METHOD AND COMPOSITIONS FOR NONINVASIVE DOSE-TO-EFFECT ADMINISTRATION OF LIPOPHILIC DRUGS

The present invention is directed to methods and compositions for noninvasively administering lipophilic drugs in a dose-to-effect manner to produce antimigraine, oxytocic, antiemetic, hypoglycemic, anti-Parkinsonian, antidiuretic, antifungal, antisecretory, or bronchodilator activity. A patient is put at ease when given the lollipop, and the lipophilic drug rapidly enters the patient's bloodstream as the lollipop is sucked. When treating the patient, the physician can observe the patient's condition and terminate the use of the lollipop when it has had a desired effect on the patient. The drug-containing lollipop can be self-administered by the patient in response to subjective symptoms and to the patient's susceptibility to the lipophilic drug.
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METHOD AND COMPOSITIONS FOR NONINVASIVE DOSE-TO-EFFECT ADMINISTRATION OF LIPOPHILIC DRUGS

BACKGROUND

1. The Field of the Invention

The present invention is related to methods and compositions for use in delivering pharmacological agents to a patient. More particularly, the present invention is directed to methods and compositions for the noninvasive administration of precisely the proper dose of potent pharmacological agents having antimigraine, oxytocic, antiemetic, hypoglycemic, anti-Parkinsonian, antidiuretic, antifungal, antisecretory, or bronchodilator properties.

2. The Prior Art.

In recent years, a host of potent new drugs have become available for clinical use in treating migraine headaches, nausea, vomiting, asthma, respiratory distress, polyuria, Parkinson's disease, systemic or oral fungal infections, esophagitis or heartburn, symptoms of diabetes, post partum and post abortion hemorrhage, and for inducing labor at term, stimulating uterine contraction during labor, or inducing abortion. Current expectations are that additional potent drugs will continue to become available in the future.

In addition to treating specific diseases and conditions, physicians can prescribe drugs that will permit the physician to regulate many body functions and processes. Yet, despite the tremendous advances in the field of pharmacology, physicians continue to administer these new drugs using substantially the same techniques that have been employed for many decades.

Thus, almost all pharmacological agents continue to be administered via two routes, by oral administration for absorption through the stomach or intestines or by intramuscular or intravenous injection, despite the fact
that both of these routes suffer from significant disadvantages under typical situations.

The simplest and most prevalent administration route is oral administration. To use this method, a pharmacological agent is incorporated into a tablet, a capsule, or into a liquid base; the patient then ingests an appropriate dose. Oral administration of a drug is extremely convenient, and for many drugs, it will continue to be the method of choice. Such administration is nonthreatening and is painless to the patient. For most patients, it is also very simple.

Nevertheless, oral administration of a drug suffers from the disadvantage that pediatric and geriatric patients frequently have difficulty swallowing pills, and such patients often refuse to cooperate in swallowing a liquid medication. Even more importantly, absorption of a drug into the bloodstream after swallowing a tablet varies from patient to patient and in the same patient from time to time. The absorption of the drug is dependent upon the movement from the stomach to the small and large intestines and the effects of secretions from these organs.

Moreover, there is often a substantial delay between the time of oral administration of a drug until it begins to have the desired therapeutic effect on the patient's system. Generally, a drug must pass from the stomach into the small and large intestines before it will be absorbed into the patient's bloodstream; unfortunately, this typically takes forty-five minutes or longer. For some applications, such a delay is unacceptable.

Further, many drugs taken orally are metabolized almost immediately -- they are removed from or rendered ineffective by the patient's system before they can have any therapeutic effect. This occurs because the veins from the stomach and the small and large intestines drain into
the liver. Thus, drugs entering the patient's bloodstream through the stomach and the intestines immediately pass through the patient's liver before distribution throughout the remainder of the patient's body.

