United States Patent

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[54] **BANDAGE FOR ADMINISTERING DRUGS**
13 Claims, 2 Drawing Figs.

[52] **U.S. Cl.** **128/268,** 424/20, 424/28
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[50] **Field of Search** ..... 128/155-—156, 268, 296; 424/19—20, 28

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ABSTRACT: Bandage for use in the continuous administration of drugs by absorption comprising a backing member bearing a pressure-sensitive adhesive layer on one surface thereof. Distributed throughout the pressure-sensitive adhesive are microcapsules comprised of a systemically active drug encapsulated with a material permeable to passage of the drug. The drug is in a form acceptable for absorption through the skin or the mucosa of the mouth.

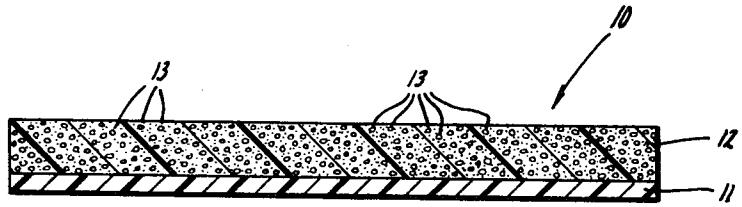


Fig. 1

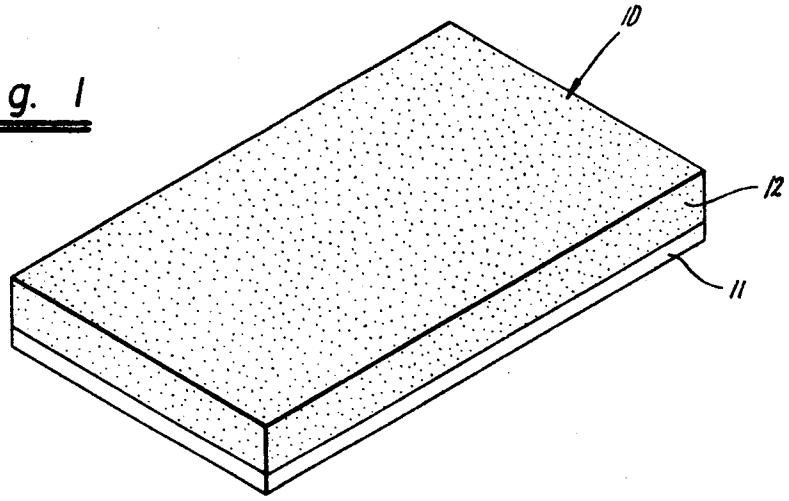
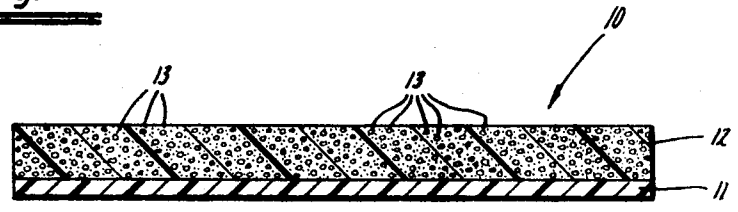


Fig. 2



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BANDAGE FOR ADMINISTERING DRUGS

BACKGROUND OF THE INVENTION

This invention relates to a bandage for use in the continuous administration of systemically active drugs.

One primary objective of drug therapy is to achieve a particular (uniform, variable, or modulated) blood level of drug in circulation for a period of time (hours, days, months). Many drugs, such as the steroidal hormones, are absorbed in a relatively short period of time, and are not long acting due to rapid metabolism and excretion following administration. To obtain the desired therapeutic effect, it is necessary in most cases to establish a dosage regime of multiple unit doses over a 24 hour period. Most drugs are administered orally or by injection and neither of these modes of administration achieves the desired blood level of drug in circulation in the typical case.

