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MEDICATION METHOD

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ABSTRACT OF THE DISCLOSURE

A method of administering medication employs a strip covering the medicament which is inserted between the gum and cheek so that absorption of the medicament at a predetermined interval through the buccal mucosa into the bloodstream may take effect, after which the strip is removed and discarded.

The present invention relates generally to improvements in the administration of medicaments and it relates more particularly to an improved method for introducing a medicament into the blood stream. This application is a continuation in part of application Ser. No. 492,301, filed Oct. 1, 1965 now abandoned.

The conventional methods of introducing a medicament into the blood stream are by direct injection and by oral administration, in the latter case the medicament being absorbed through tre membrane which lines the passage of the medicament. Many medicaments are completely ineffective or of radically reduced efficacy when orally administered since they either are not absorbed or are adversely affected before entering the blood stream and thus do not possess the desired activity. On the other hand, the direct injection of the medicament into the blood stream, while assuring no modification of the medicament in administration, is a difficult, inconvenient and highly uncomfortable procedure and requires a high degree of skill.

Sublingual tablets and any other form of sublingual administration are subject to the limitations that there are smaller surfaces for the transmission through the mucosal membrane, that in the case of sublingual location a substance there placed causes salivation, and by reason of the additional fluid and the position in the mouth is likely to lead to swallowing of at least a portion of the medicament. Buccal tablets are known also but there are important drawbacks accompanying their use and they have enjoyed little success. In some instances larger dosages are required to be inserted in the buccal tablet than are needed in the case of the buccal strip of the present invention. In addition they usually take a great deal of time to deliver the medicament to the buccal surface. The buccal tablet also causes pressure between the lip and the gum, which may be uncomfortable and painful. This pressure also may cause the tablet to disintegrate and thus more of the contents are likely to be swallowed.

It is therefore a principal object of the present invention to provide an improved method for the introduction of medication into the blood stream.

A further object of the present invention is to provide an improved method for the administration of hormones.

The above and other objects of the present invention will become apparent from a reading of the following description in which examples are given merely by way of illustration and are not intended to limit the scope of the invention.

It has been found that certain medicaments when slowly released to the oral mucosa and particularly to the buccal membrane are absorbed thereby and efficiently enter the blood stream and unexpectedly effect a highly superior therapy or activity. Thus, in a sense of the present invention contemplates the employment of a medication form for introducing a pharmaceutically active material into the blood stream for a predetermined period comprising a film or strip carrying a pharmaceutically active material releasable therefrom in an aqueous medium for absorption through the oral mucosa buccal tissue. In another sense the present invention involves the method of introducing a medicament into the blood stream comprising positioning a fibrous absorbent strip carrying a medicament releasable therefrom in overlying contact with the oral mucosa buccal tissue.

While the present method is employed to great advantage in the administration of hormones, for example, progesterone, estrone, testosterone, cortisol, desoxycorticosterone, it may be employed to advantage with other medicaments, for example, protelytic enzymes such as trypsin, chymotrypsin, strepeokinase, streptodornase, appetite depressants, antispasmodics and sedatives, where rapid entrance to the blood stream is highly desirable.

The base of the subject medication form or buccal strip is advantageously an absorbent web such as a strip of woven or non-woven fabric, filter paper or cotton gauze, and is of a dimension which may be comfortably retained between the gum and cheek of the subject and can support in a releasable form a sufficient dosage of the medicament to be administered. The buccal strip may be advantageously between one and ten centimeters long, for example five centimeters, and between one-half and three centimeters wide, for example, one centimeter.

The medicament may be carried by the buccal strip in its pure state or it may be admixed with suitable carriers which facilitate the support of the medicament by the buccal strip and its suitable release to the buccal face. Examples of such carriers are Carbowax, polyvinylpyrrolidone, carboxymethyl cellulose, gum arabic and other water soluble or dispersible thickening agents and adhesives.

As an example of a medication form, its preparation and use in accordance with the present invention, a piece of Pellon 2100 (100% Polyamide fiber) fabric was immersed in a 20% dispersion of progesterone in a molten mixture of 15% Carbowax 400 and 85% Carbowax 4000 to fully impregnate the fabric. The impregnated fabric was then allowed to cool. The progresterone carrying fabric is cut into one by two centimeter strips, each strip containing about 26 milligrams of progesterone.

In the administration of the progesterone in accordance with the present invention the subject merely places and retains the progesterone carrying buccal strip described above between the confronting faces of the gum and the cheek and in contact with the buccal membrane. The buccal strip releases the progesterone which directly enters the blood stream through the buccal membrane. The rate of release of the progesterone averaged about 2 mgm. minute and the buccal strip was substantially depleted of medicament in approximately 15 minutes. At the end of such period the strip is removed and discarded.

Subjects who were administered progesterone in dosages of 26 mg. at intervals of 24 hours for five days by the use of the buccal strip medication form in the manner set forth above had withdrawal bleeding two to five days following cessation of medication.

