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Zaffaroni

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[54] **BANDAGE FOR CONTROLLED RELEASE OF VASODILATORS**

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[52] **U.S. Cl.** **128/268,** 128/260

[51] **Int. Cl.** **A61f 7/02**

[58] **Field of Search** 128/155, 156, 260, 128/268, 296; 424/18-22

[56] **References Cited**

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[57] **ABSTRACT**

Medical bandage for use in the continuous administration to circulation of controlled quantities of systemically active coronary vasodilators over a prolonged period of time by absorption through the external body skin or mucosa is comprised of a backing member, a pressure-sensitive adhesive coating, and a reservoir containing the drug confined within a wall member. The wall member is formed from drug release rate controlling material to continuously meter the flow of a therapeutically effective amount of the drug from the reservoir to the skin at a controlled and predetermined rate over a period of time.

19 Claims, 5 Drawing Figures

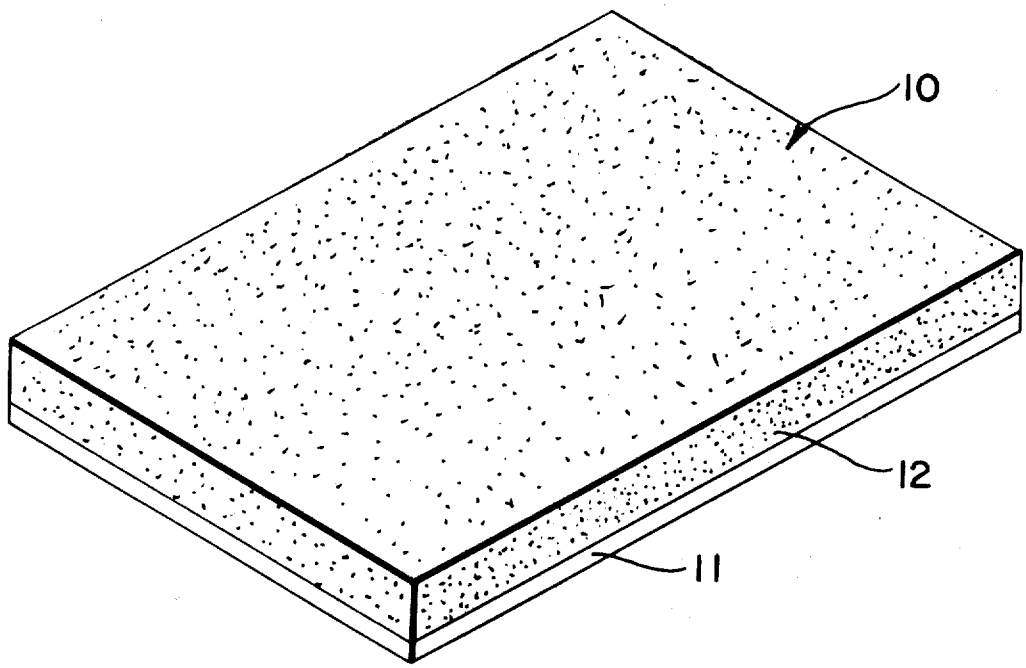
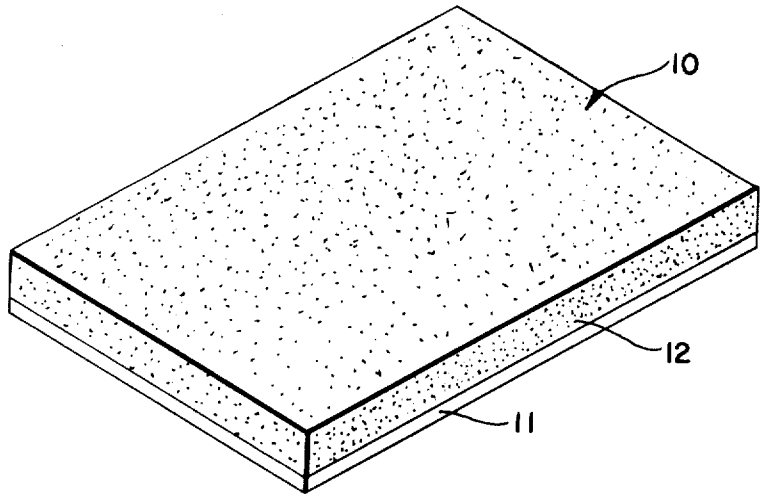