With oral administration of drugs, it is difficult if not impossible to achieve a constant blood level of drug in circulation. This is true even though the drug is administered at periodic intervals according to a well-defined schedule. One reason for this is that the rate of absorption of drugs through the gastrointestinal tract is affected by the contents of the tract. 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 administered before or after a bowel movement, can control the rate of absorption of the drug in the gastrointestinal tract. As most of the absorption of drugs takes place in the small intestine, the time of passage through the small intestine is another governing factor. This in turn is affected by the rate of peristaltic contracting, adding further uncertainty. Also important is the rate of circulation of blood to the small intestine.

The almost inevitable result of oral administration of drugs through the gastrointestinal tract is that the level of drug in circulation surges to a high each time the drug is administered, followed by a decline in concentration in the blood and body compartments. Thus, a plot of drug in circulation following a dosage schedule of several tablets a day has the appearance of a series of peaks, which may surpass the toxic threshold, and valleys. Each time the blood level decreases below a critical point needed to achieve the desired therapeutic effect that effect will no longer be obtained. Worse still, with antimicrobial drugs, the disease-producing micro-organisms rapidly multiply when the concentration of drug in circulation descends below a critical point. It is likely that the drug-resistant mutant strains which are becoming increasingly prevalent and represent one of the major problems in the therapeutics of infectious diseases are formed precisely at such times.

One approach to this problem has been the advent of the so-called sustained release or time-capsule in oral dosage form. While many of these perform satisfactorily in vitro and in animal or clinical studies under controlled conditions of nutrition and activity, there is little or no evidence that these dosage forms are effective for achieving a continuous and predictable level of drug in circulation over a prolonged period of time under the normal conditions encountered by the outpatient.

Many effective therapeutic agents are destroyed by microbial flora of G.I. secretions or are poorly absorbed in the gastrointestinal tract.

Administration of drugs by injection is inconvenient, painful, and the risk of local tissue reaction and of infection is serious. Moreover, the typical result of administration by injection is a surge in blood level concentration of the drug immediately after injection, followed by a decline and another surge in concentration upon subsequent injections.

Other dosage forms such as rectal suppositories and sublingual lozenges also produce nonuniform 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.

Dosage forms described above all bring about a pulse entry of drug, that is, a concentrated dose of drug is brought into contact with an organ of entry at a particular time unit. Undoubtedly, this creates drug concentrations beyond the capacity of the active centers to accept (that is, the saturation point is exceeded by many orders of magnitude) and, also, until dilution in body fluids takes place, may exceed the capacity of metabolic and excretory mechanisms. The result is that a toxic level of drug is allowed to build, for a period of time, with detrimental effects for particular tissues or organs. To obtain persistence of effect, the usual industrial approach is to make the initial dose high or to modify the drug structure to obtain a longer metabolic half-life of the drug in circulation long. Raising the initial dosage only worsens the problem. Many derivatives with long half-lives have a lower therapeutic index (ratio between the median toxic dose and the median effective dose) than that of the parent compounds; and therefore these approaches are not the answer to the problem.

To avoid the problems discussed above, it has been suggested that systemically active drugs can be administered through the skin. Percutaneous administration can have the advantage of permitting continuous administration of drug to circulation over a prolonged period of time to obtain a uniform delivery rate and blood level of drug. Commencement and termination of drug therapy are initiated by the application and removal of the dosing device from the skin. Uncertainties of administration through the gastrointestinal tract and the inconvenience of administration by injection are eliminated. Since a high concentration of drug never enters the body, problems of pulse entry are overcome and metabolic half-life is not a factor of controlling importance.

Despite these advantages of administering systemically active drugs through the skin, prior devices designed for this purpose were either impractical or inoperative and did not provide continuous administration and delivery rate. This form of administration has not been accepted by the medical profession and the only prior art manner of obtaining continuous delivery rate remains the continuous intravenous drip.

SUMMARY OF THE INVENTION

Accordingly, an object of this invention is to provide a device for the administration of systemically active drugs which overcomes the aforesaid disadvantages inherent in prior art modes of administration.

Another object of this invention is to provide a reliable and easily applied device for continuously administering controlled quantities of systemically active drugs through the skin.

