controlled delivery is a matter of convenience and an assurance against a
5 lapse of memory.

6 Sustained delivery is also desired for many other active agents. For antifouling
7 agents, it is highly desirable to sustain delivery of an effective amount of the antifouling
8 agent for as long as possible, to maximize the time between applications of the agent. For
9 pesticides, pheromones, and other active agents used to control pest populations, sustained
10 delivery of these agents for at least the duration of a growth or reproduction cycle is highly
11 desirable. See generally U.S. Patent No. 4,017,303, issued April 12, 1977 to Coplan et al.

12 For these and other types of active agents, several concerns present themselves. It
13 is generally desirable to release an active agent at a controlled rate, to maintain a constant
14 level of the active agent. Unfortunately, many of the systems used for the modulated
15 delivery of active agents do not release these active agents at a controlled rate. Systems
16 using layered structures that ablate or dissolve one layer at a time tend to release their
17 active agents in cycles, with the levels of active agents oscillating between highs and lows.

18 Liposomal tubules and other microstructures, which have been proposed for use in
19 a system for the modulated delivery of an active agent, (see Price et al., *supra*) have several
20 shortcomings. These tubules must be manufactured: they do not occur naturally. They
21 release their entrapped contents very quickly, over a time scale of minutes. They do not

1 inherently permit a low solubility active agent to be readily introduced into a use environ-
2 ment, at a desired effective rate, such as effectively delivering a hydrophobic active agent
3 *in vivo*. However, liposome tubules do have several advantages: they are small enough to
4 be injected or to be incorporated in a coating such as an antifouling paint, and they have
5 broad applicability to a range of active agents and use environments.

6 Metal tubules and other microstructures have also been proposed for use in the
7 modulated release of an active agent. These metal structures typically are made by
8 metallizing a lipid microstructure. In addition to the additional processing and cost concerns
9 inherent to metallized tubules, there is the additional environmental unfriendliness associated
10 with many metals used in these applications (e.g., copper).

11 Polymers and other carriers are sometimes used for the modulated release of an
12 active agent that has at least some solubility in these carriers. In these applications, the
13 active agent is mixed with the carrier, to dissolve the active agent in the carrier. As the
14 active agent diffuses through the carrier to the interface of the carrier and the use
15 environment, the active agent is released into the use environment. Typical examples of
16 such systems are flea and tick collars for pets. Unfortunately, many active agents have
17 undesirably low solubility in many of the available carriers. A consequence of this low
18 solubility is that in many instances, the delivery system will contain only an undesirably small
19 amount of the active agent, limiting the useful life of the delivery system. For example, flea
20 and tick collars for pets have undesirably short useful lives, shorter than the flea and tick
21 seasons in many parts of the country. A delivery system that would permit the inclusion of

1 a larger volume of active agent in a delivery system is desired. Also, many of these polymers
2 used in modulated release applications are environmentally unfriendly.

3
4 **SUMMARY OF THE INVENTION**

5 Accordingly, it is an object of this invention to provide an improved structure and
6 method for the controlled release of active agents, including drugs (including antibiotics),
7 antifouling agents, biocides, pesticides, herbicides, molluskicides, pheromones and other
8 scents, etc.

9 It is a further object of this invention to provide a structure and method for the
10 controlled release of an active agent over a time scale of days, months, or years.

11 It is a further object of this invention to provide a structure and method for the
12 controlled release of an active agent where all the components of the delivery system are
13 environmentally friendly, thus making the system as a whole environmentally friendly.

14 It is a further object of this invention to provide a structure and method for the
15 controlled release of an active agent using naturally occurring microtubules.

16 It is a further object of this invention to provide a broadly-applicable, low-cost
17 structure and method for the controlled release of an active agent.

18 It is a further object of this invention to provide a structure and method for the
19 controlled release of a low solubility active agent into a use environment at a desirable
20 effective rate.

