ABSTRACT

A bandage for use in the continuous administration of drugs to the skin or mucosa, comprising a backing member defining one exterior surface, a surface of pressure-sensitive adhesive defining a second exterior surface, and disposed therebetween a reservoir containing drug formulation confined therein. The reservoir can comprise a distinct layer of the bandage or a plurality of microcapsules distributed throughout the adhesive surface, and in either case the drug can be confined within an interior chamber of the reservoir or distributed throughout a reservoir matrix. The drug passes through drug release rate controlling microporous material which continuously meters the flow of drug by viscous or diffusive transfer to the skin or mucosa at a controlled and predetermined rate over a period of time.

7 Claims, 5 Drawing Figures
BANDAGE FOR THE ADMINISTRATION OF DRUG BY CONTROLLED METERING THROUGH MICROPOROUS MATERIALS

RELATED APPLICATIONS


BACKGROUND OF THE INVENTION

This invention relates to a device for the administration of drug and, more particularly, to a medical bandage for the controlled continuous metering of flow of systemically or topically active drug to the skin or mucosa over a period of time.

"Topically active" drugs, as that term is used in this specification and the appended claims, are agents which, when applied to the skin or mucosa, primarily cause a pharmacological or physiological response at or near the site of their application. "Systemically active" drugs, as that term is used in this specification and the appended claims, are agents which, when applied to the skin or mucosa, are absorbed through the body surface to which applied and are transported from their site of application by the recipient's circulatory system or lymphatic system, to cause a pharmacologic or physiologic response at a remote site in the body.

Systemically active drugs are conventionally administered either orally or by injection, with the primary objective of the mode being to achieve a given desired blood level of drug in circulation over a period of time. However, these prior art methods possess certain shortcomings resulting in the failure to obtain these goals. For example, the oral route is inadequate for several reasons even though the drug is administered at periodic intervals according to a well defined schedule. The rate of absorption of drug through the gastrointestinal tract is affected by both the contents of the tract and the time of passage of drug through the small intestine. Therefore, such variables as whether the drug is administered before or after eating and the type and quantity of food eaten (for example, high or low fat content), or whether administered before or after a bowel movement, affect the rate of absorption of the drug which takes place in the small intestine. Additionally, the time of passage of drug through the small intestine is affected by the rate of peristaltic contracting, adding further uncertainty. Also important is the rate of circulation of blood to the small intestine and the fact that many drugs administered by this route are rendered inactive by gastric acid and digestive enzymes of the gastrointestinal tract or liver where the drug can be metabolized to an inactive product by that organ. These factors make it difficult to achieve a desired time course of concentration of the drug in the blood. The almost inevitable result of oral administration of drugs through the gastrointestinal tract is that the level of drug in circulation surges to a peak level at the time the drug is administered, followed by a decline in concentration in the blood and body compartments. Thus, a plot of drug in circulation after administration of several tablets a day has the appearance of a series of peaks which may surpass the toxic threshold of the drug, and valleys which fall below the critical point needed to achieve the desired therapeutic effect.

The administration of drugs by injection can entail certain disadvantages. For example, very strict asepsis must be maintained to avoid infection of the blood, the vascular system or heart. Drug administration by poor intravenous injection technique may result in perivascular injection when it is not intended; and the typical result of injection into the blood is a sudden rise in the blood concentration followed by an uncontrolled decline. Additionally, administration of drugs by injection is inconvenient and painful. Other dosage forms for systemic administration of drug, such as rectal suppositories and sublingual lozenges, also produce non-uniform levels of the therapeutic agent in circulation. These dosage forms require great patient cooperation, have low patient acceptability, and are sparingly used throughout most of the world.

A large number of locally acting drugs are available to treat skin disorders or other conditions which manifest themselves in a manner such that they are susceptible to treatment via the skin. These drugs are conventionally topically administered to the skin with the active agent carried in the form of ointments, creams, salves, liniments, powders, dressings, and the like. The popularity of these types of formulations resides in the fact that it is quite easy to topically apply the agent to the skin in this manner. In most cases, however, it is not possible to determine how much of the preparation has been taken up or effectively administered to the skin since only non-uniform levels of the agent are available, nor is there any assurance that sufficient medication will be available for the duration of periods that it is required. A further undesirable feature is the unsightliness of these formulations which often discourages patients from using them during their waking hours of the day when they are most likely to be seen by others. Further, the preparations are subject to rub off onto clothing, thus causing much inconvenience and annoyance to the user.

SUMMARY OF THE INVENTION

Accordingly, an object of this invention is to provide a bandage for the improved continuous administration of a predetermined controlled quantity of topically or systemically active drug to or through the skin or body mucosa over a period of time, which overcomes the disadvantages inherent in the aforesaid prior art modes of administration.

Another object of this invention is to provide a bandage which can be adapted to deliver controlled quantities of drug having a wide variety of chemical and physical properties and over a wide range of drug delivery rates.

In accomplishing these objectives, one feature of the invention resides in a bandage for the continuous administration of controlled quantities of drug to the skin or mucosa, comprised of a laminate of: (1) a backing member; bearing (2) a discrete middle reservoir layer containing a drug confined within a body, the body being formed from drug release rate controlling microporous material permeable to the passage of the drug, to continuously meter the flow of a therapeutically ef-
ective amount of the drug to the skin or mucosa from
the reservoir at a controlled and predetermined rate
over a period of time; and (3) a pressure-sensitive adhe-
sive surface adapted for contact with the skin or mu-
cosa and positioned on one surface of the reservoir re-
more from the backing member.

Another aspect of this invention resides in a bandage
comprised of a laminate of: (1) a backing member;
bearing (2) a discrete middle reservoir containing a
drug confined therein, the reservoir being formed of
material permeable to passage of the drug; and (3) a
pressure-sensitive adhesive surface adapted for contact
with the skin or mucosa and positioned on one surface
of the reservoir remote from the backing member and
wherein one or more drug release rate controlling mi-
croporous membranes are interposed between the sur-
face of the reservoir and pressure-sensitive adhesive so
as to continuously meter the flow of a therapeutically
effective amount of the drug from the reservoir at a
controlled and predetermined rate over a period of
time. The reservoir can be a container having the agent
confined therein or a solid or microporous matrix hav-
ing agent dispersed therein.

