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Jenkins

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[54] **TRANSDERMAL DEVICE**

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[51] **Int. Cl.**[5] **A61F 13/02**

[52] **U.S. Cl.** **424/448**; 424/449

[58] **Field of Search** 424/448, 449

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[57] **ABSTRACT**

The invention pertains to a method of preparing a device for transdermal delivery of an active ingredient which is solid at room temperature and in which part or all of the active ingredient is present in a saturated or supersaturated solution. In the first step, a mixture is prepared which includes at least a polymer adhesive, a vehicle for the polymer adhesive, an active ingredient and a solvent mixture for the active ingredient which solvent mixture comprises at least two solvents having different boiling points. The mixture is then formed into a film and dried. The vehicle for the polymer adhesive and at least one of the solvents and the solvent mixture have boiling points below the drying temperature of the film, while at least one of the solvents in the solvent mixture has a boiling point above the drying temperature of the film. Thus, at least one of the solvents remains in the film after drying and the solubility of the active ingredient contained in the remaining solvent is greater than 10%.

29 Claims, 3 Drawing Sheets

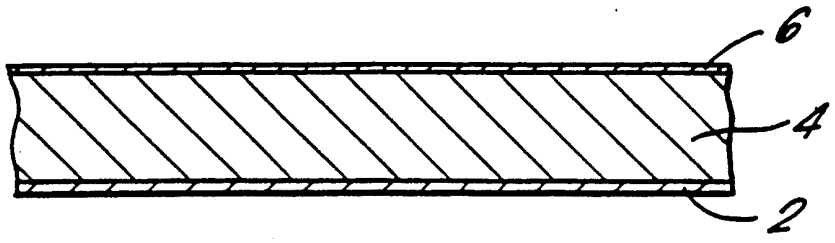


FIG. 1.

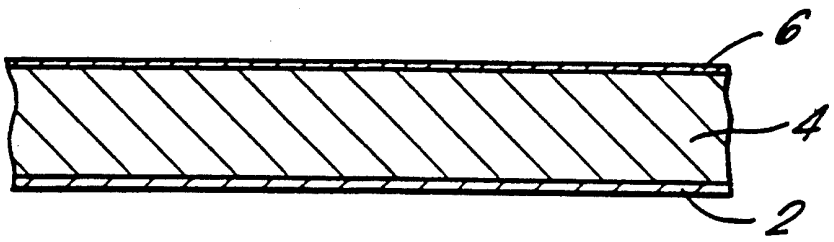
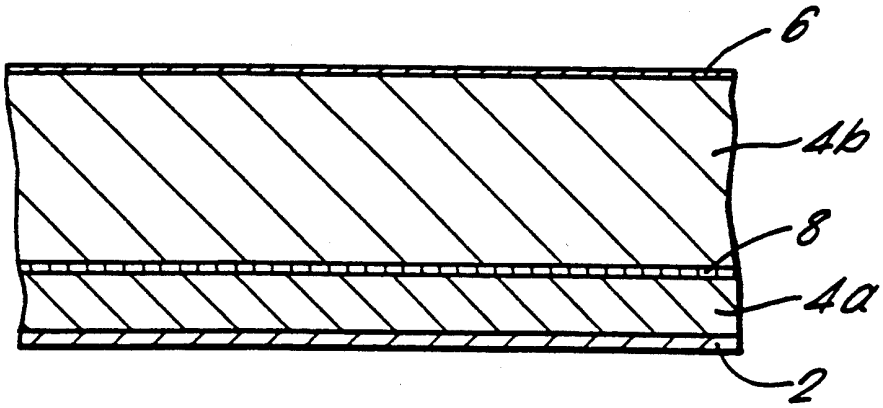


FIG. 2.