Still another object of this invention is to provide a device for administering systemically active drugs through the oral mucosa.

A further object of this invention is to provide a complete dosage regime for a particular time period, the use of which requires patient intervention only for initiation and termination.

In accomplishing these objects, one feature of this invention resides in a bandage for use in the continuous administration of systemically active drugs by absorption. The bandage is comprised of a backing member bearing a pressure-sensitive adhesive layer on one surface thereof. The pressure-sensitive adhesive has distributed therethrough microcapsules acting as an external drug reservoir and comprising a systemically active drug encapsulated with a material permeable to passage of the drug. The drug is in a form suitable for absorption through the skin or oral mucosa.

Other objects, features, and advantages of the invention will be apparent to those skilled in the art from the detailed description of the invention which follows, and from the drawings.

BRIEF DESCRIPTION OF DRAWINGS

In the drawings:

FIG. 1 is a perspective view of the bandage of the invention and

FIG. 2 is a cross-sectional view of the bandage of the invention.

As illustrated in FIGS. 1 and 2, the bandage 10 of this invention is comprised of a backing member 11 bearing a pressure-sensitive adhesive layer 12 on one surface thereof. Adhesive layer 12 has microcapsules 13 of a systemically active drug encapsulated with a material permeable to passage of the drug uniformly distributed therethrough.

DETAILED DESCRIPTION OF THE INVENTION

To use the bandage 10 of the invention, it is applied to the patient's skin. Adhesive layer 12 should be in firm contact with the skin, forming a tight seal therewith. Drug within microcapsules 13, whether in solid form or solution, migrates through the walls of the microcapsules, acting as a solubility membrane, and into adhesive layer 12, as by diffusion. Ordinarily, one would expect the drug migration to cease when sufficient drug has reached the outer surface of microcapsules 13 to create an equilibrium or when adhesive layer 12 has become saturated with the drug. However, when adhesive layer 12 is in contact with the patient's skin, drug molecules which are continuously removed from the outer surface of microcapsules 13 migrate through the adhesive to the outer surface of the adhesive layer and are absorbed by the skin. Absorbed drug molecules pass through the skin and enter circulation through the capillary network. While the bandage may be applied to any area of the patient's skin, the lower back and buttocks are 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 liquidtight 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.

Those skilled in the art will appreciate that the bandage of this invention significantly differs from prior art wound dressings or bandages containing antiseptics or topically active drugs. The bandage of this invention contains an encapsulated systemically active drug and is applied to unbroken skin, to introduce the drug to circulation in the bloodstream and produce a pharmacologic response at a site remote from the point of application of the bandage. Thus, the bandage functions as an external drug reservoir and provides a complete dosage regime for a particular time period.

In practicing this invention, one can employ any systemically active drug which will be absorbed by the body surface to which the bandage is applied. The term "systemically active drug" is used herein in its broadest sense as indicating a substance or composition which will give a pharmacologic response at a site remote from the point of application of the bandage. Of course, the amount of drug necessary to obtain the desired therapeutic effect will vary depending on the particular drug used. Suitable drugs include, without limitation, antimicrobial agents such as penicillin, tetracycline, oxytetracycline, chlortetracycline, chloramphenicol, and sulfonamides; sedatives and hypnotics such as pentabarbital sodium, phenobarbital, secobarbital sodium, codeine, (α-bromoisovaleryl) urea, carbromal, and sodium phenobarbital; psychic energizers such as 3-(2-aminopropyl) indole acetate and 3-)2-aminobutyl) indole acetate; tranquilizers such as reserpine, chlorpromazine hydrochloride, and thiopropazate hydrochloride; hormones such as adrenocorticosteroids, for example, 6α-methylprednisolone, cortisone, cortisol, and triamcinolone; androgenic steroids, for example, methyltestosterone, and fluoxymesterone; estrogenic steroids, for example, estrone, 17β-estrodiol and ethinyl estradiol; progrestational steroids, for example, 17α-hydronyprogesterone acetate, medroxyprogesterone acetate, 19-norprogesterone, and norethindrone; and thyroxine; antipyretics such as aspirin, salicylamide, and sodium salicylate; antispasmodics such as atropine, methscopolamine bromide, methscopolamine bromide with phenobarbital; antimalarials such as the 4-aminoquinolines, 8-aminoguinolines, and pyrimethamine; and nutritional agents such as vitamins, essential amino acids, and essential fats.