1 These and additional objects of the invention are accomplished by the structures and
2 processes hereinafter described.

3 The present invention is a composition for, and a method of, delivering an active
4 agent at a controlled rate. The composition of the invention is a hollow ceramic or inorganic
5 microtubule, where the active agent is contained within the lumen of the microtubules.
6 Typically, the agent is adsorbed onto an inner surface of the microtubule. The method of
7 the invention is disposing this novel composition in a use environment. In a preferred
8 embodiment of the invention, a microtubule is a tubule having an inner diameter of less than
9 $0.2\ \mu\text{m}$, and microtubules are tubules having an average inner diameter less than $0.2\ \mu\text{m}$.
10 In a preferred embodiment, the hollow ceramic or inorganic microtubule is a mineral
11 microtubule, such as halloysite, cylindrite, boulangerite, or imogolite. In a more preferred
12 embodiment of the invention, the mineral microtubule has a biodegradable polymeric carrier
13 disposed in its lumen. In a preferred embodiment of the invention, the inner diameter of
14 the microtubules varies from about $0.20\ \mu\text{m}$ to about $0.35\ \mu\text{m}$, or averages about $0.40\ \mu\text{m}$.
15 In another preferred embodiment, of the invention, the inner diameter of the microtubules
16 varies from about $200\ \text{\AA}$ to about $1000\ \text{\AA}$.

18 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

19 A. Adsorption/Desorption Processes

20 Chemical agents, including the active agents of interest to the present invention, can
21 enter or exit from the internal volume (lumen) of a cylindrical tubule by several mechanisms.

1 For example, active agents can enter or exit tubules by capillary action, if the tubules are
2 sufficiently wide. Capillary attraction and release occurs in tubules having inner diameters
3 of at least about 0.2 μm . Capillary attraction is relatively weak: agents in tubules having
4 inner diameters of at least about 10 μm typically will be released in a matter of hours,
5 without the use of other barriers to release.

6 In contrast to capillary action, adsorption/desorption processes occur over much
7 smaller distance scales, typically on the order of about 1000 Å. Thus, for tubules in this size
8 range, adsorption/desorption is the controlling process for the release of an active agent
9 inside the interior volume of a microtubule. For a molecule of an active agent contained
10 within the interior volume of a microtubule to reach the end of the tubule, so that the
11 molecule can be released into the environment, the molecule must diffuse through the
12 interior of the tubule while repeatedly being adsorbed and then desorbed by the inner
13 surface of the tubule. This process, which may be conceptualized as a chromatography type
14 of process, is much slower than capillary action, by several orders of magnitude.

15 16 B. Mineral Microstructures

17 Several naturally occurring minerals will, under appropriate hydration conditions, form
18 tubules and other microstructures suitable for use in the present invention. The most
19 common of these is halloysite, an inorganic aluminosilicate belonging to the kaolinite group
20 of clay minerals. See generally, Bates et al., "Morphology and structure of endellite and
21 halloysite", *American Mineralogists* 35 463-85 (1950), which remains the definitive paper on

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halloysite. The mineral has the chemical formula $Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$. In hydrated form the mineral forms good tubules. In dehydrated form the mineral forms broken, collapsed, split, or partially unrolled tubules.

The nomenclature for this mineral is not uniform. In the United States, the hydrated tubule form of the mineral is called endellite, and the dehydrated form is called halloysite. In Europe, the hydrated tubule form of the mineral is called halloysite, and the dehydrated form is called meta-halloysite. To avoid confusion, mineralogists will frequently refer to the hydrated mineral as halloysite 10 Å, and the dehydrated mineral as halloysite 7 Å.

