A process for improving the release kinetics of a monolithic active agent delivery device comprising a shaped body of a dispersion of particulate active agent, such as a drug, with a polymer matrix, such as ethylene/vinylacetate copolymer, by substantially reducing the initial burst of active agent from the device when it is placed in its environment of use. The process involves prior to placing the body in its use environment removing, such as by water washing, the particulate drug from the exterior surface of the body to form an agent depleted layer of polymer matrix voided by the removal of the agent, the thickness of the layer being at least 5% of the overall body thickness.

14 Claims, 10 Drawing Figures
FIG. 4

DEVICES OF EXAMPLE 1B

FIG. 5

DEVICES OF EXAMPLE 2A

FIG. 6

DEVICES OF EXAMPLE 2B
PROCESS FOR IMPROVING RELEASE KINETICS OF A MONOLITHIC DRUG DELIVERY DEVICE

BACKGROUND OF THE INVENTION

1. Field of the Invention
This invention relates to a process for improving the active agent release kinetics of a monolithic active agent delivery device.

2. Description of the Prior Art
Monolithic devices for sustainedly releasing drugs or other active agents are well known in the art. One type of monolithic device consists of a shaped body of particulate, usually solid, drug dispersed uniformly in a polymer matrix permeable to the drug by diffusion. The polymer matrix may be substantially imperforate and homogeneous in which case the drug dissolves in and permeates through the polymer material itself. Alternatively, the matrix may be microporous, the pores of which contain a drug-permeable liquid or gel medium, in which case the drug will preferentially dissolve in and permeate through the medium in the pores. It is of course possible to use a polymer matrix which is both microporous and made of a polymer permeable to the drug in which case movement of the drug through the matrix is via a combination of the above described modes.

Another type of monolithic device for use in releasing active agents into aqueous environments, such as drugs into the various cavities of the human body, consists of a shaped body of discrete particulate osmotic solute/active agent depots dispersed in and surrounded by an active agent impermeable but water permeable polymer matrix whose cohesive strength is exceeded by the osmotic pressure generation ability of the individual depots. Such devices release their active agent by an osmotic bursting mechanism in which water is imbibed osmotically into the depots nearest the exterior surfaces of the device, thereby dissolving those depots contents and generating pressure therewithin sufficient to cause the surrounding polymer matrix to rupture thus allowing release of the agent therefrom and access by the environment to the next nearest depots and serially so forth. These monolithic "osmotic bursting" devices are the subject matter of commonly assigned, co-pending application Ser. No. 354,359 filed Apr. 25, 1973 and now abandoned, the disclosure of which is incorporated by reference herein.

These monolithic devices are attractive commercially because they are inexpensive and easily fabricated relative to other devices such as laminated devices or capsule devices. Also, in the case of some drugs, a monolithic device is the only type of device capable of practically and sustainedly releasing the drug at a therapeutically effective rate.

The active agent release kinetics of these monolithic devices exhibit a feature which is often undesirable, namely the release begins at a high rate—called an "initial burst"—which rapidly decreases to a significantly lower rate. The kinetics of monolithic diffusion for a device having a thin rectangular cross sectional shape (i.e., the device is shaped as a flat slab) may be expressed by the equation:

\[ \frac{dM_d}{dt} = A \frac{D C_a}{C_2/2} \]

in which \( M_d \) is the agent released at time \( t \), \( C_a \) is the agent solubility in the polymer matrix, \( C_2 \) is the total concentration of agent in the polymer matrix, \( C_a \) being much greater than \( C_p \), \( D \) is the agent's diffusion coefficient in the polymer matrix and \( A \) is the surface area of the device (both sides). Equations defining the release kinetics of other simple geometries, such as a cylinder and a sphere are also known.

In a plot of the above equation with \( dM_d/dt \) plotted against \( t \), the release rate in the initial stage of release is extremely high and drops off very quickly to a level markedly below the rate in the initial stage. Corresponding plots for monolithic diffusion devices of other simple geometry, such as a rod-like cylinder or sphere, follow the same general release rate pattern as the simple slab described above.

The release kinetics for monolithic osmotic bursting devices have been found empirically to also exhibit an initial burst which decreases rapidly to a significantly lower rate. However the release rate plateaus after the initial decrease in the osmotic bursting devices whereas it continuously decreases in the diffusion devices.