Still another embodiment of this invention resides in
an adhesive bandage comprising a laminate of: (1) a
backing member, bearing (2) a pressure-sensitive adhe-
sive on one surface thereof adapted for contact with
the skin or mucosa, said pressure-sensitive adhesive
having distributed therethrough, (3) a plurality of dis-
crete microcapsules, each of which microcapsules
comprises a drug confined within a body of drug re-
lease rate controlling porous material to continuously
meter the flow of a therapeutically effective amount
of the drug to the skin or mucosa of the patient from
the microcapsules at a controlled and predetermined rate
over a period of time.

Other objects, features and advantages of the inven-
tion will become more apparent from the following de-
scription when taken in conjunction with the accompa-
nying drawings.

The term "reservoir", as used herein to define the
drug containing portion of the subject bandage, is in-
tended to connote a broad class of structures capable
of fulfilling the intended function, and includes both
discrete porous microcapsules, as well as distinct reser-
voir compartments or layers. Likewise, as will be here-
inafter more completely developed, the foregoing term
encompasses containers having one or more interior
drug containing chambers, as well as solid matrices and
microporous matrices having a systemically or topically
active drug distributed therethrough.

The term "drug or agent", when not further quali-
fied, includes both topically active and systemically ac-
tive drugs, as hereinbefore defined.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings:

FIG. 1 is a cross-sectional view of an embodiment of
the medical bandage of the invention, wherein the drug
is uniformly distributed throughout a matrix of micro-
porous material permeable to the passage of the drug
by flow through the pores of the material and the mate-
rial is laminated to a backing member. The matrix ma-
terial which acts as a reservoir for the drug bears a
coating of the pressure-sensitive adhesive thereon;

FIG. 2 is a cross-sectional view of still another em-
bodyment of the invention, wherein the adhesive ban-
dage of the invention is comprised of a backing mem-
ber having a reservoir on one surface thereof of drug
uniformly distributed throughout a matrix material per-
meable to passage of the drug, and on the surface of the
reservoir remote from the backing member bearing a
pressure-sensitive adhesive coating. A microporous
membrane is interposed between the reservoir layer
and the pressure-sensitive adhesive coating;

FIG. 3 is a cross-sectional view of another embodi-
ment of the bandage of the invention, wherein the res-
ervoir laminated to the backing member is a hollow
container permeable to passage of drug by flow
through the pores of one surface thereof, and having
the drug confined within the interior chamber thereof.
The reservoir bears a coating of pressure-sensitive ad-
hesive thereon;

FIG. 4 is a perspective view of the medical adhesive
bandage of the invention, wherein the drug is microen-
capsulated with a porous material permeable to the
passage of the drug, and the microcapsules are uni-
formly distributed throughout the pressure-sensitive
coating;

FIG. 5 is a cross-sectional view of the bandage of the
invention shown in FIG. 4.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with this invention there is provided a
bandage suitable, by virtue of the microporous materi-
als employed therein, for the predetermined controlled
administration of drug to the skin or mucosa of the
body over a period of time. To use the bandage of the
invention it is applied to the patient's skin or mucosa
and should be in firm contact therewith so as to form
a tight seal. Flow of drug from the reservoir is metered
through the pores of the rate release controlling mate-
rial in accordance with the laws of hydrodynamics or
diffusion, as hereinafter discussed, at a predetermined
rate. In operation, drug molecules are continuously re-
moved from the reservoir and migrate to the skin or
mucosa of the patient. In the case of systemic drugs,
the drugs are absorbed by the skin or mucosa and enter
circulation through the capillary network.

The reservoir containing the drug is formed of mate-
rial permeable to the drug to permit passage of the
drug. Depending upon the particular embodiment as
described above, the drug reservoir can be of micropor-
ous material or otherwise. However, as is apparent in
the latter case, the drug must first pass through a micro-
porous membrane material prior to reaching the skin or
mucosa. It is therefore critical to the practice of this in-
vention for all embodiments that, at some point after or
concurrent with the release of drug from the reservoir
and prior to reaching the skin or mucosa, the drug pass
through the drug release rate controlling microporous
membrane or matrix material to meter the flow thereof.
The rate of passage or permeation of drug through the
microporous material is determined by the transfer
mechanism which can be either by:

1. diffusive flux of drug molecules as is the case, as
hereinafter described, where the micropores of the
rate controlling microporous membrane or matrix
material are impregnated with a diffusive medium
for the drug in which the drug molecules can di-
solve in and flow through to a direction of lower
chemical potential; or
2. pressure induced viscous type flow of drug molecules through the pores in the microporous membrane or matrix rate controlling material. Thus, the microporous material has a structure that enables the drug to pass through the pre-existing pores or capillaries, either by diffusive permeability or microporous hydrodynamic flow, depending upon the mode of use as described hereinafter. Since the microporous rate controlling material is preferably selected so that the drug is substantially insoluble therein, as hereinafter described, flow of drug through the structure of the material can be neglected.

For drug transfer mechanism (1) set forth above, i.e., wherein the drug diffuses through a diffusive medium for the drug, the release rate can be controlled in accordance with Fick's First Law, depending on the particular design by selection of dependent variables such as the diffusivity and solubility of the drug in the diffusive medium and the thickness and porosity of the material properly modified by a tortuosity factor. For drug transfer mechanism (2), i.e., flow of drug through the pores of the microporous rate controlling material, the pressure differential, the thickness of the membrane, the viscosity of the permeant drug, the size of the permeant molecule relative to the pore size, the absolute value of the pore size, and the number of pores or percent voids in the material are the controlling factors governing permeability. For the simplest type of flow mechanism of this type, e.g., viscous flow, the amount of drug passing through the porous structure is given by Poiseuille's equation for viscous flow.

Therefore, the selection of appropriate materials for fabricating the microporous rate controlling membrane or matrix material will be dependent on the particular drug to be used in the bandage. Both organic and inorganic polymeric materials can be shaped into a wide variety of forms with tailored morphology and a wide range of chemical and physical properties to advantageously control release of a wide variety of drugs, including those with large molecular structures such as insulin, and over a large drug dosage range by appropriate pore size selection. Additionally, by impregnating the interconnected pores of the microporous structure with a diffusive medium for the drug to be administered, a given microporous membrane or matrix material can be adapted to control the release of drugs having a wide range of chemical properties by diffusive permeability. Thus, by varying the composition, pore size, and effective thickness of the microporous rate controlling material, the viscosity of the drug to be administered by appropriate formulation or by impregnating the material with suitable solvent, the dosage rate per area of bandage can be controlled since the material functions to meter the flow of drug from the device. Therefore, bandages of the same surface area can provide different dosages of a drug by varying the above discussed parameters.