Bates et al. present data on the tubes, which is summarized below:

	Range (Å)	Median (Å)
Tube diameter:	400-1900	700
Hole diameter:	200-1000	400
Wall thickness:	100-700	200

Tube lengths range from 0.1 to about 0.75 μm . Morphologically, both hydrated and dehydrated halloysite comprise layers of single silica tetrahedral and alumina octahedral units. They differ in the presence or absence of a layer of water molecules between the silicate and alumina layers. The basal spacing of the dehydrated form is about 7.2 Å, and the basal spacing of the hydrated form is about 10.1 Å (hence the names halloysite 7Å and halloysite 10Å). The difference, about 2.9 Å, is about the thickness of a monolayer of water molecules.

1 A theory for the formation of hollow tubular microcrystals is presented in Bates et
2 al. Water molecules interposed between the gibbsite (Al_2O_3) and silicate (SiO_2) layers
3 results in a mismatch between the layers, which is compensated by curvature of the layers.

4 Halloysite $10\text{\AA}$ dehydrates to halloysite $7\text{\AA}$ at about 110°C . All structural water is lost
5 at about 575°C . The interlayer water in halloysite $10\text{\AA}$ may be replaced by organic liquids
6 such as ethylene glycol, di- and triethylene glycol, and glycerine.

7 Another mineral that will, under appropriate hydration conditions, form tubules and
8 other microstructures is imogolite.

9 Another mineral that will, under appropriate conditions, form tubules and other
10 microstructures is cylindrite. Cylindrite belongs to the class of minerals known as sulfosalts.

11 Yet another mineral that will, under appropriate conditions, form tubules and other
12 microstructures is boulangerite. Boulangerite also belongs to the class of minerals known
13 as sulfosalts.

14 15 C. Embodiments of the Invention

16 In preferred embodiments of the invention, an active agent is adsorbed onto the inner
17 surface of the lumen of a mineral microstructure. Skilled practitioners will be able to
18 employ known techniques for introducing a wide range of active agents into the lumen of
19 a mineral microstructure according to the invention, thereby making a structure for the
20 modulated release of the active agent. Such structures according to the invention may be

1 used as-is, i.e., as free structures which may be dispensed as desired. Dispensing techniques
2 include scattering, spreading, injecting, etc.

3 An important aspect of the microstructures is the size of the lumen. Preferred inner
4 diameters range from about 200 Å to about 2000 Å. Preferred lengths range from about 0.1
5 μm to about 2.0 μm. Lumen size selection is governed in part by the availability of ceramic
6 or inorganic microstructures within the suitable size range. Lumen size selection is also
7 governed by the choice of active agent, and the choice of any carrier, coating, or matrix (see
8 *infra*). The physical and chemical properties (e.g., viscosity, solubility, reactivity, resistance
9 to wear, etc.) of the active agent, any carrier, any coating and any matrix will be considered
10 by a skilled practitioner. Lumen size selection is also governed by the desired release profile
11 for the active agent.

12 Such structures may be included in a surrounding matrix, such as a paint or a
13 polymer. After release from the mineral microstructures, the active agent then diffuses
14 through the surrounding matrix to interface with the use environment. If the surrounding
15 matrix is ablative in the use environment, then the diffusion distance through the matrix is
16 mitigated or eliminated by this ablation.

17 Suitable surrounding matrices will typically be insoluble in the use environment.
18 These matrices include paints (including marine paints), stains, lacquers, shellacs, wood
19 treatment products, and all manner of applied coatings.

20 In another embodiment of the invention, the lumen of the microstructure contains
21 both an active agent and a carrier. This carrier further modulates the release of the active

1 agent from the lumen of the microstructure. The active agent may be soluble or mobile in
2 the carrier. In this case, the release rate of the active agent will depend on the solubility and
3 diffusion rate of the active agent through the carrier and any coating or matrix. The active
4 agent may be insoluble or immobile in the carrier. In this case, the release rate of the active
5 agent will depend on the release rate of the carrier from the tubule, and any coating or
6 matrix.