Unfortunately, upwards of sixty percent of a drug (and essentially one hundred percent of certain drugs) may be removed from the patient's bloodstream during this first pass through the liver. Therefore, when utilizing oral administration, much larger doses of the drug than would otherwise be necessary must be administered to the patient to compensate for the large percentage of the drug removed during the first pass through the liver and obtain the desired effect in the patient.

Adverse reactions from the large doses necessary to elicit a systemic or local effect despite metabolism by the liver include nausea, vomiting, involuntary movement, gastrointestinal bleeding, duodenal ulcers, and epigastric abdominal distress. Other dose-related side effects may adversely affect renal and hepatic functions, especially in the geriatric patient. Some drugs, if present in the liver in excess, may also be hepatotoxic.

The result is that the oral route of administration is inefficient for many drugs, particularly many antimigraine, antiemetic, hypoglycemic, bronchodilator, oxytocic, anti-
Parkinsonian, antidiuretic, antifungal, or antisecretory acting drugs.

In some instances, a dose approximately one hundred times the actual effective dose must be administered to the patient in order to retain a sufficient dose of the drug in the blood after the first pass through the liver. Thus, oral administration results in a highly inefficient use of the drug. Further, in addition to the other adverse effects resulting from large amounts of the drug being removed by the liver, oral administration is also disadvantageous because of the cost in providing such a large dose of the drug.

A yet further difficulty encountered when administering drugs orally is that dosages are prepared or determined for use with an "average" patient. This is entirely acceptable for many drugs, but some drugs have a widely varying effect on different patients, even when weight and size differences between patients are considered. The effects of these drugs can vary depending upon the patient's habits, subtle genetic differences between patients, the patient's blood volume, the patient's age, and numerous other known and unknown individual variations in susceptibility to the particular drug utilized.

Underdosing a patient because of a low susceptibility to the drug fails to evoke the response sought by the physician. Overdosing the patient can result in dangerous depression of vital body functions. Moreover, the slow and uncertain response time for the onset of an observable reaction to a drug when taken orally makes it even more difficult to determine a proper dose for a particular patient. The physician may not learn for an hour, or with some drugs for a few days, whether the patient was underdosed or overdosed.
In order to avoid these serious disadvantages inherent in the oral administration modality, physicians frequently resort to the injection modality for administering many drugs. Injecting a drug (generally intravenously or intramuscularly) results in rapid entry of the drug into the patient's bloodstream; in addition, this type of delivery avoids the removal of large quantities of the drug by the patient's liver that accompanies oral administration. Rather, the drug becomes rapidly distributed to various portions of the patient's body before exposure to the liver; thus, the drug is removed by the liver at a substantially slower rate.

Most patients have at least some aversion to receiving injections. In some patients, particularly children and certain "high strung" adults, this aversion may be so pronounced as to make the use of injections of serious concern to the physician. Since intense psychological stress and anxiolysis can exacerbate a patient's debilitated condition, it sometimes becomes undesirable to use injections where the patient is seriously ill or suffers from a debilitating condition or injury.

To compound the problem facing a physician, the individual variation in susceptibility and metabolism with respect to various drugs, which makes it difficult to select an appropriate dose for oral administration, is even more profound when utilizing the injection modality of administration. This is because smaller doses have an increased effect due to the rapidity with which the drug enters the bloodstream and because large doses of the drug, when injected, are not immediately metabolized by the liver.

In order to prevent overdosing a patient with potent drugs, a prudent physician typically injects a patient with a lower than average dose, and later supplements the dose
with additional injections as they appear necessary. This "titration" makes necessary the use of repeated injections, which in turn greatly increases the stress on the patient. It is not uncommon for a patient to come to fear that it is time for yet another injection every time the patient sees a member of the hospital staff, which is often the case for those most in need of potent drugs.

In view of the foregoing, it will be appreciated that it would be an important advancement in the art of administering drugs if suitable methods and compositions could be provided for administering drugs in order to provide for rapid onset of the desired action and precise dosage delivery in each patient so as to avoid the dangers of overdosage and underdosage.