The microporous rate controlling materials of this invention are known in the art and can be visualized as a plurality of sponge-like fused polymer particles which provide a supporting structure having therethrough a dispersion of microscopic sized interconnecting voids or pores. The rate controlling structures formed from the materials can be isotropic, wherein the structure is homogeneous throughout the cross-section of the matrix or membrane material, or anisotropic wherein the structure is non-homogenous. These rate controlling structures are commercially available and can be made by a multitude of different methods, e.g., etched nuclear track, and materials employed, e.g., polyelectrolyte, ion exchange polymers, as described in R. E. Kesting, Synthetic Polymer Membranes, McGraw Hill, Chapters 4 and 5, 1971; J. D. Ferry, Ultrafiltration Membranes, Chemical Review, Vol. 18, Page 373, 1934. Materials possessing from 5 percent to 95 percent voids and having an effective pore size of from about 10 angstroms to about 100 microns can be suitably employed in the practice of this invention. Materials with pore sizes significantly below 50 angstroms can be considered to be molecular diffusion type membranes and matrices. In order to obtain the most advantageous results, the materials should be formed into structures with the desired morphology in accordance with methods known to those skilled in the art to achieve the desired release rate of drug. Additionally, the material must have the appropriate chemical resistance to the drug used and be non-toxic when used as an element of the bandage of the invention.

Materials useful in forming the microporous rate controlling materials used in this invention include, but are not limited to the following.

Polycarbonates, i.e., linear polymers of carbonic acids in which carbonate groups recur in the polymer chain, by phosgenation of a dihydroxy aromatic such as bisphenol A. Such materials are sold under the trade designation Lexan by the General Electric Company.

Polyvinylchlorides; one such material is sold under the trade designation Geon 121 by B. G. Goodrich Chemical Company.

Polyamides such as polyhexamethylene adipamide and other such polyamides popularly known as "nylon". One particularly advantageous material is that sold under the trade name "NOMEX" by E. I. DuPont de Nemours & Co.

Modacrylic copolymers, such as that sold under the trade designation DYNEL and formed of polyvinylchloride (60 percent) and acrylonitrile (40 percent), styrene-acrylic acid copolymers, and the like.

Polysulfones such as those of the type characterized by diphenylene sulfone groups in the linear chain thereof are useful. Such materials are available from Union Carbide Corporation under the trade designation P-1700.

Halogenated polymers such as polychloroethylene fluoride sold under the trade designation Kynar by Pennsalt Chemical Corporation, polyvinylfluoride sold under the trade name Tedlar by E. I. DuPont de Nemours & Co., and the polyfluorohalocarbon sold under the trade name Aclar by Allied Chemical Corporation.

Polychloroethers such as that sold under the trade name Penton by Hercules Incorporated, and other such thermoplastic polyethers.

Acetal polymers such as the polyformaldehyde sold under the trade name Delrin by E. I. DuPont de Nemours & Co., and the like.

Acrylic resins such as polyacrylonitrile polymethyl methacrylate, poly n-butyl methacrylate and the like.

Other polymers such as polyurethanes, polyimides, polybenzimidazoles, polyvinyl acetate, aromatic and aliphatic, polyethers, cellulose esters, e.g., cellulose triacetate; cellulose; colloidion (cellulose nitrate with 11% nitrogen); epoxy resins; olefins, e.g., polyethylene polypropylene; porous rubber; cross-linked poly (ethylene oxide); cross-linked polyvinylpyrrolidone; cross-linked
poly (vinyl alcohol); polyelectrolyte structures formed of two ionically associated polymers of the type as set forth in U.S. Pat. Nos. 3,549,016 and 3,546,142; derivates of polystyrene such as poly (sodium styrenesulfonate) and polyvinylbenzyltrimethylammonium chloride); poly(hydroxyethyl methacrylate); poly(isobutyl vinyl ether), and the like, may also be utilized. A large number of copolymers which can be formed by reacting various proportions of monomers from the aforesaid list of polymers are also useful for preparing rate controlling structures useful in the invention.

As illustrated in FIG. 1, the bandage 20 of the invention is comprised of drug 24 uniformly distributed in the interstices of the microporous matrix material forming reservoir 22. The matrix material is laminated to backing member 21 and bears a pressure-sensitive adhesive coating 23 thereon. The microporous matrix material 22 functions to control the release rate of the drug impregnated therein. The reservoir can be prepared by employing any of the known impregnating techniques. Thus, the drug can be added to the rate controlling material in liquid form and uniformly distributed therethrough by mixing, and subsequently converted to a microporous structure by the various methods known to the art. One such method calls for dissolving a natural or synthetic polymer in a suitable solvent in which it has sufficient solubility to permit the preparation of a solution that is sufficiently viscous for conventional film casting. The preferred method is to cast a film of a polymer solution having the drug therein, and, shortly after casting, to immerse it in a non-solvent or "diluent," a medium which is compatible with the solvent, but not a solvent for the polymer. The original solution then forms two phases, one polymer-rich and one polymer-poor. Under the proper conditions, both of these phases are physically continuous, so that the resulting polymer membrane is mechanically reasonably strong, but it is completely interlaced with continuous pores. The size and uniformity of the pores depend on the conditions of preparation. Alternatively, preformed microporous materials can be impregnated with drug by immersion in a bath of the drug to diffuse the drug into the material. While the matrix material can be of any convenient thickness, typically a thickness of from 20 to 200 microns is employed.

FIG. 2 illustrates a further modified form of the invention wherein the adhesive bandage 30 of the invention is comprised of a backing member 21 having a reservoir 32 on one surface thereof. A microporous rate controlling membrane 35 is interposed between the reservoir 32 and a pressure-sensitive adhesive coating 23. Drug 24 is impregnated in polypropylene matrix material 32 which acts as the reservoir for the drug. Matrix material 32 can be solid material as illustrated, or microporous as illustrated for reservoir 22 in FIG. 1. If desired, additional membranes can be juxtaposed next to membrane 35 in order to achieve optimum rate release properties. The matrix material 32 when solid or microporous should have a release rate to drug which is higher than that of the rate controlling microporous membrane 35, such that passage through the latter is the rate controlling step. Materials used to form the matrix reservoir 32 of FIG. 2, when solid, can be those heretofore exemplified for preparing the microporous rate controlling material and, in addition, include hydrophobic polymers such as plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized soft nylon, plasticized polyethylene terephthalate, natural rubber, C9-C14 olefins, e.g., polyethylene, polysisoprene, polysobutylene, polybutadiene; silicone rubbers, especially the medical grade polydimethylsiloxanes, as described in U.S. Pat. No. 3,279,996, hydrophilic polymers such as the hydrophilic hydrogels of esters of acrylic and methacrylic acid (as described in U.S. Pat. Nos. 2,967,576 and 3,220,960, and Belgian Patent No. 701,813), modified collagen, cross-linked polyvinylalcohol, and cross-linked partially hydrolyzed polyvinylacetate. Of course, these materials used to form the matrix must be permeable to passage of the drug, as by diffusion. Accordingly, selection of appropriate materials will, in each instance, be dependent on the particular drug to be administered.

