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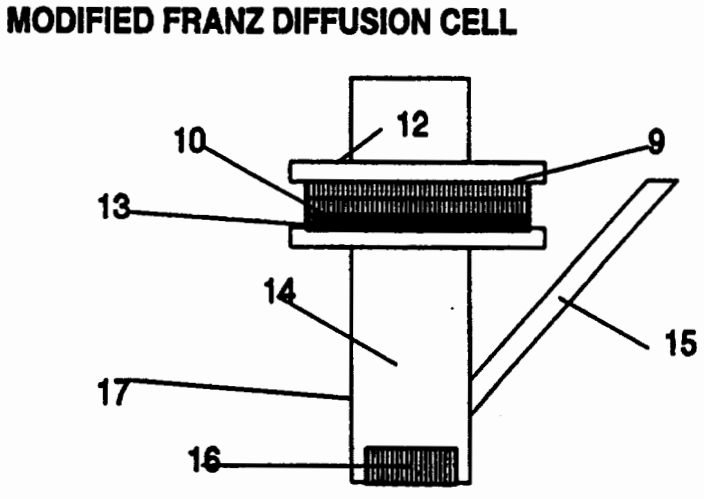

(57) Abstract

A composition for use in a transdermal drug delivery system is described. The composition comprises an adhesive, an estrogen, and a flux enhancer.

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Transdermal delivery device containing an estrogen

The present invention relates to a device for the administration of estradiol alone or in combination with progestin(s), encompassing a specific enhancer that achieves elevated transdermal fluxes and optionally an anti-oxidant that achieves better product stability and to a method for manufacturing such device.

17â-estradiol is the main estrogen produced by the ovaries in pre-menopausal women (J.A. Balfur and R.C. Heel, Drugs 40, 4, 561 - 582, 1990).

17-â estradiol, the naturally occurred estrogen, has mainly been used in two areas, such as fertility control and estrogen replacement therapy.

Oral administration of estradiol results in an almost complete degradation of this hormone in the digestive tract, due to the phenomenon of first-pass hepatic metabolism. Since a large amount of the administered estradiol, approximately 90%, is destroyed, a large excess should be administered in order to achieve an effective therapeutic result.

It is well-known, that oral administration of estradiol is associated with a number of major side effects such as thrombophlebitis and thrombosis, pulmonary embolism, coronary thrombosis, myocardial infraction, cerebral thrombosis, cerebral hemorrhage and hypertension.

Estrogen replacement therapy is a special need for females on menopause or oophorectomy (loss of one or both ovaries by surgery) and/or pituitary failure. It can also contribute to osteoporosis (loss of bone mass) and atherosclerosis.

Administration of estradiol to post-menopausal women has been found to make post-menopausal symptoms (hot flushes, sweating, nervousness, sleep disturbance) less intense.

Co-administration of progestin has been shown to be advantageous for eliminating the side-effects caused by the administration of estradiol itself. Thus, in both fertility control and estrogen replacement therapy, the available therapeutic dosage schemes contain an effective amount of progestin. [Y.W. Chien, T-Y. Chien and Y-C. Huang, U.S patent #4906169 (transdermal Estrogen/Progestin Dosage Unit, System and Process), March 6, 1990].

It has been of great importance to develop a delivery system which will provide certain advantages such as minimization of side effects, prolonged and controlled rate of administration of the hormones, rapid termination of the treatment, and improvement of patient compliance.

The introduction of transdermal systems was found to satisfy the above requirements, which, thus, permits the use of the natural estrogen, 17â-estradiol, and the use of lower daily doses with the same efficacy because of reduced first-pass hepatic metabolism and continuous drug input.

A number of transdermal delivery systems of various designs exist. They are in general well tolerated, with only 2.5-7% of patients overall having been reported to discontinue the use of transdermal delivery due to severe irritation problems.

The most frequent problem relates to insufficient adhesion of the transdermal "patch" to the skin during wear, resulting in patch loss. Typically, estradiol delivery systems are designed to be worn and to deliver the drug for 3 - 4 days.

Several sizes of transdermal estradiol patches already exist on the market, for example, 5, 10, 16 and 20 cm^2 containing 2, 4, 3.2 and 8 mg of estradiol respectively; the drug is delivered at a rate of 0.21 ig/cm^2/hr corresponding to delivery rates of 0.025, 0.05, 0.08 and 0.1 mg per 24 hours (for up to 4 days).

A number of patented systems exist for the delivery of estradiol through the skin, wherein, some selectively presented, (e.g. - Chien, Yie., W. and Chien, Te-Yen, WO 87/07138, Transdermal Absorption Dosage Unit For Estradiol and other Estrogenic Steroids and Process for Administration - Transdermal drug delivery device using a polymer-filled microporous membrane to achieve delayed onset, by Venkatraman S., Cygnus Therapeutic Systems WO 93/03693 - Solid matrix system for transdermal drug delivery, by Chia-Ming Chiang et al, Cygnus Therapeutic Systems, US Patent # 5,252,334 (12.10.1993) - Estradiol transdermal delivery system, by Kim B. et al., Paco Pharmaceutical Services, U.S. Patent #4,906,475/6.3.1990 - Transdermal estrogen/progestin dosage unit, system and process, by Chien Y. et al., Rutgers, the State University of New Jersey, WO 90/06736).

There are basically two types of transdermal drug delivery systems:

a) *Liquid reservoir*

Drug impermeable covering **1**.
Drug formulation reservoir **2**.
Rate-controlling membrane **3**.
Adhesion layer **4**.
Release liner **5**.

(as illustrated in Figure 1)

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