FIG. 1



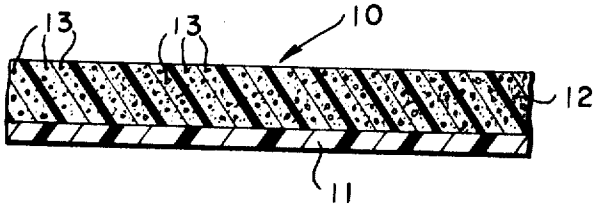


FIG. 2

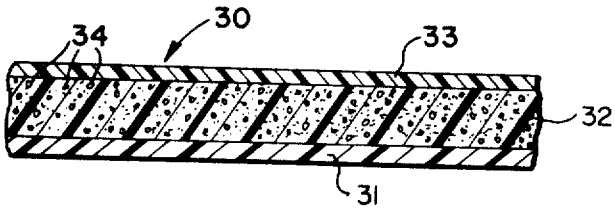


FIG. 3

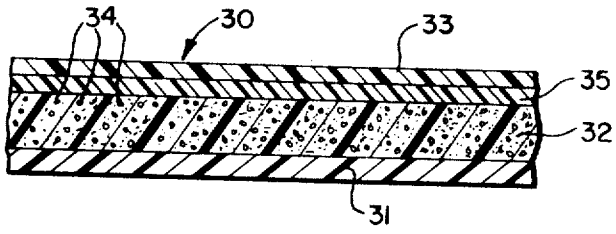


FIG. 4

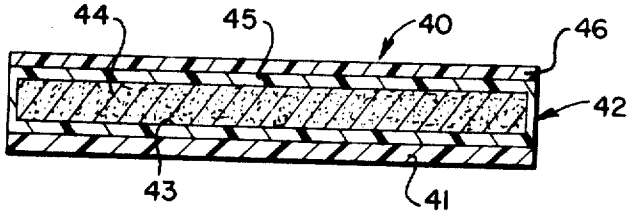


FIG. 5

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BANDAGE FOR CONTROLLED RELEASE OF VASODILATORS

CROSS REFERENCE TO RELATED APPLICATIONS

Alejandro Zaffaroni copending application, Ser. No. 812,116, filed Apr. 1, 1969, assigned to the assignor of the present invention and now issued on Aug. 10, 1971 as U.S. Pat. No. 3,598,122;

Alejandro Zaffaroni copending application, Ser. No. 812,117, filed Apr. 1, 1969, also assigned to the assignor of the present invention and also now issued on Aug. 10, 1971 as U.S. Pat. No. 3,598,123.

BACKGROUND OF THE INVENTION

This invention relates to a medical bandage and, more especially, to a medical bandage for use in the continuous administration to circulation of controlled quantities of systematically active coronary vasodilators over a period of time by absorption through the external body skin or mucosa.

Clinically, systemic vasodilators, e.g., nitroglycerin (glyceryl trinitrate, glonoin), have long been used to abate vasomotor spasm. These have a place in the treatment of peripheral, coronary, and pulmonary arterial embolism or occlusion, angina pectoris, coronary disease, and certain forms of peripheral vascular disease; they are not of value in hypertension. Nitroglycerin, for example, may also be extremely effective for relief of visceral smooth-muscle spasm, especially intestinal, biliary, or ureteral colic.

The systemic coronary vasodilators such as nitroglycerin are moreover conventionally administrated in the form of peroral or sublingual tablets, particularly the latter. While the desired vasodilation effect usually commences within a minute or two after placing sublingual tablet under the tongue of the patient, such effect is not long lived. For example, orally or sublingually administered nitroglycerin usually loses its vasodilation capacity in from about 30 to 45 minutes. The other systemic vasodilators are effective only for a period of up to a maximum of about six hours with dangerously large doses. It is therefore necessary in most instances to establish a dosage regimen of multiple unit doses over a prolonged period of time, e.g., 12 or 24 hours.

Even with the oral administration of these drugs at periodic intervals according to a well defined schedule, it is difficult to achieve a constant desired vasodilation effect in the patient. The almost inevitable result of oral administration of these drugs is that the level of the agent 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 desired toxic threshold, and valleys which fall below the critical point needed to achieve the desired therapeutic effect.