FIG. 3 illustrates a further form of the invention wherein bandage 40 includes a backing member 21 and a reservoir 42 in the form of a hollow container having an interior chamber 43 containing drug 34. Wall or surface 45 of reservoir 42, remote from backing member 21, is of a microporous membrane structure permeable to passage of drug 34, to meter the flow of drug to pressure-sensitive adhesive layer 23 on the outer surface thereof. The sides of the reservoir 42, other than rate controlling microporous membrane 45, preferably are impermeable to passage of the drug, and can be made of the same materials used to make the backing member as hereinafter described. As discussed, one face of the drug reservoir bears a backing member 21. The purpose of the backing is to prevent passage of the drug through the surface of the reservoir distant from the adhesive layer. An ancillary purpose of the backing is to provide support for the bandage where needed. When the outer surface of the reservoir 33 is impermeable to the drug and strong enough, the backing becomes unnecessary. The other surface of the reservoir bears a coating of a pressure-sensitive adhesive.

If desired, additional microporous rate controlling membranes can be juxtaposed on top of membrane 45 to further tailor the rate of flow of drug. Of course, in each instance, the membrane will have different characteristics than the reservoir membrane 45 of the particular device. This use of a pair of multiplicity of membranes, that is, the reservoir wall and the further membrane, allows for precise metering of drug out of the reservoir; for the thickness, porosity and composition of both membranes can be varied to provide for wide range of dosage levels for a given area of bandage. It will be appreciated that this type of membrane can be used with either the matrix (FIGS. 1 or 2) or container type (FIG. 3) of reservoir. To provide additional mechanical strength, if necessary, the rate controlling microporous membrane 45 can be supported by an appropriate mesh or screen having a greater release rate to drug than does membrane 45.

The reservoir of the embodiment in FIG. 3 can be formed by molding into the form of a hollow container with the drug trapped therein. While the non-rate controlling walls of the reservoir can be of any convenient thickness, usually they have a thickness of from 0.01 to 7 millimeters. The rate controlling membranes 35 and 45, in FIGS. 2 and 3, respectively, can have varying thickness depending upon the nature of the membrane, its porosity and the number of membranes used in com-
combination. Typically, a thickness of from 20 to 200 microns is employed.

It will, of course, be appreciated that the pressure-sensitive adhesive surface need not form a continuous layer on the subject bandage. Particularly in the case of a bandage having a distinct reservoir layer, equally advantageous results are obtained by providing an annular surface of adhesive around the periphery of the bandage face. In this manner a liquid tight adhesive seal between the bandage and the patient's skin or mucosa is maintained, and at the same time, drug may be directly absorbed by the skin from the exposed surface of the drug reservoir layer without first migrating through an adhesive layer. As a further alternative, in the embodiment of the invention employing a distinct reservoir layer, to prevent passage of the drug into the adhesive layer prior to use, the adhesive can be supplied separately from the reservoir and backing, with the device assembled at the point of use. For example, the adhesive in sheet form can have both surfaces protected with a release film and the wall of the reservoir can be similarly protected. At the point of use, the release films can be removed from the reservoir and one surface of the adhesive, the adhesive sheet applied to the reservoir wall to complete assembly of the bandage, the remaining release film then removed from the adhesive, and the bandage then applied to the patient.

As previously discussed, one type of drug transfer mechanism is that of flow through the pores or pinholes in microporous rate controlling material. A driving force, i.e., a pressure differential across the microporous material, is necessary to cause the flow of drug by this mode. The bandage of the type illustrated in FIG. 3, wherein the reservoir is a hollow container, can be conveniently adapted to meter the flow of drug by a microporous hydrodynamic mechanism by pressurizing the container. This can suitably be accomplished by admixing with the drug a solid particulate material which liberates gas on contact with the drug formulation. For example, in the case wherein the formulation is of an aqueous nature, a conventional effervescent powder such as sodium bicarbonate or citric acid can be inserted immediately prior to use through an opening in the reservoir wall so provide for this purpose. After insertion of the effervescent material, the opening is sealed, for example, by means of an adhesive tape. The pressure can be controlled by adjusting the particle size of the effervescent powder composition and the quantity thereof. Pressure in an amount of from 1 mm to 50 mm of mercury can be satisfactorily employed, with the actual amount depending upon the desired release rate and the other parameters previously discussed regarding viscous flow.

FIGS. 4 and 5 illustrate an adhesive bandage of the invention including a backing member bearing a pressure-sensitive coating 12 on one surface thereof. Adhesive coating 12 has unevenly distributed therethrough microcapsules 13 comprising drug encapsulated with a microporous rate controlling material permeable to passage of the drug. Thus, in the embodiment illustrated herein, porous microcapsules 13 constitute the drug reservoir.

To provide the microcapsules, the encapsulating material can be uniformly impregnated with the drug to form microcapsules which are a porous matrix having the drug distributed therethrough. Alternatively, particles of drug can be encapsulated with a thin microporous coating of the encapsulating material to form microcapsules having an interior chamber containing the drug. If desired, particles of a matrix, such as starch, gum acacia, gum tragacanth, and polyvinylchloride, can be impregnated with the drug and encapsulated with other materials such as the microporous rate controlling materials previously described, which function to meter the flow of drug to the adhesive; use of a microporous matrix and a different rate controlling membrane coating to slows the passage of the drug from the microcapsules, which is desirable with drugs that are released too rapidly from available encapsulating materials, is therefore also contemplated herein.