In both types of devices this initial burst of active agent may be undesirable because it results in overdosing, toxicity or side reactions, or may not conform to the optimal dosage regimen for a particular active agent.

The initial high level or "burst" in the release rate of active agent from a monolithic device may be reduced by coating the body with a layer of pure polymer matrix. Such a coated device is taught (the coating is used for a different purpose) in U.S. Pat. No. 3,577,512 issued May 4, 1971 to T. H. Shepherd et al. However this coating procedure has the disadvantage of lowering the entire release rate profile (i.e., the entire \( dM_d/dt \) vs. \( t \) plot) of the device. Such lowering may result in release rates below those required for efficacy. Also, if the device has an irregular shape, it is usually quite difficult to devise a manufacturing procedure to make a continuous, uniform coating on the device in a reproducible manner.

SUMMARY OF THE INVENTION

This invention is a process for improving the release kinetics of the above described monolithic active agent delivery devices by substantially eliminating the initial burst of active agent release without significantly lowering the entire release rate profile of the device. This novel process comprises, prior to placing the device in its intended environment of use, removing the particulate agent from the external surface of the device to form an agent depleted layer of polymer matrix voided by the removal of the particulate agent.

In a preferred embodiment of this process the removal of particulate agent from the surface of the device is done by washing the device in a liquid which does not deleteriously affect the polymer matrix at a temperature which enhances the removal of agent from the matrix.

The devices made by the invention process are placed in fluid containing environments into which the agent is released by diffusion or by osmotic bursting. Depending on the particular active agent involved the environment may be a body cavity, a stream, an aquarium, soil, a chemical reactor or the like. Embodiments intended to release drug within body cavities may be placed within the gastrointestinal tract, mouth, eye,
3,923,939

uterus, vagina and other cavities.

**BRIEF DESCRIPTION OF THE DRAWINGS**

In the drawings:

FIG. 1 is a vertical, sectional view of a disc-shaped monolithic diffusion type drug delivery device made in accordance with the invention process;

FIG. 2 is an enlarged view of a portion of the section of FIG. 1 taken along line 2–2 of FIG. 1;

FIG. 3 is a graphic representation of the release kinetics of a prior art monolithic diffusion drug delivery device;

FIG. 4 is a graphic representation of the improvements in the release kinetics of the device represented in FIG. 3 which may be realized by subjecting that device to the process of this invention;

FIG. 5 is a graphic representation of several prior art devices of the same geometry as the device of FIG. 3 but having different loadings of active agent; and

FIG. 6 is a graphic representation of the improvements in the release kinetics of the devices of FIG. 5 which may be realized by subjecting those devices to the process of this invention;

FIG. 7 is a vertical, sectional view of a disc-shaped monolithic osmotic bursting drug delivery device made by the invention process;

FIG. 8 is an enlarged view of a portion of a section of FIG. 7 taken along line 8–8 of FIG. 7;

FIG. 9 is a graphic representation of the release kinetics of a prior art monolithic osmotic bursting drug delivery device; and

FIG. 10 is a graphic representation of the improvement in the release kinetics of the device of FIG. 9 which may be realized by treating that device in accordance with the process of this invention.

**DETAILED DESCRIPTION OF THE INVENTION**

FIG. 1 depicts a disc-shaped monolithic diffusion type active agent delivery device, generally designated 10, comprising a particulate active agent 11, such as drug, dispersed in a polymer matrix 12. The particles of agent 11 may be liquid, semi-solid or solid but are preferably solid.

"Active agents" as used herein include those compositions of matter which when dispersed in their environment of use produce a predetermined, beneficial and useful result. Such agents include for example pesticides, herbicides, germicides, biocides, algicides, rodenticides, fungicides, insecticides, anti-oxidants, plant growth promoters and inhibitors, preservatives, surfactants, disinfectants, catalysts, fermentation agents, nutrients, drugs, plant minerals, sex steriliants, plant hormones, air purifiers, micro-organism attenuants and the like.

"Drug" as used herein broadly includes physiologically or pharmacologically active substances for producing a localized effect at the administration site or a systemic effect at a site remote from the administration site. Such drugs include inorganic and organic compounds, for example, drugs which act on the central nervous system such as hypnotics and sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants and anti-parkinson agents, antipyretics and anti-inflammatory agents, local anesthetics, anti-spasmodics and antitussive agents, prostataglanoids, anti-microbials, hormonal agents, estrogenic steroid, progestational steroids, such as for contraceptive purposes, sympotmimetic drugs, cardiovascular drugs, diuretics, antiparasitic agents, hypoglycemic drugs and ophthalmic drugs.