Administration of systemically active medicinal coronary vasodilators by injection is inconvenient, painful, and not any more effective than the sublingual route which is employed in generally all cases. Moreover, the typical result of administration by injection also is a surge in the blood level concentration of the vasodilator immediately after injection, followed by a decline and another surge in concentration upon subsequent injection. Some ointment preparations also have been developed, but these too have met with little success.

Therefore, there exists a serious need for a reliable dosage unit for the administration to circulation of controlled quantities of the coronary vasodilators which does not interfere with normal functions of the patient and which is lasting for a period of up to 12 hours, and even longer.

SUMMARY OF THE INVENTION

Accordingly, it is an object of this invention to provide a device for the administration of vasodilators 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 vasodilators through the skin or mucosa.

A further object of this invention is to provide a complete dosage regimen of vasodilators 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 therapeutic bandage for the systemic administration of controlled quantities of coronary vasodilators into the circulatory system by direct application of said bandage to the skin or mucosa. The bandage is comprised of a laminate of: (1) a backing member defining one face surface of the bandage; (2) a pressure-sensitive adhesive adapted for contact with the skin or mucosa, the external surface of said pressure-sensitive adhesive defining the other face surface of the bandage and disposed between the face surfaces defined by (1) and (2); and (3) at least one reservoir comprised of a coronary vasodilator drug formulation confined within a wall member, said wall member being formed from drug release rate controlling material to continuoualy meter the flow of drug from the said reservoir to the skin or mucosa at a controlled and predetermined rate over a prolonged period of time.

The term "reservoir" as used herein refers both to microcapsules as well as distinct reservoir compartments or matrix layers.

An embodiment of the invention described above resides in a bandage comprised of a laminate of: (1) a backing member; bearing (2) a discrete middle reservoir layer containing a coronary vasodilator agent confined within a wall member, said wall member being formed from drug release rate controlling material permeable to the passage of agent, to continuously meter the flow of a therapeutically effective amount of the agent to the skin 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 and positioned on one wall of the reservoir remote from the backing member.

Another aspect of this invention resides in a bandage as described immediately above including a solubility membrane interposed between the wall of the reservoir and the pressure-sensitive adhesive layer.

Still, another embodiment of this invention resides in a medicated adhesive bandage comprising a laminate of: (1) a backing member; bearing (2) a pressure-sensitive adhesive on one surface thereof adapted for contact with the skin, said pressure-sensitive adhesive having distributed therethrough, (3) a plurality of discrete microcapsules, each of which microcapsules comprises a coronary vasodilator agent confined within

a wall member, the wall member being formed from drug release rate controlling material, to continuously meter the flow of a therapeutically effective amount of the agent to the skin from the microcapsules at a controlled and predetermined rate over a period of time.

Still a further feature of this invention resides in a method for effecting vasodilation by directly applying to the skin or mucosa of a patient a bandage releasing a therapeutically effective amount of a coronary vasodilator to circulation.

Other objects, features and advantages of the invention will become more apparent from the following description when taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings:

FIG. 1 is a perspective view of the medical bandage of the invention wherein the coronary vasodilator is microencapsulated with a material permeable to passage of the agent and the microcapsules are uniformly distributed throughout the pressure-sensitive adhesive coating;

FIG. 2 is a cross-sectional view of the medical bandage of the invention shown in FIG. 1;

FIG. 3 is a cross-sectional view of another embodiment of the invention wherein the coronary vasodilator is uniformly distributed throughout a matrix laminated to the backing member and bearing a coating of the pressure-sensitive adhesive;

FIG. 4 is a cross-sectional view of another embodiment of the invention wherein a solubility membrane is interposed between the reservoir layer and the pressure-sensitive adhesive coating; and

FIG. 5 is a cross-sectional view of still another embodiment of the invention wherein the reservoir laminated to the backing member is a hollow container permeable to passage of the coronary vasodilator and having the drug within an interior chamber thereof.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided a medical bandage containing a coronary vasodilator therein for the predetermined controlled metering of the drug to the skin over a period of time.

As illustrated in FIGS. 1 and 2, the adhesive bandage 10 of the invention has a backing member 11 bearing a pressure-sensitive adhesive coating 12. Dispersed throughout pressure-sensitive adhesive coating 12 are microcapsules 13 of coronary vasodilator encapsulated with a material permeable to passage of drug.