Any of the encapsulation or impregnation techniques known in the art can be used to prepare the microcapsules to be incorporated into the pressure-sensitive adhesive in accord with the embodiment of FIGS. 4 and 5. The porous microcapsules can be made by techniques as set forth in U.S. Ser. No. 751,251, corresponding to German Patent No. 1,939,066, entitled "Microcapsules with Anisotropic Microporous Liquid Permeable Polymeric Outer Skin and Internal Microporous Support Partitions or Structure," Bixler, Michaels, and Sternberg, or by standard coacervation methods. The coacervation method of fabrication, as conventionally employed, consists essentially of the formation of three immiscible phases, a liquid manufacturing phase, a core material phase and a coating phase with deposition of the liquid polymer coating on the core material and rigidizing the coating, usually by thermal, cross-linking or desolvation techniques to form microcapsules. Usually, the microcapsules made by the above techniques have an average particle size of from several tenths of a micron to 5,000 microns, although this feature is not critical to the practice of the invention. Techniques for preparing microcapsules, such as the classic Bungenberg de Jong and Kass method are reported in Biochem. Z, Vol. 232, Pg. 338 to 345, 1931, Colloid Science, Vol. 11, "Reversible System", edited by H. R. Kruyt, 1949, Elsevier Publishing Company, Inc., New York; J. Pharm. Sci., Vol. 59, No. 10, Pg 1367 to 1376, 1970, and Remington's Pharmaceutical Science, Vol. 16, Pg. 970, 1970, Mack Publishing Company, Easton, Pennsylvania. Thus, the drug can be added to the encapsulating material in liquid form and uniformly distributed there-through by mixing and then forming the microcapsules by any of the above set forth methods. Alternatively, the porous microparticles can be made by the above techniques and impregnated with drug. Still another method is to impregnate a porous solid encapsulating material with a drug by immersion in a bath of the drug to diffuse the drug into the material, and subsequently the solid material can be reduced to fine microcapsules by grinding, each of the microcapsules comprising drug coated with and distributed throughout the encapsulating material. Further, the microcapsules can be encapsulated with a microporous coating by suspending dry particles of the drug in an air stream and contacting that stream with a stream containing the encapsulating material to coat the drug particles. Usually, the micro-capsules have an average particle size of form 1 to 1000 microns, although this is not critical to the invention. The microcapsules, however made, are then mixed by conventional methods, e.g., stirring, ballmilling, and the like, with a pressure-sensitive adhesive. The mixture of microcapsules and pressure-sensitive adhesive is then
coated onto a backing member, usually to provide an adhesive layer 0.01 to 7 millimeters thick, although these limits can be exceeded if more or less drug is required. The purpose of the backing is to provide support for the bandage and to prevent passage of the drug through the adhesive surface away from the body surface to which the bandage is applied.

As above discussed, the microporous rate controlling materials can be adapted to control the release of drug by diffusive permeation wherein the micropores are impregnated or otherwise filled with a diffusive medium for the drug to be administered. The material can be impregnated with the diffusive medium by methods well known to the art, e.g., as by immersion in a bath of the material to permit the diffusive medium material to fully saturate the micropores. The impregnation technique can be employed with any of the embodiments represented herein. In embodiments illustrated in FIGS. 1, 4 and 5 the micropores can be concurrently impregnated with both drug and diffusive medium material.

In cases where the pressure-sensitive adhesive and microporous rate controlling material employed are water permeable, body fluids will self-migrate into the microporous material after the bandage has been in contact with the skin for a suitable period of time to provide the diffusive medium, as hereinafter described, without the necessity of carrying out a separate impregnation step. Additionally, the pores can be self-filled by migration of the diffusive medium by contact with the composition employed to prepare the drug formulation, as later described.

The diffusive medium is one which enables the drug to dissolve therein and flow by diffusion at the desired rate. It can be either of a liquid or solid nature and be a poor or good solvent for the drug. A medium with poor solvent properties for the drug is desired when the required release rate is low and of course the converse is true when the desired release rate is high.

The art provides many useful approaches to enable selection of particular solvent-drug systems. Specific attention is called to Remington’s Pharmaceutical Sciences, Chapters 19 and 71. The solvent selected must be non-toxic and one in which the rate controlling microporous material has the required solubility. The materials which are useful for impregnating the micropores can be polar, semi-polar or non-polar. Exemplary are any of the pharmaceutically acceptable solvents such as water, alcohols containing 2 to 10 carbon atoms, such as hexanol, cyclohexanol, benzylalcohol, 1,2-butanediol, glycerol, and amyl alcohol; hydrocarbons having 5 to 12 carbon atoms such as n-hexane, cyclohexane, and ethyl benzene; aldehydes and ketones having 4 to 10 carbon atoms such as heptyl aldehyde, cyclohexanone, and benzaldehyde; esters having 4 to 10 carbon atoms such as amyl acetate and benzyl propionate; etheral oils such as oil of eucalyptus, oil of rue, cumin oil, limonene, thymol, and 1-pinene; halogenated hydrocarbons having 2 to 8 carbon atoms such as n-hexyl chloride, n-hexyl bromide, and cyclohexyl chloride; or mixtures of any of the foregoing materials. Also suitable are many of the conventional non-toxic plasticizers used in the fabrication of microporous rate controlling material, e.g., octyl diphenyl phosphate. When these plasticizers are used in the diffusive material, flow of the drug used, advantageously, the necessity for filling the pores by a separate step is thus obviated. Other plasticizers known to the art can be employed, such as long-chain fatty amides, higher alcohols, and high boiling esters such as di(isocty) sebacate or di(2-ethyl hexyl) phthalate.

It is preferred that the diffusive medium also be incorporated in the reservoir in combination with the drug in the form of a pharmaceutically acceptable carrier as hereinafter described.

In practicing this invention one can employ any systemic active drug which will be absorbed by the body surface to which the bandage is applied, consistent with their known dosages and uses. Of course, the amount of drug necessary to obtain the desired therapeutic effect will vary depending on the particular drug used. Suitable systemic drugs include, without limitation, Anti-microbial Agents such as penicillin, tetracycline, oxytetracycline, chloramphenicol, chlorpheniramine, and sulfonamides; Sedatives and Hypnotics such as pentobarbital sodium, phenobarbital, secobarbital sodium, codeine, (α-bromoisovaleryl) urea, carbamol, and sodium pheno-barbital; Psychic Energizers such as 3-(2-aminopropyl) indole acetate and 3-(2aminobuty) indole acetate; Tranquilizers such as serpine, chlorpromazine hydrochloride, and thiopropazate hydrochloride; Hormones such as adrenocorticosteroids, for example, 6α-methylprednisolone; androgens, steroids, for example, methyltestosterone, and fluoxymesterone; estrogenic steroids, for example, estrone, 17β-estradiol and ethinyl estradiol; prostaglandin steroidal, for example, 17α-hydroxyprogesterone acetate, medroxyprogesterone acetate, 19-norprogesterrone, and norethandrone; and thyroxine; Antipyritics such as aspirin, salicylamide, and sodium salicylate; morphine and other narcotic analgesics; Anti-diabetics, e.g., insulin; Cardiovascular Agents, e.g., nitroglycerin, and cardiac glycosides such as digitoxin, digoxin, ouabain; Anti-spasmodics such as atropine, methscopolamine bromide, methscopolamine bromide with phenobarbital; Anti-malarials such as the 4-aquoquinolines, 9-aminoquinolines, and pyrimethamine; and Nutritional Agents such as vitamins, essential amino acids, and essential fats.