It will also be appreciated that it would be an important advancement in the art of administering drugs if suitable methods and compositions could be provided that avoid immediate metabolism of the drug through the patient's liver and yet not involve injection of the drug.

It would be an additional important advancement if methods and compositions could be provided that would permit a physician and/or a patient to easily control the amount of the drug the patient receives according to the patient's own subjective need for medication.

Such methods and compositions are disclosed and claimed herein.

BRIEF SUMMARY AND OBJECTS OF THE INVENTION

The present invention is directed to novel methods and compositions for use in administering potent antimigraine, antiemetic, hypoglycemic, bronchodilator, oxytocic, anti-Parkinsonian, antidiuretic, antifungal, or antisecretory drugs. The present invention is capable of introducing the drug into the patient's bloodstream almost as fast as an
injection -- and much faster than by oral administration. Yet, the delivery modality is nonthreatening, painless, and minimizes the dangers of overdosing and underdosing.

These significant advantages are achieved by incorporating into a candy matrix a drug or combination of drugs capable of being absorbed through the mucosal tissue found in a patient's mouth, pharynx, and esophagus. The resultant mixture is then advantageously formed into a lollipop, which, as discussed in greater detail hereinafter, can be administered in a dose-to-effect manner to achieve a systemic effect on the patient.

Even patients that have difficulty swallowing a pill or tablet or refuse to swallow a pill, tablet, and/or a liquid, will give little resistance to sucking on a lollipop. Particularly when dealing with children, a lollipop evokes a pleasurable response in the patient and gives the patient something nonthreatening on which to concentrate.

An antimigraine, antiemetic, hypoglycemic, bronchodilator, oxytocic, anti-Parkinsonian, antidiuretic, antifungal, or antisecretory acting drug administered by way of a lollipop will quickly enter the patient's bloodstream through the veins which serve the mucosal tissues in the mouth and pharynx, thereby serving to further lessen any remaining tension and fear. Appropriate monitoring of the patient's reaction (e.g., pain, asthma, hemorrhage, urine output, etc.) to these potent drugs will indicate when the drug has evoked a suitable response. The lollipop may then be removed, or its rate of consumption may be decreased.

It will be appreciated that the ever-present risk of overdosing a patient is substantially minimized, if not almost eliminated, by the dose-to-effect administration method of the present invention. The rate at which the
drug is to be absorbed by the body can be varied by varying the rate the lollipop dissolves.

Accordingly, the drug dose is given over a period of time rather than all at once (as in a pill or other bolus injection), and the administration rate can be reduced if such appears necessary. If a patient begins showing signs of any overdose, he will simply stop sucking the lollipop and/or the physician can easily remove the lollipop from the patient's mouth.

Unlike the use of injections or oral ingestion of medication where a relatively large bolus dose of medication is given intermittently, use of a lollipop can permit the patient to take very small doses of a drug on an almost continuous basis. Moreover, such administration can be regulated in response to the patient's own need for medication in light of his own subjective experience and his own personal susceptibility to the particular drug utilized. The result is that lower amounts of drugs can be used to achieve a more even medication of the patient.

It is, therefore, a primary object of the present invention to provide noninvasive methods and compositions capable of rapidly inducing an antimigraine, antiemetic, hypoglycemic, bronchodilator, oxytocic, anti-Parkinsonian, antidiuretic, antifungal, or antisecretory affect through the dose-to-effect administration of appropriate drugs without the dangers of overdosage or underdosage.

It is another important object of the present invention to provide methods and compositions that would allow for more physician control over the administration of these potent drugs so that individual patient differences in susceptibility and metabolism can be taken into account.

Yet another primary object of the present invention is to provide methods and compositions for drug administration which minimize the psychological trauma generally
associated with injections and the adverse physical and psychological problems often associated with the oral administration of potent drugs.