Drugs which alone do not pass through the skin or oral mucosa can be dissolved in an absorbable, pharmacologically acceptable solvent to achieve passage through the external body layer. Suitable solvents include 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; ethereal oils such as oil of eucalyptus, oil of rue, cumin oil, limonene, thymol, and 1-pinene; halogenated hydrocarbons having two to eight carbon atoms such as n-hyxyl chloride, n-hyxyl bromide, and cyclohexyl chlorides; or mixtures of any of the foregoing solvents. Also, with drugs which do not pass through the skin or oral mucosa, simple pharmacologically acceptable derivatives of the drugs, such as ethers, esters, amides, acetals, etc. having the desired absorption property can be prepared and used in practicing the invention. 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.

Materials used to encapsulate the drug or drug solution and form the microcapsules to be distributed throughout the adhesive must be permeable to the drug to permit passage of the drug, as by diffusion, through the walls of the microcapsules at a relatively low rate. Normally, the rate of passage of the drug through the walls of the microcapsules is dependent on the solubility of the drug or drug solution therein, as well as on the microcapsule wall thickness. This means that selection of appropriate encapsulating materials will be dependent on the particular drug used in the bandage. By varying the encapsulating material and the wall thickness, the dosage rate per area of bandage can be controlled.

One presently preferred class of encapsulating materials are the organopolysiloxane rubbers, commonly known as silicone rubbers. Suitable silicone rubbers are the conventional heat-curable silicone rubbers and the room-temperature-vulcanizable silicone rubbers.

Conventional silicone rubbers which are converted to the rubbery state by the action of heat are predominantly linear organopolysiloxanes having an average degree of substitution of about two organic groups attached directly to silicon per silicon atom. Preferably, the organic groups are monovalent hydrocarbon radicals such as alkyl, aryl, alkenyl, alkaryl, aralkyl, and of these, the methyl, phenyl and vinyl radicals are most preferred.

Variation of the organic groups in the silicone rubber can be used to vary the solubility of the drug in the polymer and hence can control the speed of the migration of the drug through the polymer. Also, drugs which are insoluble in one type of silicone rubber may be soluble in a different type of polymer. One especially preferred class of silicone polymers are the pure dimethylpolysiloxanes.

Room-temperature-vulcanizable silicone rubbers are also commercially available and are known to the art. In general, they employ the same silicone polymers as discussed above although the polymers often contain a greater amount of silicon-bonded hydroxy groups. This type of silicone rubber will cure at room temperature in the presence of an appropriate catalyst, such as stannous 2-ethylhexoate.

Exemplary patents disclosing the preparation of silicone rubbers are U.S. Pat. Nos. 2,541,137, 2,723,966, 2,863,846, 2,890,188, 2,927,907, 3,002,951, and 3,035,016.

Another class of materials suitable for encapsulating drugs are the hydrophilic polymers of monoesters of an olefinic acid, such as acrylic acid and methacrylic acid. Exemplary polymers of this class include poly (hydroxyethylacrylate) and poly (hydronyethylmethacrylate). These polymers are com-

mercially available and their preparation is described in U.S. Pat. Nos. 2,976,576 and 3,220,960, as well as in Belgian Pat. No. 701,813. When using these hydrophilic polymers, the drug is normally dissolved in a solvent such as a lower alcohol to promote passage of the drug through the polymer.

Other exemplary materials for use as encapsulating media in this invention include polyvinylalcohol, polyvinylacetate, plasticized polyvinylchloride, plasticized nylon, collagen, modified collagen, gelatin, and waxes such as polyethylene wax, oxidized polyethylene wax, hydrogenated castor oil, etc.