In the osmotic bursting devices the active agent must either itself be water soluble to the extent that the osmotic pressure of a saturated solution thereof exceeds the osmotic pressure of the external environment of use or it must be mixed with a compatible osmotically effective solute such as an inorganic or organic salt capable of generating such an osmotic pressure. Such pressure provides the necessary driving force by which the osmotic bursting mechanism is effected. Methods of calculating or measuring osmotic pressure are well known. See for example, S. Glasstone, *Textbook of Physical Chemistry*, MacMillan & Co., London (1960).

As indicated above, in the monolithic diffusion devices the polymer forming the polymer matrix may be substantially imperforate and homogeneous or microporous. Examples of substantially imperforate polymers which may be used are poly(methylmethacrylate), poly(butylmethacrylate), plasticized poly(vinyl chloride), plasticized soft nylon, natural rubber, poly(isoprene), poly(isobutylenes), poly(butadiene), poly(ethylene), poly(vinylidene chloride), cross-linked poly(vinylpyrrolidone), chlorinated poly(ethylene) poly(4,4'-isopropylidene diphenylene carbonate), ethylene-vinylacetate copolymer, plasticized ethylene-vinylacetate copolymer, vinylidene chloride-acrylonitrile copolymer, vinyl chloride-diethyl fumarate copolymer, silicone rubbers, especially the medical grade poly(dimethylsiloxanes), ethylene-propylene rubber, silicone-carbonate copolymers, vinylidene chloride-vinyl chloride copolymer, vinyl chloride-acrylonitrile copolymer and vinylidene chloride-acrylonitrile copolymer.

Microporous materials which may be used in making monolithic devices have pores which range in size from at least about 10A to several hundred microns, but usually not more than about 100 microns. Examples of materials from which microporous structures may be made are regenerated, insoluble, nonreodible cellulose, acetylated cellulose, esterified cellulose, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate diethylamino-acetate, poly(urethanes), poly(carbonates), modified insoluble collagen, cross-linked poly(vinyl alcohol), epoxy resins and poly(olefins) or poly(vinylchlorides). These materials may be made microporous by well known procedures such as coprecipitation or leaching out incorporated salts, soap micelles, starch or like materials. See, for example, J. D. Ferry, *Chemical Reviews*, 18, 373 (1935).

Diffusive media which may be used to fill the pores of the porous materials should be compatible with the environment of use. Also the active agent should leave only limited solubility in the medium (10 ppm to 10,000 ppm on a weight basis) so that the active agent is released by diffusion rather than by simple dissolution.

Representative media are saline, glycerin, ethylene glycol, propylene glycol, water, emulsifying and suspending agents such as methyl cellulose mixed with water, mixtures of propylene glycol monostearate and oils, gum tragacanth, sodium alginate, poly(vinyl pyrrolidone), poly(oxyethylene stearate), fatty acids such as linoleic, and silicone oil. Other representative media are set forth in *Remington's Pharmaceutical Sciences*, pages 246 to 269 and 1338 to 1380, 1970, published by Mack Publishing Co., Easton, Pas.
The polymers used to make the osmotic bursting devices may be defined in terms of their permeabilities to active agent and water and their tensile strength and maximum elongation (which delimit their cohesive and rupture strength). Normally these materials will have water permeabilities of about

\[ \frac{g}{mm^2 \cdot 24 \text{ hr} \cdot 100\% \text{ rel. humidity}} \]

a tensile strength of about 14 to 700 kg/cm² (preferably 35 to 210 kg/cm²), and a maximum elongation of 10% to 2000% (preferably 200% to 1700%). They also should have a high degree of impermeability to the active agent i.e., active agent permeabilities less than 10⁻⁷ cm²/sec.