7 In another embodiment of the invention, the microstructure is coated with a coating
8 material. This coating further modulates the release of the active agent from the lumen of
9 the microstructure. By carefully selecting a coating for its chemical and physical properties,
10 very precise control of the release of the active agent from the lumen of the microstructure
11 can be achieved.

12 For example, a thermoset polymer may be used as a coating in a preferred embodi-
13 ment of the invention. By carefully selecting the degree of crosslinking in a thermoset
14 polymer coating, and thus the porosity of the thermoset polymer coating, one can obtain
15 a precise degree of control over the release of the active agent from the lumen of the
16 microstructure. Highly crosslinked thermoset coatings will retard the release of the active
17 agent from the lumen more effectively than less crosslinked thermoset coatings.

18 Likewise, the chemical properties of a coating may be used to modulate the release
19 of an active agent from the lumen of a microstructure. For example, it may be desired to
20 use a hydrophobic active agent in an aqueous use environment. However, if one were to
21 load a highly hydrophobic active agent into the lumen of a microstructure according to the

1 invention, and then place this loaded microstructure in an aqueous use environment, the
2 active agent typically would release into the use environment unacceptably slowly, if at all.

3 This problem of active agents that are highly insoluble in an intended use environ-
4 ment is a common one. Many antibiotics are highly insoluble in the serum. This problem
5 can be largely mitigated by coating the microstructures with a coating material in which the
6 active agent has an intermediate solubility (i.e., a solubility somewhere between the solubility
7 of the active agent in itself and the solubility of the active agent in the use environment).

8
9 **D. Active Agents**

10 A wide range of active agents will be suitable for use in the present invention. These
11 suitable active agents include pesticides, antibiotics, antihelmets, antifouling compounds,
12 dyes, enzymes, peptides, bacterial spores, fungi, hormones, etc.

13 Suitable herbicides include tri-chloro compounds (triox, ergerol), isothiazoline, and
14 chlorothanolil (tufficide). Suitable pesticides include malathion, spectricide, and rotenone.
15 Suitable antibiotics include albacilin, amforol, amoxicillin, ampicillin, amprol, anaprime,
16 aureomycin, aziumycin, chloratetracycline, oxytetracycline, gallimycin, fulvicin, garacin, gento-
17 cin, liquamicin, lincomix, nitrofurizone, penicillin, sulfamethazine, sulfapyridine, fulfaquin-
18 oxaline, fulfathiozole, and sulkamycin. Suitable antihelmets include ivermectin, vetisulid,
19 trichorofon, tribrissen, tramisol, topazone, telmin, furox, dichlorovos, anthecide, anaprime,
20 acepromazine, pyrantel tartrate, trichlofon, fanbentel, benzimidazoles, and oxibenzidole.

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1 Suitable antifouling agents include ergerol, triazine, decanolactone, angelicalactone, galacti-
2 lone, any lactone compound, capsicum oil, copper sulphate, isothiazalone, organochlorine
3 compounds, organotin compounds, tetracyclines, calcium ionophores such as 504, C23187,
4 tetracycline. Suitable hormones include estrogen, progestin, testosterone, and human growth
5 factor.

6 7 E. Carriers

8 Carriers are selected in view of their viscosity and the solubility of the active agent
9 in the carrier. The carrier typically should possess a sufficiently low viscosity to fill the
10 lumen of the microstructure. Alternatively, a low viscosity carrier precursor may be used,
11 and the carrier formed *in situ*. For example, the lumen may be filled with a low viscosity
12 monomer, and this monomer subsequently may be polymerized inside the lumen. Accord-
13 ingly, suitable carriers include low molecular weight polymers and monomers, such as poly-
14 saccharides, polyesters, polyamides, nylons, polypeptides, polyurethanes, polyethylenes,
15 polypropylenes, polyvinylchlorides, polystyrenes, polyphenols, polyvinyl pyrrolidone, polyvinyl
16 alcohol, ethyl cellulose, gar gum, polyvinyl formal resin, water soluble epoxy resins, quietol
17 651/nma/ddsa, aquon/ddsa/nsa, urea-formaldehyde, polylysine, chitosan, and polyvinyl acetate
18 and copolymers and blends thereof.