Additionally, in practicing this invention one can employ a wide variety of topically active drugs consistent with their known dosages and uses. Suitable drugs include, without limitation: Anti-spiants, e.g., aluminim chloride; Deodorants, e.g., hexachlorphene, methylbenzethonium chloride; Astringents, e.g., tannic acid; Irritants, e.g., methyl salicylate, camphor, cantharidin; Keratolytics, e.g., benzoyc acid, salicycic acid, resorcinol, iodochlorhydroxyquin; Antifungal Agents, such as toluate, griseofulvin, nystatin and amphotericin; Anti-inflammatory Agents, such as corticosteroids, e.g., hydrocortisone, hydrocortisone acetate, prednisonone, methylprednisolone, triamcinolone acetonide, fludrocortisone, flurandrenolone, flumethasone, dexamethasone sodium phosphate, bethamethasone valerate, fluorocinolone acetonide; fluorometholone; and pramoxine HCl; Ant-inflammatory Agents, e.g., methyltestate; and Antibacterial Agents, such as bacitracin, neomycin, erythromycin, tetracycline HCl, chlorotetracycline HCl, chloramphenicol, oxytetracycline, polymyxin B, nitrofurazone, mafenide (α-amino-p-toluene sulfonamide), hexachlorphene, benzalkonium chloride, cetalkonium chloride, methylbenzethonium chloride, and neomycin sulfate.
It will be appreciated, with regard to the aforesaid list of drugs, that characterization of the drug as either "systemically or topically" active is done for purposes of convenience only. Further, a given drug can be both systemically and topically active depending upon its manner of use.

In addition to the aforementioned drugs, simple pharmacologically acceptable derivatives of the drugs, such as ethers, esters, amides, acetals, salts, etc., or formulations of these drugs, having the desired polymeric permeability or transport properties can be prepared and used in practicing the invention. Drugs mentioned above can be used alone or in combination with others and each other. Of course, the derivatives should be such as to convert to the active drugs within the body through the action of body enzyme assisted transformations, pH, etc.

The above drugs and other drugs can be present in the reservoir alone or in combination form with pharmaceutical carriers. The pharmaceutical carriers acceptable for the purpose of this invention are the art known carriers that do not adversely affect the drug, the host, or the material comprising the drug delivery device. Suitable pharmaceutical carriers include sterile water; saline, dextrose; dextrose in water or saline; condensation products of castor oil and ethylene oxide combining about 30 to about 35 moles of ethylene oxide per mole of castor oil; liquid glyceryl triester of a lower molecular weight fatty acid; lower alkanols; oils such as corn oil; peanut oil, sesame oil and the like, with emulsifiers such as mono-or di-glyceride of a fatty acid, or a phosphatide, e.g., lecithin, and the like; glycols; polyalkylene glycols; aqueous media in the presence of a suspending agent, for example, sodium carboxymethylcellulose; sodium alginate; poly(vinylpyrrolidone); and the like, alone, or with suitable dispensing agents such as lecithin; polyoxyethylenes stearate; and the like. The carrier may also contain adjuvants such as preserving, stabilizing, wetting, emulsifying agents, and the like.

The drug can also be mixed in the reservoir with a transporting agent, that is, a material that aids or assists the drug delivery device to achieve the administration of a drug to a drug receptor, for example, by enhancing penetration through the skin. The transporting aids suitable for the purpose of the invention are the therapeutically acceptable transporting aids that do not adversely affect the host, the drug, or alter or adversely affect the materials forming the drug delivery device. The transporting aids can be used alone or they can be admixed with acceptable carriers and the like. Examples of transporting aids include monovalent, saturated and unsaturated aliphatic cycloaliphatic and aromatic alcohols having 4 to 12 carbon atoms, such as hexanol, cyclohexane and the like; aliphatic cycloaliphatic and aromatic hydrocarbons having from 5 to 12 carbon atoms such as hexane, cyclohexane, isopropylbenzene and the like; cycloaliphatic and aromatic aldehydes and ketones having from 4 to 10 carbon atoms such as cyclohexanone; acetamide, N,N-di(lower alkyl) acetamides such as N,N-diethyle acetamide, N,N-dimethyl acetamide, N-(2-hydroxyethyl) acetamide, and the like; and other transporting agents such as aliphatic, cycloaliphatic and aromatic esters; N,N-di(lower alkyl) sulfoxides; essential oils; halogenated or nitrated aliphatic, cycloaliphatic and aromatic hydrocarbons; salicylates; polyalkylene glycol silicates; mixtures thereof; and the like.

The amount of active agent to be incorporated in the bandage to obtain the desired therapeutic effect will vary depending upon the desired dosage, the permeability of the rate controlling materials of the bandage which are employed to the particular agent to be used, and the length of time the bandage is to remain on the skin or body mucosa. Since the bandage of this invention is designed to control drug administration for an extended period of time, such as 1 day or more, there is no critical upper limit on the amount of agent incorporated into the bandage. The lower limit is determined by the fact that sufficient amounts of the agent must remain in the bandage to maintain the desired dosage. In order to achieve a therapeutic effect in a human adult, the daily release dosage of atropine should be in the range of between 200 and 600 micrograms per day. Thus, for example, using atropine and with a bandage intended to remain in place for 1 week, and with a release rate of 500 micrograms of atropine per day, at least 3.5 mg of atropine would be incorporated in the bandage. Generally, the drug delivery bandages made according to the invention can release at a controlled rate about 25 nanograms to about 1 gram of drug or larger amounts per day. Of course, other devices for use for different time periods such as week or month are also readily made by the invention.