Typical polymers for forming the osmotic bursting devices include unplasticized cellulose acetate, cellulose nitrate with 11% nitrogen, cellulose diacetate, cellulose triacetate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, cellulose acetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbatome, cellulose acetate phthalate, cellulose acetate methyl carbatome, cellulose acetate succininate, cellulose acetate dimethiminoacetate, cellulose acetate ethyl carbatome, cellulose acetate chloroacetate, cellulose acetate ethyl oxatome, cellulose acetate methyl sulfonate, cellulose acetate butyl sulfonate, cellulose acetate propionate, cellulose acetate butyl sulfonate, cellulose acetate propionate, cellulose acetate p-toluene sulfonate, triacetate of locust gum bean, cellulose acetate with acetylated hydroxy-ethyl cellulose, hydroxylated and unhydroxylated ethylene-vinyl acetate copolymers, highly plasticized polyvinyl chloride, homo- and copolymers of polyvinyl acetate, polymers of acrylic acid and methacrylic acid, polyvinyl alky ethers, polyvinyl fluoride, polycarbonates, polymeric epoxides, copolymers of an alkylene oxide and alkyl glycidyl ether, semi-permeable polyurethanes, semi-permeable polyglycolic or polylactic acid and derivatives thereof and derivatives of polyestrene such as poly(sodium styrenesulfonate) and poly(vinylbenzyltrimethylammonium chloride). Ethylene-vinyl acetate copolymers, either alone or mixed with other materials, are especially useful for forming the osmotic bursting device. Preferred among the ethylene-vinyl acetate copolymers are those having a melt index above about 20 g/min and a vinyl acetate content above about 20%, such as from 20-45%.

In the diffusion devices the concentration of active agent dispersed in the polymer matrix will primarily depend upon the desired dosage level for the device. Normally the concentration of active agent will be in the range of 5 to 70 weight percent based on the polymer matrix. Its particle size will usually be in the range of 0.1 to 100 microns.

In the osmotic bursting devices the active agent depot loading (which depends on the size and number of deposes percent volume) is important. The deposes will usually comprise 5% to 70% by weight of the device. In this range sufficient polymer is present to adequately encapsulate the deposes and maintain the device's integrity after a substantial amount of the agent deposes have been released. The depot size will usually range between 0.1 and 100 microns in diameter.

The shape of the device made from the above described active agent/polymer dispersions will depend on the intended environment of use. In most environments complex shapes will be unnecessary and thus for convenience and economy the device will have a simple shape such as flat disc, a cylindrical rod, or a sphere. For specific embodiments such as an embodiement intended for use in the eye to release an ophthalmic drug therein, the device will usually be in the shape of a flat disc, oval, ellipse or kidney.

The device will be sized according to the environment and desired dosage. Drug delivery devices for implanting in the body will be sized in accordance with the dimensions of the implant size. For instance for ocular inserts for inserting in a cul-de-sac of the eye the device will normally have a length of 4 to 20 mm, a width of 1 to 15 mm and a thickness of 0.1 to 4 mm and will usually contain 1 to 200 mg ophthalmic drug.

The active agent/polymer dispersions may be formed by mixing the two components by conventional techniques. Likewise, the dispersions may be formed into shaped bodies by conventional techniques such as solvent casting, extruding, roll milling, melt pressing, cutting, punching and the like.

After the dispersion is formed into the desired shape (this may be its final form for introducing into the use environment or some intermediate form such as a large sheet or roll) but before it is placed in the environment of use, the particles of active agent are removed from the exterior surface layer of the body in accordance with the process of this invention. This may be done by washing the body with a liquid which is inert relative to the polymer matrix (in other words the liquid should not deleteriously affect the polymer matrix either physically or chemically such as by dissolving, disintegrating, or chemically reacting with the matrix). For convenience and economy the wash liquid will usually be aqueous, with water being preferred.

In a diffusion device the washing of the device causes active agent which is dissolved in the polymer matrix at the surface to diffuse into the wash liquid which in turn causes agent particles located at or near the surface to dissolve into the polymer and be diffused therefrom. In the case of the osmotic bursting devices the washing causes any agent at the surface to be dissolved and water to be imbibed by the encapsulated agent deposes causing them to burst and release their contents. In both types of devices this washing ultimately results in the active agent being depleted from a surface layer of desired thickness. In the device shown in FIGS. 1 and 2 the drug has been depleted from a layer, designated A, at the exterior surface of the device leaving voids 14. The number and size of the voids in the matrix will depend on the concentration and particle size of the dispersed active agent. In this regard it has been observed that the voids tend to irreversibly shrink, i.e., the porosity of the layer decreases, if the device is permitted to dry after the washing. This phenomenon is believed to make the layer of a dried device act more like a coating of pure matrix in that it may be less permeable to the agent than the remainder of the matrix. In any event voids 14 affect the release kinetics of device 10 because they form preferred pathways (indicated by small arrows) for the active agent to diffuse along.