To provide the microcapsules, the encapsulating materials can be uniformly impregnated with the drug or drug solution to form microcapsules which are a matrix having the drug distributed therethrough. Alternatively, particles or solutions of drugs can be encapsulated with thin coatings 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 another material such as the encapsulating materials previously discussed which function as a solubility membrane to meter the flow of drug to the adhesives; use of a matrix and a different solubility membrane can slow the passage of the drug from the microcapsules which is desirable with drugs that are released too rapidly from available encapsulating materials. In contrast, by encapsulating a solution of the drug, the solvent speeds passage of the drug through the microcapsule walls.

Any of the encapsulation or impregnation techniques known in the art can be used to prepare the microcapsules to be incorporated into the adhesive base in accord with this invention. Thus, the drug or drug solution can be added to the encapsulating material in liquid form and uniformly distributed therethrough by mixing; or solid encapsulating material can be impregnated with the drug by immersion in a bath of the drug to cause the drug to diffuse into the material. 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. Alternatively, fine particles or solutions of the drug can be encapsulated with a coating. One suitable technique comprises suspending dry particles of the drug in an airstream and contacting that stream with a stream containing the encapsulating material to coat the drug particles. Usually, the microcapsules have an average particle size of from 1 to 1,000 microns, although this is not critical to the invention.

The microcapsules, however made, are then mixed with a pressure-sensitive adhesive. Any of the well-known dermatologically acceptable pressure-sensitive adhesives which permit drug migration can be used in practicing this invention. Exemplary adhesives include acrylic resins such as polymers of esters of acrylic 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, isooctanol, n-deconal, 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-branched alkyl maleamic acids wherein the alkyl group has 10 to 24 carbon atoms, glycol diacrylates, or mixtures of these; elastomeric silicone polymers; polyurethane elastomers; rubbery polymers, such as polyisobutylene, polyisoprene, and polybutadiene; vinyl polymers, such as polyvinylalcohol, polyvinyl pyrrolidone, and polyvinylacetate; cellulose derivatives such as ethyl cellulose, methyl cellulose, and carboxymethyl cellulose; natural gums such as guar, acacia, pectins, etc. For use in contact with the oral mucosa rubbery polymers, such as polyisobutylene, with or without gum modifiers gives good results, as do polyvinyl alcohol, polyvinyl pyrrolidone, cellulose derivatives and others. The adhesives may be compounded with tackifiers and stabilizers as is well known in the art.

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. Backing members can be flexible or nonflexible and suitable materials include cellophane, cellulose acetate, ethyl cellulose, plasticized vinyl acetate-vinyl chloride copolymers, polyethylene terephthalate, nylon, polyethylene, polyvinylidene chloride, coated flexible fibrous backings such as paper and cloth, and aluminum foil.

The required surface area of the bandage will depend on the activity of the drug and the rate of its absorption through the skin. Usually, the adhesive face of the bandage has a surface area of 0.5 to 400 square centimeters, although smaller or larger bandages can be used.

It will be appreciated that on encapsulating the drug with a material, such as silicone rubber, the drug immediately begins to migrate into and through the encapsulating material. On mixing the microcapsules with the adhesive the drug passing through the walls of the microcapsules will enter the adhesive, eventually saturating the adhesive with the drug. To prevent passage of the drug away from the exposed surface of the adhesive prior to use, the adhesive surface of the bandage generally is covered with a protective release film or foil, such as waxed paper, prior to use. Alternatively, the exposed rear surface of the backing member can be coated with a low-adhesion backsize and the bandage rolled about itself.

The following examples will serve to illustrate the invention without in any way being limiting thereon.

EXAMPLE I

2-hydroxyethyl methacrylate (100 grams) is mixed with tertiary butyl peroctoate (0.20 gram). Ethylene glycol dimethacrylate (0.20 gram) is added along with 4 grams of sodium bicarbonate as a foaming agent. The mixture is heated to 70° C. and the resulting solid, firable polymeric foam is ground into fine powder of 20-micron average particle size. The polymeric powder (10 grams) is mixed with chloramphenicol antibiotic (2 grams) dissolved in ethyl alcohol and the resultant mixture placed on a mechanical roller until the polymeric powder has absorbed the antibiotic. The solution is then filtered.