Materials used to encapsulate the drug 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 therein or the porosity of the wall, 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 and movement of drug to the adhesive regulated.

Suitable materials for use in encapsulating the drug include hydrophobic polymers such as polyvinylchloride either unplasticized or plasticized with long-chain fatty amides or other plasticizer; plasticized nylon; unplasticized soft nylon; silicone rubber; polyethylene, and polyethylene terephthalate; and hydrophilic polymers such as esters of acrylic and methacrylic acid (as described in U.S. Pat. Nos. 2,976,576 and 3,220,960 and Belgian Pat. No. 701,813); modified collagen; cross-linked hydrophilic polyether gels (as described in U.S. Pat. No. 3,419,006); cross-linked polyvinylalcohol; and cross-linked partially hydrolyzed polyvinylacetate.

One presently preferred class of 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 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.

To provide the microcapsules, the encapsulating material can be uniformly impregnated with the drug to form microcapsules which are a matrix having the drug distributed therethrough. Alternatively, particles of drug 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 other materials such as the encapsulating materials previously described which function as a solubility membrane to meter the flow of drug to the adhesives; use of a matrix and a different solubility membrane coating can slow the passage of the drug from the microcapsules which is desirable with drugs that are released too rapidly from available encapsulating materials.

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. 1 and 2. Thus, the drug can be added to the encapsulating material in liquid form and uniformly distributed therethrough by mixing and subsequently converting to a

solid by curing or cooling; or solid encapsulating material can be impregnated with a drug by immersion in a bath of 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 of the drug can be encapsulated with the coating. One suitable technique comprises 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 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 any of the previously described pressure-sensitive adhesives and the mixture coated onto the backing member to provide the therapeutic medical bandage, usually the coating being sufficient 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, as in the embodiment of FIGS. **1** and **2**, 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.

Further embodiments of the adhesive bandage of the invention are illustrated in FIGS. **3**, **4** and **5**. As illustrated in FIG. **3**, adhesive bandage **30** of the invention is comprised of a coronary vasodilator agent **34** uniformly distributed in a reservoir **32** which is a polymeric matrix material. The matrix material is laminated to backing member **31** and bears a pressure-sensitive adhesive coating **33** thereon. The polymeric matrix material has a release rate for the particular drug used which continuously controls the dosage of drug administered.

FIG. **4** illustrates a further modified form of the invention wherein the adhesive bandage **30** of the invention is comprised of a backing member **31** having a reservoir **32** on one surface thereof. A solubility membrane **35** is interposed between the reservoir **32** and a pressure-sensitive adhesive coating **33**. Coronary vasodilator drug **34** is confined in polymeric matrix material **32** which acts as the reservoir for the drug and controls the rate of release therefrom. The solubility membrane, as with the walls of the reservoir, usually is formed of a material in which the drug is soluble and capable of diffusing through. Any of the materials previously mentioned for use in microencapsulation may be used as the solubility membrane. Of course, in each instance, the solubility membrane will have different characteristics than the reservoir wall of the particular device. This use of a pair of solubility membranes, that is, the reservoir wall and the further solubility membrane, allows for precise metering of drug to the adhesive layer for the thickness 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 solubility membrane can be used with either the matrix or container type of reservoir.

FIG. **5** illustrates a further form of the bandage **40** including a backing member **41** and a reservoir **42** in the form of a hollow container having an interior chamber **43** containing coronary vasodilator drug **44**. Wall **45** of reservoir **42**, remote from backing member **41**, is permeable to passage of drug **44**, as by diffusion, to meter the flow of drug to pressure-sensitive adhesive layer **46** on the outer surface thereof.

Suitable materials for forming the reservoir, whether of the matrix or hollow container type, are those materials permeable to passage of the drug previously described as suitable encapsulating materials. The reservoir can be formed by molding into the form of a hollow container with the drug trapped therein. Alternatively, the reservoir can be in the form of an envelope formed from sheets of polymeric material permeable to passage of the drug and enclosing the drug. While the walls of the reservoir can be of any convenient thickness, usually they have a thickness of from 0.01 to 7 millimeters. When the reservoir comprises a matrix with the drug distributed therethrough, it can be prepared by adding the drug to the matrix material in liquid form or solvent solution form and subsequently converting the matrix to a solid by curing, cooling or evaporation of solvent.