Yet another primary object of the present invention is to provide methods and compositions that will permit a patient to control the amount of medication administered according to the individual variations in the susceptibility to the particular medication used and in response to the patient's subjective experience of pain or other biological indicator.

These and other objects and features of the present invention will become more fully apparent from the following description and appended claims.

**DETAILED DESCRIPTION OF THE INVENTION**

As discussed above, the present invention is directed to methods and compositions for use in the noninvasive administration of antimigraine, antiemetic, hypoglycemic, bronchodilator, oxytocic, anti-Parkinsonian, antidiuretic, antifungal, or antisecretory agents. Advantageously, the present invention permits exceptional control over the effect of the drug administered, despite individual susceptibility to and metabolism of that drug by the patient.

While maintaining the convenience of oral administration, the present invention provides for many of the advantages of the injection modality of drug administration. At the same time, the present invention avoids the disadvantages identified above with respect to these two traditional routes of administration. The present invention achieves these results by utilizing yet a third administration route -- absorption through the mucosal tissues in the mouth and around the pharynx and esophagus.
A very few drugs, such as nitroglycerin, have historically been administered by absorption through mucous tissue because the transmucosal route is faster than oral administration, and unlike injections can be easily self-administered. While such drugs are easily given by the transmucosal route, they have not, unfortunately, been given by a dose-to-effect method. In dose-to-effect drug administration, the drug is administered until a predetermined effect is obtained; thereafter, the administration process is modified or terminated. By contrast, the prior art has consistently utilized the procedure of administering a bolus of the drug.

Despite some limited use, the transmucosal route has not been favored for routine use. Instead, where a delay in drug action is acceptable, the oral route has been preferred by most physicians, and injections have been used where delay is not acceptable.

Transmucosal dose-to-effect delivery of a drug is somewhat slower to provide active concentrations of a drug in a patient's system than is the use of an intravenous injection. Nevertheless, it has been discovered that the transmucosal route can be adapted so that any loss in the speed of drug uptake is more than offset by the ability to administer the drug noninvasively (much to the appreciation of the patient) and by the ability to control the dose received by the patient vis-a-vis the effect of the drug.

A drug must be lipophilic in order to be absorbed across mucosal tissue. However, this requirement is not a serious limitation since a large number of drugs are naturally lipophilic or can be provided in a lipophilic form.

In accordance with the present invention, a suitable drug is dispersed within a carbohydrate mass, a compressed powder form, or other suitable matrix in the form of a lollipop. (The method of manufacturing a suitable com-
pressed powder lollipop which is usable for certain potent
drugs within the scope of the present invention is
described in detail in U.S. patent application Serial No.
07/060,045, filed June 8, 1987, in the name of the
inventors hereof, and entitled "COMPOSITIONS AND METHODS OF
MANUFACTURE OF COMPRESSED POWDER MEDICAMENTS." That
application is incorporated herein by specific reference.)

The drug-containing lollipop is then given to a
patient to suck on so that the drug will be released into
the patient's mouth as the carbohydrate mass or compressed
powder matrix dissolves. Being lipophilic, a significant
portion of the drug is absorbed into and/or through the
mucosal tissues of the mouth, pharyngeal, and esophageal
areas. The drug rapidly enters the patient's bloodstream,
and importantly, the blood in the veins draining from the
mouth and the pharyngeal and esophageal areas passes
through the central nervous system and then through a
substantial portion of the body (so that the drug can be
absorbed) before the blood passes through the liver (where
most of the drug is inactivated). In case of a localize
effect, the drug quickly contacts the affected area in
order to provide effective relieve as soon as possible,
while minimizing the amount of the drug administered to the
patient.