19 Frequently, skilled practitioners may desire to select a carrier that has a very highly
20 selective binding affinity for an active agent of interest. A carrier that has a highly selective
21 binding affinity for an active agent will tend to release that active agent very slowly. Thus,

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1 very slow release rates may be achieved by the use of carriers with high binding affinities for
2 the active agent to be released. Skilled practitioners will recognize that a consequence of
3 the extensive research that has been done on surface acoustic wave (SAW) analysis is that
4 a large number of polymers have been identified as selective adsorbents for particular
5 organic analytes. See generally, D.S. Ballantine, Jr., S.L. Rose, J.W. Grate, H. Wohltjen,
6 *Analytical Chemistry* 58 3058-66 (1986), and references therein, incorporated by reference
7 herein. See also R.A. McGill et al., "Choosing Polymer Coatings for Chemical Sensors",
8 *CHEMTECH* 24 (9) 27-37, and references therein, incorporated by reference herein.

9 Preferred carriers include polylactate, polyglycolic acid, polysaccharides (e.g., alginate
10 or chitosan), and mixtures thereof. Each of these carriers is biodegradable. When used in
11 combination with a naturally occurring mineral microtubule, such biodegradable carriers
12 provide an environmentally friendly delivery system.

13 14 F. Examples

15 Having described the invention, the following examples are given to illustrate specific
16 applications of the invention, including the best mode now known to perform the invention.
17 These specific examples are not intended to limit the scope of the invention described in this
18 application.

Example 1:

Preparation of Environmentally Friendly Microtubules,
and Measurement of Release Rate TherefromPreparation of halloysite microcylinders

The halloysite was obtained as a crude sample of the lump clay deposit and was hydrated in distilled water, containing 5% by weight sodium metaphosphate. The clay was then crudely crushed by hand, using a metal hammer to break up the large lumps, and foreign material and rocks were sorted by hand. The sample was then transferred into a common kitchen blender adding 200 g of the sample to 1 liter of water. The mixture was allowed to agitate at a medium speed for a period of 30 minutes. The material in suspension was removed and fresh water containing 5% by weight Na metaphosphate was added and the process repeated until the clumps would no longer break down. Following this step the suspension was allowed to stand in a 3 L graduate cylinder for 10 minutes, and then the suspended portion of the sample was removed for further processing. The gravity settlement allowed further separation of quartz sand particles from the halloysite. The resultant suspension was spun in an IEC Model C-6000 centrifuge in 1 L bottles and the supernatant removed and replaced with fresh distilled water, and the process was repeated an additional two cycles. The resultant slurry was then filtered through a cloth paint filter cone to remove any remaining large clumps, which were then ground in a mortar and pestle and retreated as before.

1 Once the halloysite sample was found to be substantially free of foreign material, it
2 was spun out of the water suspension and allowed to air dry. This yielded a white cake of
3 halloysite that was then powdered in a mortar and pestle, to yield a friable white powder.

4 Method of entrapment

5 The powder of dry halloysite microcylinders were treated by the following scheme.
6 The active agent which is to be employed by the first method of entrapment should be a
7 solid at or below 40 °C. In this method both the halloysite and the agent are heated to a
8 temperature just above the melting point of the agent. The best method should be a
9 vacuum oven, if possible, under a partial vacuum to aid in removal of retained gasses within
10 the core of the microcylinders.

11 The halloysite was observed to be "wet" with the active agent. Following this step
12 the vacuum was released and the resultant agent/microcylinders complex was suspended in
13 a dispersant that was not a solvent for the agent, and was at the same temperature as the
14 agent/halloysite. With sufficient agitation, the temperature was lowered until the agent
15 became a solid again. The agitation optionally may be stopped at this point and the suspen-
16 sion allowed to settle. The dispersant was removed and the resultant halloysite/agent
17 complex was then suspended in a solvent for the agent. This resulted in the removal of the
18 exogenous agent from the microcylinder.