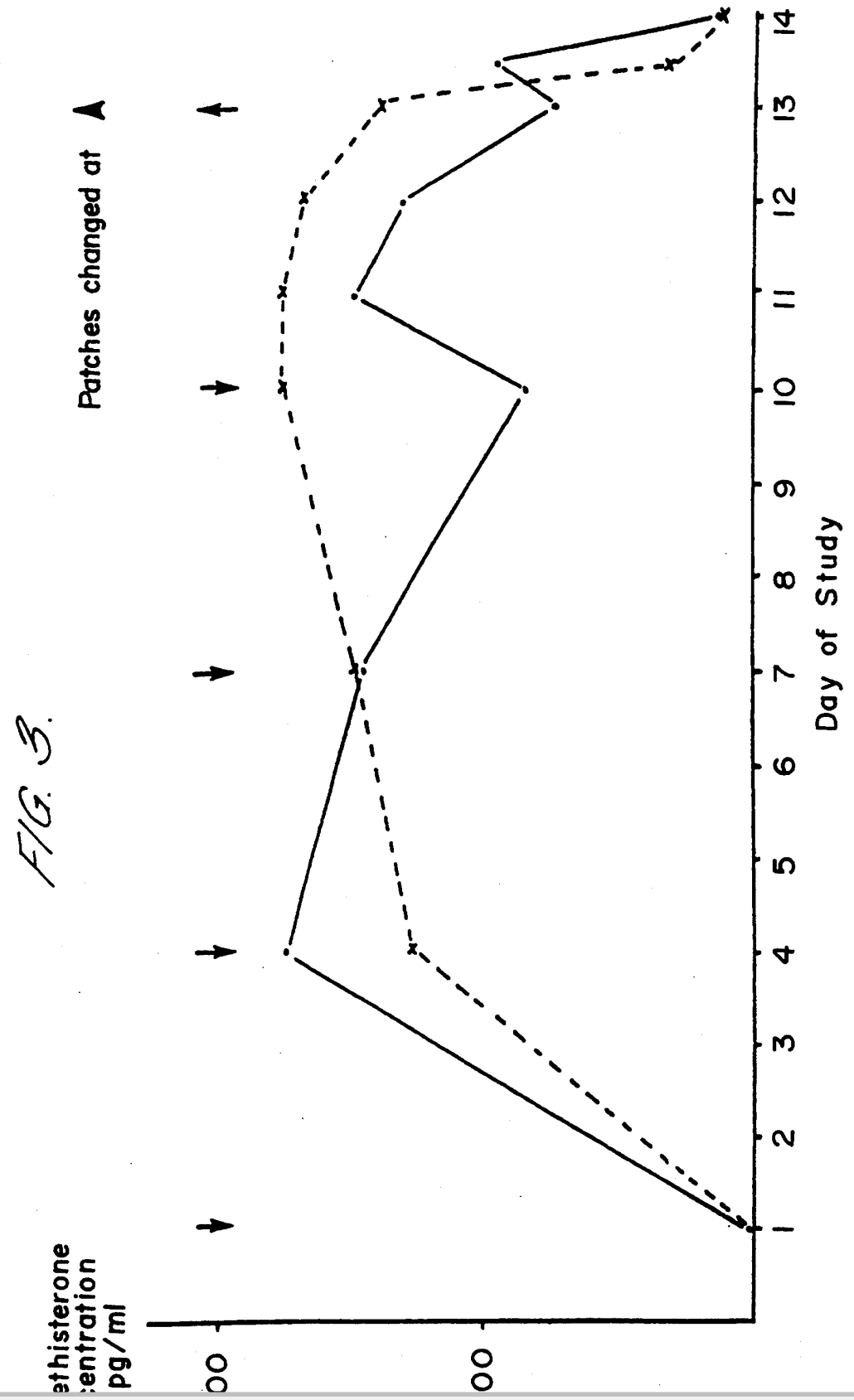


FIG. 3.