The use of a carbohydrate or compressed powder
matrix (i.e., "candy") to administer a drug offers some
important advantages, particularly when dealing with pediat-
tric patients. First, a candy lollipop is familiar and
lacks the menace of a syringe and needle. Being a
substance normally associated with pleasure, the drug-
containing candy lollipop immediately evokes a positive
psychological response.
Importantly, it has been found that the use of drug-containing candy in the form of a lollipop can permit the physician to control the dosage of the drug administered to the patient in order to relieve a migraine headache, asthma, nausea, vomiting, or bronchospasm, or to induce childbirth, increase urine output, relieve the effects of Parkinson's disease, or treat systemic or oral fungal infections, polyuria or gastric and duodenal ulcers, thereby resulting in dose-to-effect drug administration. Use of such drug-containing lollipops also permits the patient in certain circumstances to exert control over the dosage received of certain medication in order to diminish feelings of discomfort or pain.

These important advantages are available because very small amounts of a potent drug may be delivered to a patient substantially continuously, and administration of the drug may be halted at any time by simply removing the candy from the patient's mouth. This not only allows a physician to monitor a patient's condition so that a particular effect is obtained and maintained, but also provides the important safety benefit of reducing the risk of overdose.

It is much less likely that a patient receiving medication in accordance with the dose-to-effect method of the present invention will become overdosed since the dose builds relatively slowly until a desired effect is achieved. Further, if a patient becomes slightly overdosed, it is likely that the patient will stop sucking the drug-containing lollipop and/or the physician or other medical personnel will observe the situation and remove the lollipop before the patient becomes seriously overdosed.

In contrast, once a typically large dose of a drug is given orally, by injection, or even sublingually or nasally, there is no retrieving it; thus, the full effects
of the administered drug will be felt. Further, a large
dose given every few hours results in wide swings in plasma
concentration of the drug, while the use of a lollipop in
accordance with the present invention evens out the plasma
concentration of that drug.

In practice, a physician can offer the patient a piece
of medicated candy on a holder, together with simple
instructions that the candy is to be sucked rather than
chewed. Children will particularly be put at ease by this
approach but so will anxious adults. The physician can
then monitor the patient's condition to ensure the desired
effect is achieved. If, for example, the drug-containing
candy contains oxytocin, the physician can monitor the
patient's uterine contractions during labor until a
suitable effect is achieved.

As mentioned above, it is preferred that the medicated
candy take the form of a lollipop. Use of a stick or other
suitable holder permits easy removal of the candy when a
physician deems that a patient has received a proper dosage
of the drug contained therein. Provision of a suitable
holder also facilitates intermittent administration of a
drug to maintain a desired condition and makes it more
convenient for a patient to intermittently self-administer
the drug in response to variations in the patient's subjec-
tive perception of physiologic condition.

The speed at which a sufficient amount of drug enters
the patient's bloodstream so as to produce a desired effect
depends on several factors. For example, a very potent
drug requires fewer drug molecules to enter the patient's
system than does a weak drug to produce a desired effect.
Accordingly, if rapid onset of bronchodilation is desired,
a potent rather than a weak drug could be used.

Additionally, the degree of lipophilicity of a drug
directly affects the rate of absorption of the drug. A
highly lipophilic drug will result in the more rapid onset of a desired patient response than will a more moderately lipophilic drug. For example, ergotrate is a very potent drug which is highly lipophilic. However, ergonovine is nearly twice as lipophilic as ergotrate and thus is capable of faster absorption. It will be appreciated, however, that other pharmacokinetic properties of a drug will affect the rate at which the effect of the drug is observed in the patient. For example, while oxytocin is not so lipophilic, its other pharmacokinetic properties make it extremely fast acting once it is absorbed into the bloodstream.

The choices of matrix and the concentration of the drug in the matrix are also important factors with respect to the rate of drug uptake. A matrix that dissolves quickly will deliver drug into the patient's mouth for absorption more quickly than a matrix that is slow to dissolve. Similarly, a candy that contains a drug in a high concentration will release more drug in a given period of time than a candy having a low drug concentration.