FIGS. 7 and 8 illustrate a monolithic osmotic bursting active agent delivery device, generally designated 15, which has been prewashed in accordance with the invention process. Device 15 comprises discrete active agent/osmotic solute deposes 16 encapsulated within a polymer matrix 17. As shown in FIG. 8 the prewashing
has depleted the active agent deposits from a layer, designated B, at the surface of the device leaving voids 18. Voids 18 are similar to voids 14 of device 10 except that voids 18 are substantially interconnected due to the bursting mechanism by which the active agent was released. The process conditions of the wash, e.g., time and temperature, will be selected to provide an agent depleted layer of predetermined thickness. Given a desired layer thickness the wash temperature and time will depend on the particular polymer and active agent involved. In a diffusion device wash times may be shortened by employing temperatures at which diffusion is enhanced. In an osmotic bursting device wash times may be shortened by using temperatures at which water inhibition by the deposits is enhanced. In almost all instances this means that elevated temperatures (above ambient temperature) below the matrix melt temperature and below that which might adversely affect the agent in any manner will shorten the wash time. For most polymers and agent wash temperatures in the range of about 50°C to about 60°C may be used advantageously. For both types of devices it is desirable to carry out the wash with agitation to ensure good clearance of the released agent from the exterior of the device. Although any degree of prewashing will improve the release kinetics of the device, it is desirable to remove active agent from a layer which represents at least about 5% of the total thickness or diameter of the device. Usually the thickness of the layer will comprise about 5% to about 25% of the overall thickness or diameter. It should be understood that in most devices the layer appears at both sides or both edges of the device and that the above percentages relate to only a single appearance of the layer. In other words in a spherical device the layer would appear at both ends of a diameter and thus the total diametrical drug depleted portion of the device would represent at least about 10% of the entire diameter.

EXAMPLES

The invention process and the improvement in release kinetics realized by using it are further illustrated by the following examples.

Example 1

A. A monolithic diffusion device such as might be used to dispense a drug intrauterinely is made by mixing 20 parts progesterone (5–10 micron particle size) into a methylene chloride solution of 80 parts ethylene-vinyl acetate copolymer (the drug loading is approxi- mately 20% by volume). This mixture is cast into a 0.2 cm thick sheet from which a rectangular body having a total surface area of 1 cm² is cut. This rectangular body is placed in a simulated uterine environment where it releases progesterone by diffusion. This release is monitored, the plot of which is shown in FIG. 3. As seen in FIG. 3 the initial release of progesterone is in the neighborhood of 150 μg/day and drops off rapidly during the first 100 days to about 40 μg/day after which the release curve slowly and continuously declines until the solid progesterone is exhausted.

B. Three rectangular bodies of a progesterone/ethylene-vinyl acetate copolymer dispersion are prepared as in A. Each is washed in water at 50°C; the first until a drug free surface layer 0.020 cm thick is formed; the second until a drug free layer 0.033 cm thick is formed; and the third until a drug free layer 0.047 cm thick is formed. Each device is then placed in the simulated uterine environment as described in A and the progesterone release therefrom is monitored and plotted, the plots of which are shown in FIG. 4. As shown by these plots the initial release rate relative to the unwashed device is decreased respectively by about 30%, 60% and 70% in the washed devices. Also the release rate during the major portion of the device’s lifetime (e.g., 100 days to 500 days) is not significantly decreased by the washing.

Example 2

A. A device identical with that of Example 1A and two other devices identical to the same except in drug loading (one contained half the amount of progesterone and the other contained double the amount of progesterone) are prepared and tested as in Example 1A. Their release plots are illustrated in FIG. 5.

B. Three devices identical to those of A are prepared and prewashed in water at 50°C until a 0.047 cm thick drug-free layer is formed in each. These washed devices are then tested as in Example 1A. Their release plots are shown in FIG. 6.

As is readily seen by comparing FIGS. 5 and 6 the washing eliminated the initial burst in the progesterone release while not significantly affecting the release rate over the bulk of each device’s lifetime.