Thus, the reservoir of the therapeutic bandage is a hollow drug container or a solid matrix. Drug is metered from the reservoir to the adhesive layer, at a rate controlled by the composition and thickness of the reservoir or of the reservoir wall. From the adhesive layer, drug is directly transmitted to and through the skin to which the therapeutic adhesive bandage is applied. 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 is impermeable to the drug and strong enough, the backing becomes unnecessary.

In the embodiment of the invention illustrated in FIG. **4**, metering of the drug from the reservoir to the adhesive is further controlled by interposing a further solubility membrane therebetween. The solubility membrane is formed of a material in which the drug is soluble and capable of diffusing through. Any of the materials previously mentioned for use in microencapsulation may be used as the solubility membrane. Of course, in each instance, the solubility membrane will have different characteristics than the reservoir wall of the particular device. This use of a pair of solubility membranes, that is, the reservoir wall and the further solubility membrane, allows for precise metering of drug to the adhesive layer for the thickness 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 solubility membrane can be used with either the matrix or container type of reservoir.

Coronary vasodilators which can be employed for use in the medical bandage of the invention include generally those agents which are suitable for systemic absorption thru the external body skin or mucosa, e.g., nasal or oral mucosa, in accordance with their known dosages and uses. Suitable coronary vasodilators include, without limitation, compounds having a nitrate ion and a large number of organic nitrates and nitrates such as amyl nitrate, nitroglycerin(glyceryl trinitrate), sodium nitrate, erythrityl tetranitrate, pentaerythritol tetranitrate, isosorbide dinitrate, mannitol hexanitrate, trolnitrate phosphate(triethanolamine biphosphate), and the like, with nitroglycerin being the preferred coronary vasodilator. Also suitable is propranolol. Drugs

mentioned above can be used alone or in combination with each other.

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; polyoxyethylene 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. 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. Exemplary of transporting aids include monovalent, saturated and unsaturated aliphatic cycloaliphatic and aromatic alcohols having four to 12 carbon atoms, such as hexanol, cyclohexane and the like; aliphatic cycloaliphatic and aromatic hydrocarbons having from five to 12 carbon atoms such as hexane, cyclohexane, isopropylbenzene and the like; cycloaliphatic and aromatic aldehydes and ketones having from four to 10 carbon atoms such as cyclohexanone; acetamide; N,N-di(lower) alkyl acetamides such as N,N-diethyl acetamide, N,N-dimethyl acetamide, N-(2-hydroxyethyl)acetamide, and the like; and other transporting agents such as aliphatic, cycloaliphatic and aromatic esters; essential oils; halogenated or nitrated aliphatic, cycloaliphatic and aromatic hydrocarbons; salicylates; polyalkylene glycol silicates; mixtures thereof; and the like.

The amount of drug 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. Since the bandage of this invention is designed to control drug administration for a period of time, such as 1 hour to 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 for anginal attacks in a human adult, the daily release dosage of nitroglycerin should be in the range of between 0.1 and 5 milligrams per day. Thus, for example, using nitroglycerin with a bandage intended to remain in place for 1 day, and with a release rate of 5 milligrams of nitroglycerin per day, at least 5 milligrams of drug 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 a week are also readily made by the invention. The effective rate of release of the active agent to the skin can be in the range of from 0.01 milligrams to 10 milligrams per square centimeter of bandage per day. The exact amount will depend on the desired dosage. These effective rates of release of active agent to the skin can be obtained by altering the permeability and thickness of the release rate controlling barrier. In the case of the microencapsulated 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, for example, milligrams 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 a polymeric material or selected combinations of polymeric materials. Standard techniques are described in *Encyl. Polymer Sci. and Technology, Vols 5* and 9, pages 65 to 85 and 795 to 807, 1968; and the references cited therein. Other methods of the determining passage of drugs by diffusion through drug permeable polymeric material are available. See Dziuk, P. J. and Cook, B., "Passage of Steroids Through Silicone Rubbers," *Endocrinology*, 78:208, 1966; U.S. Pat. No. 3,279,996; Folkman and Edmonds, *Circulation Research*, 10:632, 1962; Folkman and Long, *J. Surg. Res.*, 43:139, 1964; and Powers, J., *Parasitology*, 51:53, April 1965, No. 2, Section 2.