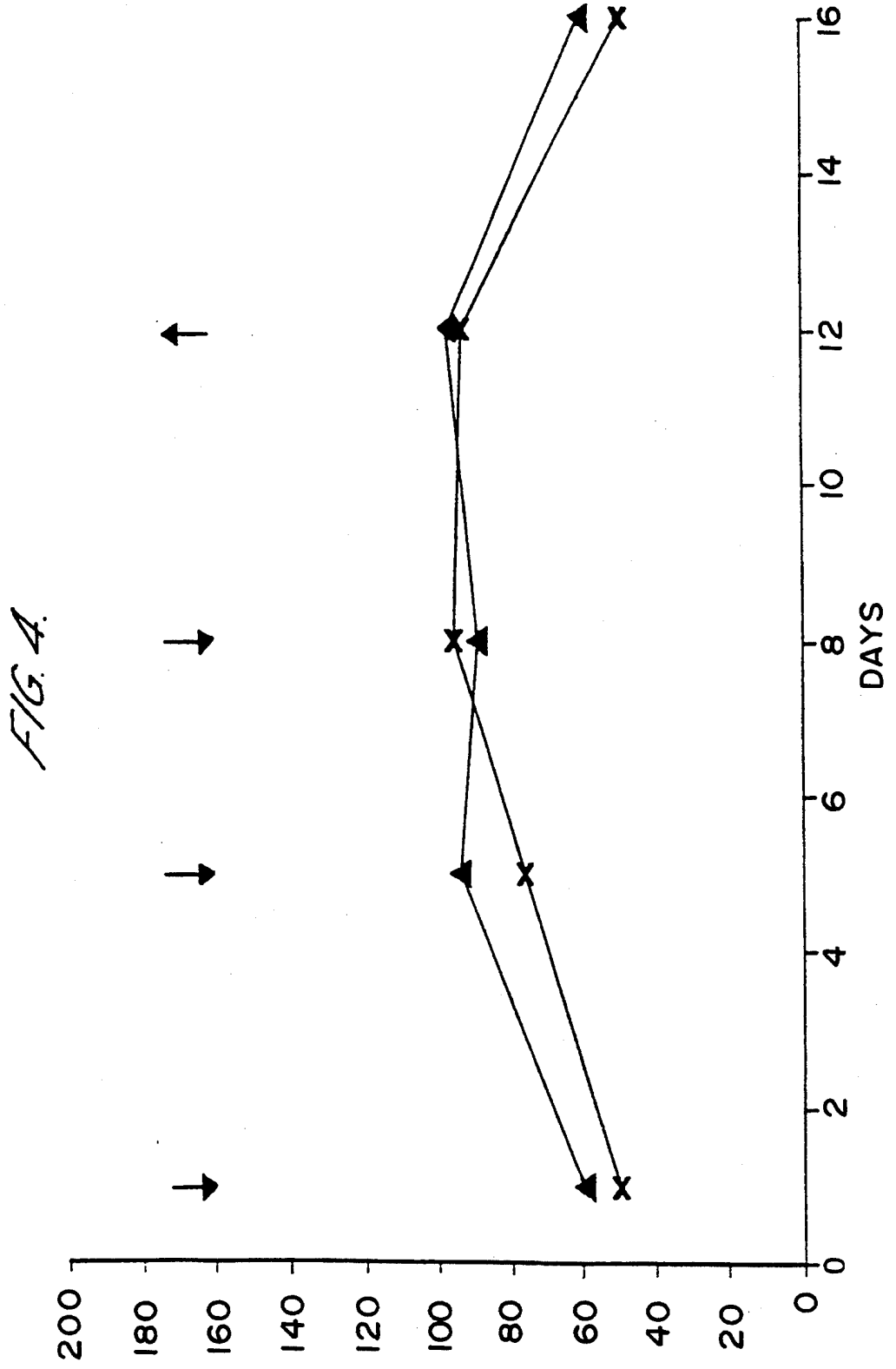


FIG. 4.

TRANSDERMAL DEVICE

The invention relates to a method of preparing a device for transdermal delivery of an active ingredient and to transdermal devices prepared by that method.

The administration of drugs through the skin is a concept which is now well established and this route has several advantages over more conventional forms of drug delivery such as injection or oral ingestion. A particular advantage is that transdermal drug delivery devices can provide a sustained and controlled release of the active ingredient over a prolonged period so that the resulting blood levels remain constant. This is in contrast to other forms of administration where surges of the agent occur in the bloodstream immediately after administration and then drop away rapidly until the next dose is given. In the case of oral administration the blood level is further influenced by contents of the intestines and therefore difficult to control. Transdermal administration permits direct access to the bloodstream without first passage through the gastrointestinal tract and liver and also without the inherent problems associated with injection such as risk of infection and need for sterile administration equipment.

