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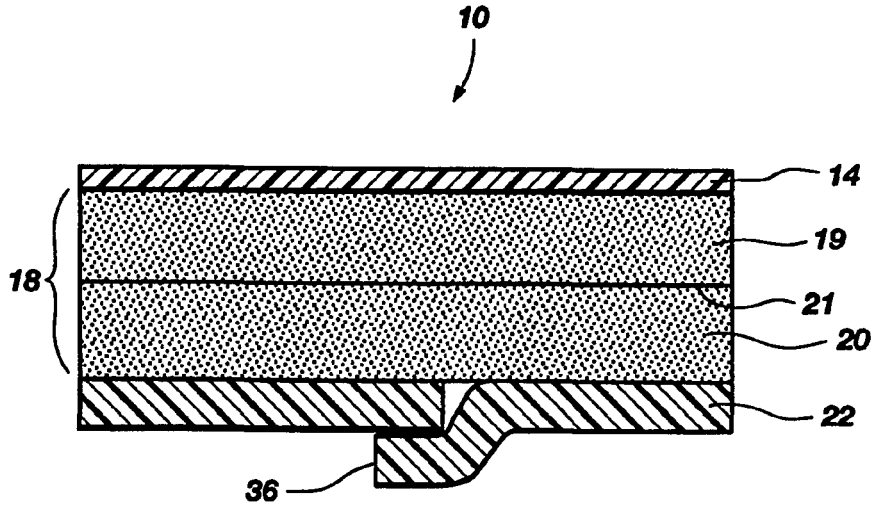

(57) Abstract

A method for making a transdermal drug delivery device for heat sensitive and volatile drugs is disclosed. The device contains a drug-containing adhesive composite layer having an impermeable backing material laminated to the distal surface thereof and a proximal peelable impermeable backing material adapted for removal for administering a drug to the skin or mucosa laminated to the proximal surface thereof. The figure provides a partly schematic, sectional view of the transdermal drug delivery device (10) including the substantially drug-impermeable distal backing (14), a drug laden adhesive composite (18) and a substantially drug impermeable proximal release liner (22). The adhesive composite (18) is comprised of a distal adhesive layer (19), a proximal adhesive layer (20) and a gelled drug layer (21) disposed therebetween. The device is produced by extruding the drug in gel form onto at least one exposed surface of a first or second adhesive laminate such that the adhesive layers and gelled drug are combined to form the drug-containing adhesive composite layer having the distal and proximal surfaces covered by the respective backing materials. This process is particularly adaptable to the formulation of nicotine-containing patches.

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DRUG-CONTAINING ADHESIVE COMPOSITE TRANSDERMAL DELIVERY DEVICE

Background of the Invention

This invention relates generally to transdermal and transmucosal drug delivery (TDD) devices. More particularly, the invention relates to TDD devices for delivering heat sensitive or volatile drugs in which the drug is extruded as a gel onto an adhesive layer following which the surface of the adhesive layer onto which the gel has been extruded is laminated with a second adhesive layer to form a drug-containing adhesive composite device. Chemical enhancers for facilitating transport of the drug through the skin or mucosa and other additives can also be mixed with the drug or into the composite. Thus, the invention encompasses a method for making TDD devices using an extrusion step to incorporate a gelled drug into a dried adhesive layer, and to drug delivery devices made using the method. These methods and devices are particularly useful for delivering nicotine into the body.

Cigarette smoking is a major risk factor in coronary heart disease and is the cause of approximately 30% of all cancer deaths. However, smoking is difficult to give up, and any smoking cessation therapy has to deal with both the pharmacological and psychological dependence on cigarettes. Modest success has been obtained by separating the treatment of these two factors, such as by satisfying the pharmacological craving with nicotine pills or chewing gum while treating the psychological addiction independently.

One of the most successful approaches relies on nicotine chewing gum, which achieves direct delivery of nicotine to the systemic circulation by buccal absorption. However, nicotine chewing gum tastes bad, may lead to mouth ulcers and heartburn, and destroys

dental appliances. Further, patient compliance is crucial to effectiveness. Other problems with orally administered nicotine include stomach upsets, nausea, rapid nicotine degradation, and irregular and unpredictable blood levels.

Another approach gaining increasing favor for treating the pharmacological dependence on cigarette smoking is transdermal delivery of nicotine. The skin is ordinarily a very effective barrier to passage of materials from the environment into the body. However, nicotine is very volatile, highly lipid soluble, and permeates the skin easily. For example, a comparison of average penetration rates of other transdermally administered agents through the skin show that nitroglycerin has a skin flux of 10-25 $\mu g/cm^2 \cdot h$, scopolamine 2-8 $\mu g/cm^2 \cdot h$, estradiol 0.01-0.03 $\mu g/cm^2 \cdot h$, clonidine 0.5 $\mu g/cm^2 \cdot h$, and nicotine 100-300 $\mu g/cm^2 \cdot h$. However, nicotine is also very irritating to skin and is very toxic. Therefore, development of acceptable TDD devices for delivering nicotine has required finding ways to minimize the irritation and safety problems while supplying effective doses of the substance.

A number of TDD devices for delivering nicotine have been described. Japanese Laid Open Application No. 61-251619 reports a non-controlled release device that holds low amounts of the substance and covers a relatively large area (70 cm^2) of skin. U.S. Patent No. 4,597,961 to Etscorn discloses a device in which a microporous membrane minimally controls release of nicotine to the skin such that it is effective for only about 45 minutes. U.S. Patent Nos. 4,920,989 and 5,016,652 to Rose et al. describe a nicotine patch that is preferably used with a nicotine aerosol spray that is delivered into a patient's mouth. U.S. Patent No. 4,943,435 to Baker et al. reports a transdermal patch for delivering nicotine for periods

of 12-24 hours that includes a nicotine reservoir and rate-controlling polymer matrix to regulate nicotine diffusion through the skin. U.S. Patent No. 4,908,213 to Govil et al. discloses a transdermal nicotine patch containing an antipruritic to counteract severe itching that may occur with transdermal administration of nicotine. U.S. Patent No. 4,877,618 to Reed teaches a transdermal nicotine patch containing a stack of alternating adhesive and interlaminar layers for providing a relatively constant rate of diffusion through the skin over an extended period of time.

Methods of fabricating TDD devices have not received much attention in the patent literature. U.S. Patent No. 4,943,435 to Baker et al. discloses a method of making a nicotine patch wherein the nicotine is preferably dissolved in an inert polymer matrix that controls the rate of nicotine release. The percentage by weight of nicotine can be varied according to the desired loading in the monolithic matrix layer, however, above about 50% nicotine by weight the polymer fails to solidify properly after casting, remaining in a gel or fluid form. Thus, this method of making nicotine patches is limited to polymers and nicotine loads that, when mixed, polymerize properly.

Another problem of drug delivery devices containing polymers and volatile drugs is that, even if polymerization is achieved in the presence of the drug, the polymer-drug combination must be allowed to dry. This is a problem for volatile drugs, such as nicotine, since the concentration of the volatile drug will diminish during drying, especially if the polymer is heated in an oven to accelerate drying. Thus, it would be advantageous to avoid fabrication methods requiring heating or drying after addition of a volatile drug to the polymer.

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