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, isooctanol, 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-branched alkyl maleamic 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, styrene-butadiene, butylether, neoprene, polyisobutylene, polybutadiene, and polyisoprene; polyurethane elastomers; vinyl polymers, such as polyvinylalcohol, polyvinyl ethers, polyvinyl pyrrolidone, and polyvinylacetate; ureaformaldehyde resins; phenolformaldehyde resins; resorcinol formaldehyde resins; cellulose derivatives such as ethyl cellulose, methyl cellulose, nitrocellulose, cellulose acetatebutyrate, 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.

It will of course be appreciated that the pressure-sensitive adhesive surface need not form a continuous layer on the subject bandages. 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 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. When the adhesive layer covers one face surface of the bandage or when the reservoir is in the form of microcapsules distributed throughout the adhesive, the adhesive must be permeable to passage of the drug, to allow 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 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.

To prevent passage of the drug away from the exposed surface of the pressure-sensitive adhesive prior to use, the adhesive surface of the bandage generally is covered 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 systemically active compounds, the therapeutic bandage usually is packaged between hermetically sealed polyethylene terephthalate films under an inert atmosphere, such as gaseous nitrogen.

Various occlusive and non-occlusive, flexible or non-flexible backing members can be used in the medical bandage of the invention. Suitable backings include cellophane, cellulose acetate, ethylcellulose, plasticized vinylacetate-vinylchloride copolymers, polyethylene terephthalate, nylon, polyethylene, polypropylene, polyvinylidenechloride, paper, cloth, and aluminum foil. Preferably, a flexible occlusive backing is employed to conform to the shape of the body member to which the bandage is applied and to enhance absorption of the organic nitrate coronary vasodilator by the skin.

To use the medical bandage of the invention, it is applied directly to the skin or mucosa of a mammalian patient, to release a predetermined therapeutically effective amount of the vasodilator to circulation. Certain of the vasodilator drugs employed herein have heretofore been conventionally administered for the treatment of individual attacks of anginal pain or for the brief relaxation of other smooth muscle rather than for maintaining drug effects for any extended period. By the use of this invention, however, prophylaxis treatment of these conditions is made possible by ensuring that an accurately measured quantity of the drug is continuously administered when the bandage is applied to the skin or mucosa. Uncertainties previously encountered in administration of vasodilators by peroral pellet or sublingual tablet, or in application of these agents from creams or ointments are avoided and a reliable, stable preparation is provided. When the patient requires immediate relief, as in the case of angina pectoris, the bandage of the present invention may be used in conjunction with the sublingual method of administering nitroglycerin, that is, a nitroglycerin tablet may be given the patient for immediate relief and the bandage applied to the patient to continue the dosage of nitroglycerin for a much longer period of time.

The adhesive layer should be in firm contact with the skin, forming a tight seal therewith. Drug within the microcapsules or the reservoir layer whether in solid form or solution, migrates through the walls of the microcapsules or the reservoir layer, acting as a solubility membrane. Ordinarily, one would expect the drug migration to cease when sufficient drug has reached the outer surface of the microcapsules or reservoir layer to create an equilibrium or when the adhesive layer has become saturated with the drug. However, when the adhesive layer is in contact with the patient's skin, drug molecules which are continuously removed from the outer surface of the microcapsules or reservoir layer 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 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.

Those skilled in the art will appreciate that the bandage of this invention significantly differs from prior art wound dressings or bandages. The bandage of this invention contains a systemically active vasodilator drug and is applied to unbroken skin, to introduce the drug to circulation in the blood stream 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 regimen for a particular time period.

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 area bandages can be used.

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

EXAMPLE 1

100 grams of 2-hydroxyethyl methacrylate is mixed with 100 grams of water and tertiary butyl peroxide (0.2 gram) is added. Ethylene glycol dimethacrylate (0.2 gram) is added to the mixture and is heated to 70°C. The resultant friable, polymeric foam is dried and ground to a powder to obtain average particle size of about 20 micron.

A 10 gram portion of the polymeric powder is mixed with 1 gram glyceryl trinitrate dissolved in ethyl alcohol and the resultant mixture placed on a mechanical roller until the polymeric powder has absorbed the glyceryl trinitrate to saturation. The solution is then filtered.