Because of the advantage of transdermal administration, in recent years a very large number of devices have been developed and described for the transdermal administration of a variety of pharmaceuticals. The devices are usually in the form of a patch or plaster to be attached to the skin. Early devices such as for example, that described in U.S. Pat. No. 3,598,122 comprised a reservoir containing the active ingredient, either in solid or liquid form. The reservoir walls were composed of a material permeable to that ingredient and it was stuck to the skin by a thin layer of adhesive which was also permeable to the active ingredient. The outer surface of the reservoir was covered with a backing material impermeable to the active ingredient. Such devices were bulky and solvents in which the active agent was dissolved tended to interfere with the ability of the adhesive to stick to the skin.

With improvements in adhesives available it was soon found possible, and indeed preferable, to prepare transdermal devices in which the adhesive layer itself provided the drug reservoir. Thus more modern transdermal devices usually comprise at least an impermeable backing material, a layer of drug-containing adhesive attached to the backing material and a release liner on the other adhesive surface which is removed for application of the device to the skin. Additional membranes are sometimes included within the device to regulate the rate of passage of the active agent from the adhesive to the skin.

Various methods have been used to achieve suitable drug/adhesive mixtures in which the active ingredient is dispersed in the adhesive without affecting the ability of the adhesive to stick to the skin. One of the earliest drugs to be administered by a transdermal device was nitroglycerin which is used in the treatment of angina pectoris and congestive cardiac failure. Nitroglycerin is well absorbed by the skin and therefore particularly amenable to transdermal administration. Conveniently it is a liquid at room temperature and so the approach that has been taken is to absorb it on to a solid such as lactose which is then dispersed in a polymer adhesive. Such devices are described in, for example U.S. Pat. No. 4,776,850, G.B. 2,081,582, and others. One or more

other "solvents" are sometimes present in the nitroglycerin adhesive mixtures either as permeation enhancers, or for the purpose of "solvent casting" the mixture onto a backing layer.

Where the active ingredient to be incorporated into a transdermal device is a solid any solvent for the agent must be carefully chosen to be compatible with the adhesive. In WO86/00814 for example the problem is overcome by choosing a single solvent which is both a solvent for the drug and a solvent for the adhesive. However such a method restricts severely the number of different drugs which are compatible with a particular adhesive and also the type of adhesive which can be used.

Alternative methods have therefore been used in which a drug/adhesive mixture is prepared which includes a solvent for the drug and a solvent for the adhesive. The mixture is spread onto an appropriate backing material and then dried to evaporate the solvents leaving the drug dispersed in the adhesive in particulate form. A variation of the method is described in WO89/07951 in which the solvents for the adhesive are evaporated during a drying stage leaving the drug, in this case oestrogen, dispersed in particulate form in very high boiling point solvents which do not significantly evaporate on drying but which have a low capacity for the drug.

While the active ingredient can be taken up by the skin from a dispersion of the solid compound, the rate of uptake can be far better controlled if the agent is in a supersaturated solution, particularly where the solvent has an adequate capacity for the active ingredient. As the ingredient is taken up by the skin more will become dissolved in solution so maintaining a concentration gradient over a prolonged period which drives uptake through the skin. Transdermal devices are known which contain saturated drug solutions. They are described for example in G.B. 2,156,215 and U.S. Pat. No. 4,201,211. However these documents fail to describe a way in which the level of saturation can be precisely controlled to produce a supersaturated solution.

The present invention provides an improved method for preparing transdermal devices which contain supersaturated solutions of an active ingredient within an adhesive layer by use of a carefully selected mixture of solvents and selective evaporation of a particular solvent or solvents by drying at a temperature above the boiling points thereof, to influence the final concentration of the solution of active ingredient in the device.

In accordance with the invention a method of preparing a device for transdermal delivery of an active ingredient which is a solid at room temperature and in which part or all of the active ingredient is present in a supersaturated solution comprises the steps of:

(a) preparing a mixture comprising at least
  (i) a polymer adhesive
  (ii) a vehicle for the polymer adhesive
  (iii) the active ingredient
  (iv) a solvent mixture for the active ingredient which comprises at least two solvents;
(b) forming the mixture prepared in step (a) into a film, and
(c) drying the film prepared in step (b) wherein the vehicle for the polymer adhesive and at least one of the solvents in the solvent mixture for the active ingredient have boiling points below the drying temperature and at least one of the solvents in the

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