The resulting microcapsules of chloramphenical antibiotic are mixed with 100 grams of a 22 percent solution in heptaneisopropylalcohol (70:30) of a rubbery copolymer of isooctyl acrylate and acrylic acid (94:6) adhesive to uniformly distribute the microcapsules through the adhesive solution. The resulting slurry is coated onto a cellophane sheet 10 centimeters in width by 10 centimeters in length and the solvent removed by evaporation.

When applied to the skin of a subject, the resulting bandage is effective to administer chloramphenicol antibiotic through the skin to circulation to provide a continuous administration of the daily dose of the antibiotic.

EXAMPLE II

Liquid dimethyl silicone rubber (100 grams, Dow-corning Silastic) is mixed with finely divided crystalline megesterol acetate (5 grams). After uniformly mixing the hormone with the unvulcanized silicone rubber, 0.5 gram of stannous octoate catalyst is added and the rubber cured at room temperature. The resulting silicone rubber body is reduced to an average particle size of 100 microns.

5 grams of the resulting encapsulated megesterol acetate are mixed with an elastomeric silicone pressure-sensitive adhesive (10 grams) to uniformly distribute the microcapsules throughout the adhesive. Immediately thereafter, the adhesive mixture is coated onto one surface of a 100-square centimeter. Mylar sheet. The resulting bandage is used for fertility regulation.

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

While there have been shown and described and pointed out the fundamental novel features of the invention as applied to the preferred embodiment, it will be understood that various omissions and substitutions and changes in the form and details of the bandage illustrated may be made by those skilled in the art without departing from the spirit of the invention. It is the intention, therefore, to be limited only as indicated by the scope of the following claims.

What I claim is:

1. A medical bandage for use in the continuous administration to circulation of controlled quantities of systemically active drugs over a prolonged period of time by absorption through the external body skin or mucosa, said bandage comprising (1) a backing member bearing (2) a pressure-sensitive adhesive on one surface thereof, said pressure-sensitive adhesive having distributed therethrough (3) a plurality of discrete microcapsules, each of which microcapsules comprising a systemically active drug formulation confined within a wall member, said wall member being formed from drug release rate controlling material to continuously meter the flow of drug from the said microcapsules to the skin or mucosa at a controlled and predetermined rate over a prolonged period of time.

2. The bandage as defined by claim 1, wherein each of said microcapsules (3) is comprised of systemically active drug formulation microencapsulated with the said drug release rate controlling wall material.

3. The bandage as defined by claim 1, wherein each of said microcapsules (3) is comprised of a matrix of the drug release rate controlling wall material, said matrix having the systemically active drug formulation distributed therethrough.

4. The bandage as defined by claim 1, wherein the systemically active drug formulation is soluble in the drug release rate controlling material.

5. The bandage as defined by claim 1, wherein the pressure-sensitive adhesive is permeable to passage of the systemically active drug formulation.

6. The bandage as defined by claim 1, wherein the drug formulation comprises a pharmacologically acceptable solvent.

7. The bandage as defined by claim 1, wherein said drug release rate controlling material is silicone rubber.

8. The bandage as defined by claim 1, wherein said drug release rate controlling material is a hydrophilic polymer of an ester of an olefinic acid.

9. The bandage as defined by claim 1, wherein the pressure-sensitive adhesive is adapted to provide a liquidtight adhesive seal between the skin or mucosa and the bandage.

10. The bandage as defined by claim 1, wherein the surface of a pressure-sensitive adhesive (3) is covered with a protective release coating (4).

11. The bandage as defined by claim 1, wherein the outer surface of the backing member (1) is coated with a low adhesion backsize (5).

12. The bandage as defined by claim 1, wherein said microcapsules have an average particle size of from 1 to 1,000 microns.

13. The bandage as defined by claim 1, wherein the adhesive face of the bandage has an area of 0.5 to 400 square centimeters.