The resulting microcapsules of glyceryl trinitrate are mixed with 100 grams of a 22 percent solution in heptane ethylacetate (70:30) of a viscoelastic copolymer of iso-octyl 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 is removed by evaporation.

When applied to the skin of a subject, a 5 × 5 cm portion of the resulting bandage is effective to administer nitroglycerin through the skin to circulation to provide a continuous administration of the daily dose of nitroglycerin for coronary vasodilation. If desired, the amount of the nitroglycerin to be administered may be increased or decreased by merely varying the size of the above described bandage for application to the skin.

EXAMPLE 2

49 grams of propylene glycol is mixed with 0.5 gram of high molecular weight carboxy vinyl resin (e.g., Carbopol resin; B.F. Goodrich) and the resultant slurry is neutralized using a ten percent aqueous sodium hydroxide solution to a neutral pH. To the resultant gel, 50 milligrams of nitroglycerin is added and thoroughly mixed with a suitable mixing equipment. One gram of the resultant gel contains 1 milligram of nitroglycerin.

Five grams of the resultant nitroglycerin gel is placed on a sheet of polyethylene to cover a 5 × 5 cm area. Another sheet of polyethylene is placed over the gel and the edges of the 5 × 5 cm area is sealed by a heat sealer to obtain a leak-proof packet like sandwich.

The resultant nitroglycerin-polyethylene sandwich is laminated over a pressure-sensitive adhesive sheet having a mylar backing member, so that about ½ cm wide adhesive edges are left uncovered for adhesion to the body surface.

The resultant device having a total dimension of 5½ × 5½ cm when applied to a body surface, is capable of delivering the nitroglycerin for up to 12 hours into the circulation through the skin.

Thus, this invention provides a reliable and easy to use device for administering nitrate vasodilators to circulation, in controlled quantities, over a prolonged period of time, by absorption through the exterior body skin or mucosa. Uncertainties resulting from administration of these agents, perorally, sublingually, or from creams, ointments and solutions, are not encountered; and a precisely determined amount of the drug is applied in a controlled manner.

Although the product of this invention has been referred to as a medical or therapeutic bandage, those skilled in the art will appreciate that the term "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, strips, sheets, plasters, and the like.

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 intended, therefore, that the invention be limited only as indicated by the scope of the following claims.

What is claimed is:

1. A medical bandage for the continuous administration to the skin or mucosa of controlled quantities of systemically active vasodilator drugs over a prolonged period of time by absorption through the external body skin or mucosa, said bandage comprising a laminate of (1) a backing member defining one face surface of the bandage; (2) a pressure-sensitive adhesive adapted for contact with the skin or mucosa, the external surface of said pressure-sensitive adhesive defining the other face surface of the bandage and, disposed between the face surfaces defined by (1) and (2); (3) at least one reservoir comprised of a systemically active vasodilator 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 reservoir 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 said reservoir comprises a discrete, middle reservoir layer sandwiched between said backing member (1) and said pressure-sensitive adhesive (2).

3. The bandage as defined by claim **2**, wherein the reservoir layer is comprised of a walled container having an interior chamber containing the systemically active vasodilator drug formulation.

4. The bandage as defined by claim **3**, wherein only that portion of the walled container which is adapted to be brought contiguous with the skin or mucosa is formed from the drug release rate controlling material.

5. The bandage as defined by claim **2**, wherein the reservoir layer is comprised of a matrix of the drug release rate controlling wall material, said matrix having the systemically active vasodilator drug formulation distributed therethrough.

6. The bandage as defined by claim **2**, further comprising a solubility membrane (4) interposed between said reservoir layer and said pressure-sensitive adhesive (2).

7. The bandage as defined by claim **2**, wherein one outer surface of the wall member comprising the reservoir layer also defines the said backing member (1).

8. The bandage as defined by claim 1, wherein said reservoir comprises a plurality of discrete microcapsules distributed throughout the said pressure sensitive adhesive.

9. The bandage as defined by claim 8, wherein each of said microcapsules is comprised of systemically active vasodilator drug formulation microencapsulated with the said drug release rate controlling wall material.

10. The bandage as defined by claim 8, wherein each of said microcapsules is comprised of a matrix of the drug release rate controlling wall material, said matrix having the systemically active vasodilator drug formulation distributed therethrough.

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

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

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

14. 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.

15. The bandage as defined by claim 1, wherein the pressure-sensitive adhesive is covered with a protective release coating.