These were patients who suffered from a variety of menstrual difficulties and were not capable of spontaneous menstruation. Menstruation could be induced in such patients by intramuscular injection of 100 mg. of progesterone. Following intramuscular progesterone, withdrawal bleeding could be demonstrated after four to five days.

Repeated use of buccal progesterone at intervals of one month, and even at shorter intervals, consistently induced withdrawal bleeding.

In contrast, subjects administered progesterone orally in the same dosages and at the same intervals as above failed to show any withdrawal bleeding. The literature reports that, on occasion, withdrawal bleeding has been induced in patients following oral administration of dosages of 500 mg. to 1500 mg. of progesterone. Such an effect cannot be obtained consistently however.

In another series of trials, buccal strips of size ¼" to 1" containing 2 mg. of estrone per strip were administered to patients, one strip per day for 15 days. It was found that approximately 95% of the estrone was removed from the buccal strip in approximately 15 minutes, so that the rate of release of the estrone averaged about .133 mg. per minute. These patients were all either prepuberal or postmenopausal. In each case vaginal cystology showed castrate cells. After as little as four days, the vaginal cells showed 2 to 3+ estrogen effect, and after eleven days, a full 4+ estrogen effect. If estrone were administered orally to such patients, a dose of at least two to three times this amount would be required. In fact, estrone is almost never administered orally because of its comparative lack of effectiveness by this route. Instead, orally active estrogen compounds such as ethinylestradiol, diethylstilbestrol or conjugated estrogens from pregnant mares' urine are used for oral administration. Estrone can produce typical estrogenic vaginal cornification if administered intramuscularly in dosages of one milligram daily for five days. However, continued intramuscular administration must be avoided since this is painful and may cause tissue damage and narcosis.

A preferred estrone buccal strip was prepared by impregnating filter paper with an alcoholic solution of estrone. The final concentration of estrone in the dried strip was determined by weight after evaporation of the alcohol to be 2 mg. per square cm. The solution that was used contained 1 gm. dissolved in 250 ml. of 96% alcohol. When strips are made up which are 1 cm. in width they may be cut appropriately to fix the dosage level in each strip.

The progesterone unit dosage administered in the present manner is advantageously between 10 and 50 milligrams and is administered at intervals between 12 and 72 hours. While the unit administration dosage of a hormone in the present form may be between 0.1 and 100 milligrams, the unit administration dosages of the hormones other than progesterone and their respective interval between administrations advantageously are:

Hormone	Buccal strip dos., milligrams	Unit interval between adm., hours
Estrone	0.5–5	12–72
Cortisol	5–50	12–72
Testosterone	5–50	12–72
Desoxycorticosterone	1–10	12–72

It was found that the buccal strips containing estrone, cortisol, testosterone and desoxycorticosterone were depleted of medicament when in contact with the buccal mucosa to the extent of 95% in about 15 minutes.

The preparation of the present medication forms employing therapeutic agents other than progesterone may

be produced in the above manner, the medicament being applied either from a solution or dispersion thereof in water or an organic solvent which is compatible with the medicament or may be carried in any suitable water dispersible or soluble vehicle. The solvent or water is removed in any well known manner which will not adversely affect the medicament such as by freeze drying, or the like.

The particular medicament and the vehicles employed in connection with it generally determine the release of the medicament and therefore the time of its passage across the buccal mucosa. Generally speaking, it is not wise to provide for too quick a release time. It has been found that a range of release time of from 5 to 20 minutes is optimal. In each case the method of administration employed includes the step for discarding the same after substantial depletion of the medicament therefrom.

While there has been described a preferred embodiment of the present invention, it is apparent that numerous alterations, omissions and additions may be made without departing from the spirit thereof.

What is claimed is:

1. The method of securing the systemic effect of a medicament comprising positioning between the confronting faces of the gum and cheek and in contact with the buccal membrane a flexible absorbent removable and discardable non-ingested fabric, gauze or paper strip, of a dimension which may be comfortably retained between the gum and the cheek and can support in a releasable form from all surfaces to the buccal face a sufficient systemic dosage of the medicament to be administered, impregnated with a medicament releaseable therefrom, admixed in a suitable water-soluble or dispersible impregnant carrier adapted to obtain a predetermined average rate of direct release from the buccal strip through the buccal membrane directly into the blood stream of a preselected species of medicament and to obtain an approximate predetermined time period in which the buccal strip is substantially depleted of said medicament, in overlying contact with the oral mucosa from opposite faces of said strip, then removing and discarding the buccal strip after a predetermined approximate time period for substantial depletion of the preselected species of medicament.

2. The method of claim **1** in which the medicament is a hormone.

3. The method of claim **1** in which the medicament is a hormone selected from the group consisting of progesterone, estrone, testosterone, cortisol and desoxycorticosterone.

4. The method of claim **2** in which the strip contains from 0.1 mg. to 100 mg. of said hormone.

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