The effective rate of release of the active agent to the skin or mucosa can be in the range of from 0.5 to 1000 micrograms per square centimeter of bandage per day. The exact amount will depend on the desired dosage as well as the condition to be treated. The desired effective rate of release of active agent can be obtained by altering the earlier discussed parameters affecting the release rate controlling barrier. In the case of the micro-encapsulated active agent, the release rate can also be controlled by varying the number of microcapsules present in a given volume of the matrix of the device. This is a particularly desirable feature of this aspect of the invention. Additionally, the duration of action of the device can be altered by controlling the amount of active agent initially incorporated consistent with the release rate. Further, the release rate of drug, as well as the duration of release of the drug from the device, can be predetermined to be in consonance with the optimum therapeutic values. Once this dosage level in micrograms per square centimeter of bandage has been determined, the total amount of drug to be incorporated in the bandage can be established by obtaining the release rate of the agent in the particular material or materials which are to be used. Those skilled in the art can readily determine the rate of permeation of agent through the porous rate controlling material or selected combinations of rate controlling materials. Standard techniques are described in many references cited.

Any of the well-known dermatologically acceptable pressure-sensitive adhesives can be used in practicing this invention. Exemplary adhesives include acrylic or methacrylic resins such as polymers of esters of acrylic or methacrylic acid with alcohols such as n-butanol, n-pentanol, isopentanol, 2-methyl butanol, 1-methyl butanol, 1-methyl pentanol, 2-methyl pentanol, 3-methyl pentanol, 2-ethyl butanol, isoctanol, n-decanol, or n-dodecanol, alone or copolymerized with ethylenically
unsaturated monomers such as acrylic acid, methacrylic acid, acrylamide, methacrylamide, N-alkoxymethyl acrylamides, N-alkoxymethyl methacrylamides, N-tert. butylacrylamide, itaconic acid, vinylacetate, N-branchened alkyl maleic acids wherein the alkyl group has 10 to 24 carbon atoms, glycol diacrylates, or mixtures of these; natural or synthetic rubbers such as silicone rubber, styrenebutadiene, butyl ether, neoprene, polyisobutylene, polybutadiene, and polyisoprene; polyurethane elastomers; vinyl polymers, such as polyvinylalcohol, polypivin ethers, polyvinyl pyrrolidone, and polyvinylacetate; ureaformaldehyde resins; phenolformaldehyde resins; resorcinol formaldehyde resins, cellulose derivatives such as ethyl cellulose, methyl cellulose, nitrocellulose, cellulose acetate butyrate, and carboxymethyl cellulose; and natural gums such as guar, acacia, pectins, starch, dextrin, albumin, gelatin, casein, etc. The adhesives may be compounded with tackifiers and stabilizers as is well known in the art.

When the adhesive layer covers one face surface of the bandage or when the reservoir is in the form of the microcapsules distributed throughout the adhesive, the adhesive must be permeable to passage of the drug to allow the drug released from the reservoir to reach the outer surface of the bandage in contact with the patient. In such cases, the rate of release of drug from the adhesive should exceed the rate of release of drug from the reservoir so that release from the reservoir by passage through the drug release controlling microporous material is the rate limiting step for drug administration by the device of the invention. Of course, when the adhesive is disposed only about the periphery of the bandage face, the adhesive need not be permeable to passage of the drug.

Various occlusive and non-occlusive, flexible or nonflexible backing members can be used in the adhesive bandage of the invention. Suitable backings include cellulose acetate, ethyl cellulose, vinyl acetate-vinyl chloride copolymers, polyethylene terephthalate, nylon, polyethylene, polypropylene, polyvinylidene chloride, paper, cloth, and aluminum foil. Preferably, a flexible occlusive backing is employed to conform to the shape of the body member to which the adhesive tape is applied and to enhance administration of the agent to the skin.

To prevent passage of the drug away from the exposed surface of the pressure-sensitive adhesive prior to use, the adhesive surface of the tape generally is coated with a protective release film or foil such as waxed paper. Alternatively, the exposed rear surface of the backing member can be coated with a low-adhesion backsize and the bandage rolled about itself. To enhance stability of the active compounds, the therapeutic bandage usually is packaged between hermetically sealed polyethylene terephthalate films under an inert atmosphere, such as gaseous nitrogen.

To use the adhesive bandage of the invention, wherein the drug is topical, it is applied directly to the area of skin to be treated, to release a therapeutically effective amount of the agent to the affected area. For administration of systemic drugs the bandage can be applied to any area of the patient's skin, with the lower back and buttocks being the areas of choice. In like manner, the bandage can be applied to the mucosa of the mouth, for example, by application to the palate or the buccal mucosa, to obtain absorption of the drug by the oral mucosa. Although obtaining a liquid tight adhesive seal between the skin and bandage is important, it becomes critical in the mouth. Without such a seal, irrigation of the oral mucosa by saliva will transfer the drug to the gastrointestinal tract, rather than to circulation through the oral mucosa. In addition, the bandage of the invention can be used to administer drugs to other mucosa of the body, for example, it can be applied to the vaginal mucosa, rectal mucosa, etc. By use of this invention, one ensures that an accurately measured quantity of the active drug is available to the site of application.

The following examples are merely illustrative to the present invention and should not be construed as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in light of the present disclosure, drawings and accompanying claims.

**EXAMPLE 1**

Porous, discrete particles of polymerized poly(vinyl chloride) of about 100 microns in diameter are prepared by mixing 100 grams of suspension grade poly(vinyl chloride) resin with 50 grams of octyl diphenyl phosphate and 10 grams of nitroglycerin. These ingredients are mixed at room temperature into a sticky, wet mass. Next, the solvent is allowed to escape to form dry, free flowing, discrete micro-capsules. 10 grams of the resulting microcapsules of polyvinylchloride/nitroglycerin are mixed with 100 grams of a 22 percent solution in hexane: isopropyl-acetate (70:30) of a viscoelastic copolymer of isooctyl acrylate and acrylic acid (94:6) adhesive to uniformly distribute the microcapsules throughout the adhesive solution. The resulting slurry is coated onto a cellophane sheet 10 centimeters in width by 100 centimeters in length and the solvent removed from the coated film.

When a 5 centimeter by 5 centimeter section is cut from the above sheet and applied to the skin of a human adult, the resulting bandage is effective to control the continuous administration of a daily therapeutically effective dosage of nitroglycerin for the prophylactic treatment of angina pectoris.