It will be appreciated that varying the concentrations of the drug in the matrix or the properties of the matrix (particularly the rate at which the matrix dissolves) can be advantageously used in designing specific compositions for specific uses. A lollipop containing meclizine of a given concentration may be used to relieve nausea, while a lollipop having a stronger concentration (and preferably a different color so as to prevent confusion) may be used when it is desired to relieve vomiting or emesis.

Another use of these properties is to prepare a multi-layer lollipop where the outer layer is of a concentration differing from that of the inner layer. Such a drug delivery system has a variety of applications. By way of example, it may be desirable to quickly get a predetermined dose of a drug into the bloodstream to obtain a desired
effect and then use a different concentration to maintain that effect.

The choice of a particular carbohydrate or compressed powder matrix is subject to wide variation. Conventional sweeteners such as sucrose or corn syrup may be utilized, or carbohydrates suitable for use with diabetic patients, such as sorbitol or mannitol might be employed. Other sweeteners, such as aspartame, can also be easily incorporated into a composition in accordance with the present invention. The candy base may be very soft and fast-dissolving, or may be hard and slower-dissolving. Various forms will have advantages in different situations.

It will be appreciated that all suitable drugs within the scope of the present invention may be prepared in the compressed powder form whereas only those drugs with relatively high melting points may be prepared in the more traditional hard candy form. It has been found that both forms operate in substantially the same way. Typical examples illustrating the method of preparing a hard candy matrix and a compressed powder candy matrix are given herein below.

EXAMPLE 1

The candy matrix or base for the drug-containing lollipop within the scope of the present invention is advantageously prepared utilizing candy preparation formulas and techniques which are known in the prior art. For example, a hard candy base is prepared by dissolving 50 grams of sucrose in 50 grams of water and heating the solution to about 240°F. Next, about 40 grams of corn syrup having a dextrose equivalent of 42 units, and a high maltose content (30%-35% maltose) is added, and the mixture is cooked at about 300°F to reduce the water content to about three percent (3%). After recooling the thickened
candy mass to about 240°F, a suitable oil flavoring (e.g., lemon or cherry) is added.

Concurrently, a solution containing a soluable drug is prepared for incorporation into a candy matrix. In this example, the drug selected is clotrimazole. Clotrimazole is a potent antifungal agent useful in treating oral candidiasis or monoliasis. Its high potency and lipophilicity make it an excellent drug for transmucosal administration in accordance with the present invention.

A suitable clotrimazole solution is prepared by dissolving 200 milligrams of clotrimazole in 10 cubic centimeters of sterile ethanol. This clotrimazole solution is mixed with 32 cubic centimeters of the hot candy mass formed as set forth above, and the resultant mixture is gently mixed as it cools to about 225°F, taking care not to induce formation of air bubbles in the candy mass.

The solution is then poured into suitable molds having a 2.0 cubic centimeter capacity that have been prelubricated with vegetable oil to prevent sticking. A four inch commercially available wax-coated compressed paper stick is next inserted into the base of each mold. The mixture is then permitted to set.

The foregoing procedure results in the preparation of 20 lollipops, each containing 10 milligrams of clotrimazole.

EXAMPLE 2

In this example, ergotamine is selected for incorporation into a compressed dosage form. Ergotamine is a potent lipophilic drug useful for relieving the pain associated with migraines. Its high potency and lipophilicity make it an excellent drug for transmucosal administration in accordance with the present invention.
A suitable matrix is prepared by combining 40 milligrams of ergotamine; 5.22 grams compressible sugar; 10.44 grams maltodextran; 300 milligrams ribotide, 400 milligrams aspartame, 800 milligrams compritol 888, 1.0 grams artificial vanilla cream, 200 milligrams natural mint; 600 milligrams cherry, and 1.0 grams artificial vanilla. Allocuats of 2000 milligrams each are then hydraulically compressed around a commercially available wax-coated compressed paper holder, using a force sufficient to provide a final volume of 2 cubic centimeters. The foregoing procedure results in the preparation of 10 lollipops, each containing 4 milligrams of ergotamine.