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

17. The bandage as defined by claim 1, wherein the vasodilator is nitroglycerin.

18. The bandage as defined by claim 1, wherein the organic nitrate vasodilator is present in an amount of from about 1 microgram to about 1 gram.

19. The method of effecting vasodilation in a mammalian organism, comprising direct application to the skin or mucosa of such organism, the bandage as defined by claim 1.

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Erratum

In the notice of the issuance of Reexamination Certificate No. B1 3,742,951 (36th) appearing on pages 69 and 70 of the Official Gazette of Nov. 23, 1982 (1024 OG 69-70), the assignment information is incorrect. The correct assignment information is as follows:

Alejandro Zaffaroni, Atherton, Calif., assignor to ALZA Corp., Palo Alto, Calif.

Issue Date 11-23-1982

REEXAMINATION CERTIFICATE (36th)

United States Patent [19]

Zaffaroni

[11] **B1 3,742,951**

[45] Certificate Issued **Nov. 23, 1982**

[54] **BANDAGE FOR CONTROLLED RELEASE OF VASODILATORS**

[75] Inventor: **Alejandro Zaffaroni**, Atherton, Calif.

[73] Assignee: **Ciba-Geigy Limited**, Basel, Switzerland

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[52] **U.S. Cl.** **128/268**; 128/260
[58] **Field of Search** ...128/155, 156, 260, 128/268; 424/18-22

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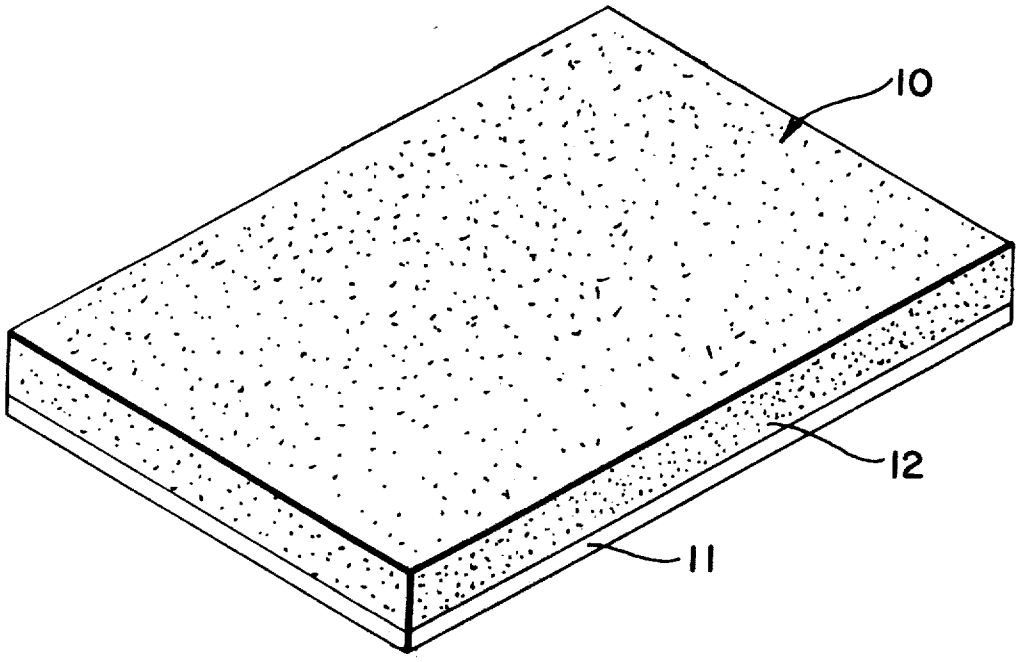
Primary Examiner—Charles F. Rosenbaum

[57] **ABSTRACT**

Medical bandage for use in the continuous administration to circulation of controlled quantities of systemically active coronary vasodilators over a prolonged period of time by absorption through the external body skin or mucosa is comprised of a backing member, a pressure-sensitive adhesive coating, and a reservoir containing the drug confined within a wall member. The wall member is formed from drug release rate controlling material to continuously meter the flow of a therapeutically effective amount of the drug from the reservoir to the skin at a controlled and predetermined rate over a period of time.



REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307.

NO AMENDMENTS HAVE BEEN MADE TO THE PATENT.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims 1-19 is confirmed.

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