**EXAMPLE 2**

Dry crystalline powdered megestrol acetate (0.3 gram) in 10 ml. ethanol is mixed with 25 parts by weight of polydimethyloxy siloxane, 15 parts by weight of silicone oil and 0.25 parts by weight of stannous octoate catalyst. The ingredients are mixed until a homogeneous mixture is produced. The mixture is then cast into a mold and allowed to cure to prepare a matrix having a surface area of 10 square centimeters and 9 mls thick. One face surface of the matrix is bonded to a sheet of cellophane. On the other face surface is placed an ethanol impregnated microporous membrane of the same external surface area as the matrix. The membrane is sold by Millipore Corporation and designated to the trade as HA, and is characterized by a porosity of 60 percent, a pore size of 0.45 microns, and a thickness of 4 mls. Dimethyl silicone rubber adhesive is coated to a thickness of 2 mls on the membrane. The adhesive face surface of the completed bandage has an area of 10 square centimeters. The bandage is effective to slowly release megesterol acetate, and when applied to the female skin, is useful for fertility control.
EXAMPLE 3

10 milligrams of betamethasone in 10 ml of propylene glycol is placed on a sheet of dimethyl silicone rubber having a thickness of 10 mils. The sheet is folded to provide a surface area of 10 square centimeters on each face and the flaps sealed with silicone adhesive to provide a thin envelope containing the drug. The top face of the envelope is removed and replaced with a propylene glycol impregnated microporous membrane sold by Amicon Corporation under the designation of PM 30. The membrane is secured to the envelope by means of adhesive to form a tight seal therewith. The membrane is characterized by having an anisotropic structure, with a minimum pore size of 70 angstrom units, an overall porosity of 70 percent, and a thickness of 4 units.

Pressure-sensitive adhesive is prepared by mixing together 90 grams of polycrylate solution (ethylacetate: hexane/5:1) containing 25 percent non-volatile matter (obtained by the catalytic polymerization of isomyracleate and acrylic acid in the ratio of 95:5 in ethylacetate and then diluting with hexane), 5 grams polyvinyllylether (reduced viscosity= 0.3 ± 0.1), 1 gram castor oil (USP) and 4 grams polyethylene glycol 400.

One face surface of the envelope is bonded to a sheet of cellophane while the external membrane surface is coated with adhesive prepared above to a thickness of 2 millimeters. The adhesive face surface of the bandage has an area of 100 square centimeters. The bandage is effective to release a therapeutically effective daily dosage of the drug when applied to the skin for control of psoriasis.

EXAMPLE 4

3 grams of a polycrylonitrile fiber sold under the trade designation Orion by E. I. DuPont de Nemours & Co. was dissolved in 30 grams of an aqueous solution comprising 70 percent by weight of zinc chloride. After the solution was cooled to about 25°C, 0.250 grams of DIGOXIN was added to the solution. Thereupon, the solution was added drop-wise through a No. 21 hypodermic needle into an acetone bath whereupon particles were formed. After being stirred for about thirty minutes in the acetone, the particles were removed and placed in a water bath for four hours at room temperature to leach our residual acetone and salt.

20 grams of polyvinyllylether (reduced viscosity= 5.0 ± 0.5)
4 grams of polyvinyllylether (reduced viscosity= 0.3 ± 0.1)
4 grams of glycerol ester of hydrogenated rosin and
2 grams polyethylene glycol 400

The resulting DIGOXIN capsules are mixed with pressure-sensitive adhesive prepared above to uniformly distribute the microcapsules throughout the adhesive. Immediately thereafter, the adhesive mixture is coated onto one surface of a 1000 square centimeter Mylar sheet. A 5 centimeter by 5 centimeter area of the resulting bandage can be used for control of cardiac disorders.

Thus, this invention provides an easy to use device for administering systemically active drugs through the skin or oral mucosa and other body mucosa. Uncertainties of administration through the gastrointestinal tract are avoided and a controlled constant level of drug in circulation can be obtained. Treatment is begun by applying the bandage to the skin or mucosa and terminated by removing it therefrom. The bandage can contain and administer the complete dosage requirements for a particular time period, for example, 24 hours. Intervention by the patient is required only to apply and remove the bandage, so that uncertainties through patient error are eliminated.

Moreover, this invention provides a reliable and easy to use device for administering topically active drugs directly to the affected areas of skin or mucosa. Uncertainties resulting from topical application of these agents, from creams and solutions, are not encountered; and a predetermined amount of the drug is applied in a controlled manner.

Although the product of this invention has been referred to as an adhesive bandage, those skilled in the art will appreciate that the term "adhesive bandage" as used herein includes any product having a backing member and a pressure-sensitive adhesive face surface. Such products can be provided in various sizes and configurations, including tapes, bandages, sheets, plasters, and the like.

What is claimed is:

1. A medical bandage for the continuous administration of controlled quantities of drug to the skin or mucosa, comprised of a laminate of: (1) a backing member; bearing (2) a discrete middle reservoir layer containing a drug confined within a body, the body being comprised of drug release rate controlling microporous material permeable to the passage of drug, to continuously meter the flow of a therapeutically effective amount of the drug to the skin or mucosa from the reservoir at a controlled and predetermined rate over a period of time; and (3) a pressure-sensitive adhesive surface adapted for contact with the skin or mucosa and positioned on one surface of the reservoir remote from the backing member.

2. The bandage as defined by claim 1 wherein the pores of the microporous rate controlling material are filled with a medium to permit controlled diffusion of the drug from the reservoir.

3. A medical bandage for the continuous administration of controlled quantities of drug to the skin or mucosa, comprised of a laminate of: (1) a backing member; bearing (2) a discrete middle reservoir layer containing a drug confined within a body, the body being comprised of drug release rate controlling microporous material permeable to the passage of drug, to continuously meter the flow of a therapeutically effective amount of the drug to the skin or mucosa from the reservoir at a controlled and predetermined rate over a period of time; and (3) a pressure-sensitive adhesive surface adapted for contact with the skin or mucosa and positioned on one surface of the reservoir remote from the backing member and wherein one or more drug release rate controlling microporous membranes are interposed between the surface of the reservoir and pressure-sensitive adhesive so as to continuously meter the flow of a therapeutically effective amount of the drug from the reservoir at a controlled and predetermined rate over a period of time.

4. The bandage as defined by claim 3 wherein the reservoir is a container having the drug confined therein.

5. The bandage as defined by claim 4 wherein the reservoir is pressurized to permit controlled microporous flow of the drug from the reservoir.

6. The bandage as defined by claim 3 wherein the reservoir is a solid or microporous matrix having the drug dispersed therein.

7. The bandage as defined by claim 3 wherein the pores of the microporous rate controlling material are filled with a medium to permit controlled diffusion of the drug from the reservoir.