In addition to modifying the physical characteristics of the lollipop, the technique used by the patient to suck the lollipop may also be used to affect the rate of the absorption of the drug. If substantial portions of dissolved candy and drug are swallowed, the normal complications of oral administration will be encountered (i.e., slow response and loss of drug in the stomach and liver).

If the candy is sucked slowly with little production of saliva, very little drug will be swallowed, but a reduction in the amount of saliva will also cause a reduction in the rate at which the medicated candy dissolves. It will be appreciated that the technique of sucking utilized can have a significant effect on the rate of drug uptake into the patient's bloodstream.

Use of a lollipop, in contrast to a simple drop or pellet, helps control proper placement of the candy within the patient's mouth since the physician, nurse, or even the patient can manipulate the candy. Accordingly, the medical professional can easily monitor placement by observation of the angle of the protruding stick. Once a suitable tech-
nique for sucking the lollipop has been selected, the remaining factors can be adjusted accordingly.

It will be appreciated from the foregoing that the present invention has broad applicability to a variety of antimigraine, antiemetic, hypoglycemic, bronchodilator, oxytocic, anti-Parkinsonian, antidiuretic, antifungal, or antisecretory agents. For example, the present invention may be utilized in the administration of antimigraine agents such as ergotamine, methysergide, propranolol, or sulocitidil; bronchodilators such as albuterol, aminophylline, beclomethasone, dyphylline, epinephrine, flunisolide, isoetharine, isoproterenol HCl, metaproterenol, oxtriphylline, terbutaline, and theophylline; oxytocic agents such as ergonovine and oxytocin; anti-Parkinsonian agents such as carbidopa and levodopa; antidiuretics such as desmopressin acetate, lypressin, and vaspressin; antifungal agents such as clotrimazole and nystatin; antisecretory agents such as sucralfate; antiemetic agents such as benzquinamide, meclizine, metoclopramide, prochlorperazine, and trimethobenzamide; and hypoglycemic agents such as insulin.

It will be appreciated that other drugs may also be utilized within the scope of the present invention. What is important is that the drug be lipophilic, potent, and fast-acting so that the desired effects can be observed by the medical professional (or the patient himself if the drug is self-administered) in sufficient time to remove the lollipop from the patient's mouth in time to prevent overdosing.

In incorporating a drug into a lollipop within the scope of the present invention, the amount of the drug used will generally differ from the amount used in more traditional injection and oral administration techniques. Depending upon the lipophilic nature of the drug, its water
solubility, its potency, and its end use, the total concentration of the drug in a typical lollipop may contain from one to fifty times the amount of the drug which may be used in an injection.

However, for purposes of example, Table I sets forth presently contemplated ranges of the dosages of certain drugs which would typically be used.