19 The second method employed utilized a suspension of the halloysite and agent in
20 solution of a suitable biodegradable polymer such as a poly-lactic/polyglycolic acid system,
21 which was diluted in a suitable solvent such as methanol. The resultant suspension was then

1 injected into a fluidized bed to flash off the solvent and yield a halloysite/agent mixture
2 which had an outer coating of an environmentally benign coating of degradable polymer.

3 The third method required the active agent to be miscible with the polylactic/polygly-
4 colic acid mixture, or that the active agent be very small particulates (nanoparticulates).
5 This mixture was then entrapped in the central core of the microcylinders by a method
6 similar to that in the original method, except that the agent was allowed to flash off in the
7 vacuum at ambient temperatures.

8 Assay for Microencapsulation

9 To determine the encapsulation efficiency, the microcylinders were crushed and
10 suspended in a suitable solvent. The suspension was agitated for several hours to ensure full
11 dissolution of the active agent. The determination of concentration of active agents was
12 made either by weight or by suitable chemical analysis.

13 Laboratory Determination of Release Rate

14 The microtubules were added to a conical 50 ml disposable centrifuge, and 50 ml of
15 deionized H₂O was added. Concentration determinations were made based on absorption
16 in a Perkin Elmer UV/Vis series 6000 spectrophotometer. A peristaltic pump was employed
17 to pump the solution through a quartz flow cell where absorption measurements were made
18 each half-hour. When necessary, the deionized H₂O was changed to prevent saturation.
19

20 Additional modification of the release characteristics has been achieved through
21 employment of a further layer of the degradable polymeric material, where the secondary

1 layer was free of any active agent. This provides a barrier coating to protect against short
2 term exposure to the entrapped agent during handling. This coating then degrades in the
3 environment at a rate that is determinable by the degree of cross-linking of the co-polymers
4 or by employment of an additional crosslinking agent. This allows for a delayed release
5 product. By mixing the thickness of the overcoating, the delay has been tailored to initiate
6 release over a considerable time period.

7 For shorter term release profiles (< 300 hr) polysaccharides (including alginate and
8 chitosan) have provided a carrier and a coating that was biodegradable. Due to the open
9 nature of the gel, the release rate has been rather fast, depending on the agent.

10
11 Obviously, many modifications and variations of the present invention are possible
12 in light of the above teachings. It is therefore to be understood that,
13 , the invention may be practiced otherwise than as specifically described.

ABSTRACT OF THE DISCLOSURE

The present invention is a composition for, and a method of, delivering an active agent at a controlled rate. The composition of the invention is a hollow ceramic or inorganic microtubule, where the active agent is contained within the lumen of the microtubules. Typically, the agent is adsorbed onto an inner surface of the microtubule. The method of the invention is disposing this novel composition in a use environment. In a preferred embodiment of the invention, a microtubule is a tubule having an inner diameter of less than $0.2\text{ }\mu\text{m}$, and microtubules are tubules having an average inner diameter less than $0.2\text{ }\mu\text{m}$. In a preferred embodiment, the hollow ceramic or inorganic microtubule is a mineral microtubule, such as halloysite, cylindrite, boulangerite, or imogolite. In a more preferred embodiment of the invention, the mineral microtubule has a biodegradable polymeric carrier disposed in its lumen. In a preferred embodiment of the invention, the inner diameter of the microtubules varies from about $0.20\text{ }\mu\text{m}$ to about $0.35\text{ }\mu\text{m}$, or averages about $0.40\text{ }\mu\text{m}$. In another preferred embodiment, of the invention, the inner diameter of the microtubules varies from about $200\text{ }\text{\AA}$ to about $1000\text{ }\text{\AA}$.