Example 3

A. An osmotic bursting device such as might be used to dispense drug to the eye is made by mixing 30 parts pilocarpine nitrate with 70 parts of ethylene/vinyl acetate copolymer on a laboratory rubber mill. The well dispersed mixture which contains pilocarpine nitrate particles with an average diameter of between 1 and 10 microns is then pressed into a flat film 500 microns thick from which an ellipse shaped body 13.5 mm by 6.5 mm is cut. This body is placed in simulated lacrymal fluid at 37°C where it releases pilocarpine nitrate by an osmotic bursting mechanism. This release is monitored, the plot of which is shown in FIG. 9. As seen in FIG. 9 the initial pilocarpine nitrate release rate is about 175μg/hour and drops off rapidly during the first 25 hours to about 25 μg/hour.

B. Five devices identical to those of A are prepared and soaked in water at 37°C for 15, 30, 60 and 120 minutes and 24 hours respectively. Each device is then tested as in A. Their pilocarpine nitrate release plots are shown in FIG. 10. As shown by these plots the washing decreases the initial release rate by about 20%, 40%, 50%, and 90% respectively. Also, there is little variation in release rate between the unwashed and washed devices after 25 hours.

Example 4

Osmotic bursting ocular inserts are made by dispersing 30 parts tetracycline hydrochloride in 70 parts ethylene/vinyl acetate copolymer (Elvax 220) on a rubber mill, melting pressing the dispersion into a flat film 500 microns thick and cutting 13.5 mm × 5.8 mm ellipses therefrom. Individual ellipses are washed, 0, 15, 30, 60 and 120 minutes respectively, in water at 50°C, dried and then placed in simulated lacrymal fluid. The average tetracycline hydrochloride release over the first 7 hours of release is respectively 26, 18, 17, 12 and 9 μg/hour.
Example 5

Inserts were made and tested as in Example 4 except that a different ethylene/vinyl acetate copolymer (Elvax 40) was used. The average tetracycline hydrochloride release over the first 7 hours is, respectively, 25, 15, 12, 9 and 6 μg/hour.

Various modifications of the invention process will be obvious to those of ordinary skill in the active agent formulations art. Such modifications are intended to be within the scope and spirit of the following claims.

We claim:

1. Method for substantially reducing the initial burst of active agent release from a monolithic active agent delivery device when said device is placed in its environment of use, said device comprising a shaped body of a dispersion of particulate active agent within a polymer matrix comprising prior to placing said shaped body in said environment, removing the particulate agent from the exterior surface of said body to form an agent depleted layer of polymer matrix voided by such removal of particulate active agent, the thickness of said layer being at least about 5% of the overall thickness of the body.

2. The method of claim 1 wherein said removing is done by washing the body in a liquid which is inert relative to said polymer matrix.

3. The method of claim 2 wherein said liquid is water.

4. The method of claim 2 wherein said device is a diffusion type device and said washing is carried out at an elevated temperature at which diffusion of the agent from the matrix is enhanced.

5. The method of claim 2 wherein the polymer matrix is an ethylene/vinyl acetate copolymer and the washing is carried out at about 50°C to about 60°C.

6. The method of claim 2 wherein the device is an osmotic bursting type device and the washing is carried out at an elevated temperature at which imbition of said liquid by the active agent is enhanced.

7. The method of claim 1 wherein the thickness of the layer is about 5% to 25% of the overall thickness of the body.

8. In a process for making a monolithic drug delivery device comprising a dispersion of solid particulate drug in a polymer matrix comprising the steps of forming a dispersion of the solid particulate drug within said matrix and forming the dispersion into a shaped body adapted for placement in the environment of use of the device, the improvement comprising the additional step of removing the solid particulate drug from the surface of said body to form a drug depleted layer of polymer matrix voided by the removal of the particulate solid drug therefrom, the thickness of said layer being at least about 5% of the overall thickness of said body.

9. The improvement of claim 8 in which the thickness of said layer is about 5% to about 25% of the overall thickness of the body.

10. The improvement of claim 8 wherein said removing is done by washing the body in a liquid which is inert relative to the polymer matrix.

11. The improvement of claim 10 wherein the liquid is water.

12. The improvement of claim 10 wherein the device is a diffusion type device and said washing is carried out at an elevated temperature at which diffusion of the drug from the matrix is enhanced.

13. The improvement of claim 12 wherein the polymer matrix is made of an ethylene/vinyl acetate copolymer and the elevated temperature is from about 50°C to about 60°C.

14. The improvement of claim 10 wherein the device is an osmotic bursting type device and the washing is carried out at an elevated temperature at which the imbition of liquid by the active agent is enhanced.