Table I

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<thead>
<tr>
<th>Drug Generic</th>
<th>Lollipop Dose Range</th>
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<tbody>
<tr>
<td>Benzquinamide</td>
<td>25-100 milligrams</td>
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<tr>
<td>Meclizine</td>
<td>25-100 milligrams</td>
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<tr>
<td>Metoclopramide</td>
<td>5-20 milligrams</td>
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<tr>
<td>Prochlorperazine</td>
<td>5-25 milligrams</td>
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<tr>
<td>Trimethobenzamide</td>
<td>100-2500 milligrams</td>
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<tr>
<th>Drug Generic</th>
<th>Lollipop Dose Range</th>
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<tr>
<td>Clotrimazole</td>
<td>10-20 milligrams</td>
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<tr>
<td>Nystatin</td>
<td>100,000-500,000 units</td>
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<th>Drug Generic</th>
<th>Lollipop Dose Range</th>
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<tr>
<td>Carbidopa</td>
<td>with levodopa 10-50 milligrams</td>
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<tr>
<td>Levodopa</td>
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<table>
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<th>Drug Generic</th>
<th>Lollipop Dose Range</th>
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<tr>
<td>Sucralfate</td>
<td>1-2 grams</td>
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<td>Bronchodilator</td>
<td>Drug Generic</td>
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<td>Albuterol</td>
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<tr>
<td>10</td>
<td>Aminophylline</td>
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<tr>
<td>15</td>
<td>Beclomethasone</td>
</tr>
<tr>
<td>20</td>
<td>Dyphylline</td>
</tr>
<tr>
<td>25</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>30</td>
<td>Flunisolide</td>
</tr>
<tr>
<td>35</td>
<td>Isoetharine</td>
</tr>
<tr>
<td>40</td>
<td>Isoproterenol HCl</td>
</tr>
<tr>
<td>45</td>
<td>Metaproterenol</td>
</tr>
<tr>
<td>50</td>
<td>Oxtriphylline</td>
</tr>
<tr>
<td>55</td>
<td>Terbutaline</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antimigraine</th>
<th>Drug Generic</th>
<th>Lollipop Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Ergotamine</td>
<td>2-4 milligrams</td>
</tr>
<tr>
<td>30</td>
<td>Methysergide</td>
<td>2-4 milligrams</td>
</tr>
<tr>
<td>35</td>
<td>Propranolol</td>
<td>80-160 milligrams</td>
</tr>
<tr>
<td>40</td>
<td>Sulocitidil</td>
<td>200-300 milligrams</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxytocic</th>
<th>Drug Generic</th>
<th>Lollipop Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>Ergonovine</td>
<td>0.2-0.6 milligrams</td>
</tr>
<tr>
<td>40</td>
<td>Oxytocin</td>
<td>5-20 units</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antidiuretic</th>
<th>Drug Generic</th>
<th>Lollipop Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>Desmopressin</td>
<td>10-50 micrograms</td>
</tr>
<tr>
<td></td>
<td>acetate</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Lypressin</td>
<td>7-14 micrograms</td>
</tr>
<tr>
<td></td>
<td>Vaspressin</td>
<td>2.5-60 units</td>
</tr>
</tbody>
</table>
Hypoglycemic

Drug Generic  Lollipop Dose Range
Insulin  5-20 units

It will be appreciated from the foregoing that the present invention has broad applicability and will be useful in a wide variety of situations. It provides a useful alternative to the traditional oral and injection routes of administration, and permits the physician extraordinary control over the dosage of a potent antimigraine, antiemetic, bronchodilator, oxytocic, anti-Parkinsonian, antidiuretic, hypoglycemic, antifungal, or antisecretory drug that is administered to a patient.

Some of the more important features and advantages of the present invention as applied to the above drug classes will be better appreciated and understood by reference to the specific discussion below:

A. Antifungal Agents

Patients with compromised immunological function, extended antibiotic therapy, or a severely debilitating condition may experience systemic or oral fungal infections. Antifungal agents act by direct or intimate contact with the fungal cell wall and therefore the activity or effectiveness is directly proportional to the length of time of contact. The current topical methodology for oral candidiasis (fungal infection) uses either a rinsing solution or a troche (lozenge). Neither preparations possess the necessary palatability to provoke effective patient compliance. Consequently, they fail to eliminate the oral fungal infection which unnecessarily extends the patient's discomfort, pain, and period of therapy. Furthermore, an oral fungal infection may ultimately result in a life-threatening systemic fungal infection.
Alternatively, a lollipop containing an acceptably flavored antifungal preparation such as clotrimazole or nystatin can be kept in the mouth for an extended period of time before complete dissolution occurs. Patients that require such oral antifungal therapy can be instructed to use a drug-containing lollipop three times a day (versus the current five to six times a day) and usually, until all observed or perceived traces of the infection have disappeared. In the event of a reappearance of the oral fungal infection, therapy can be resumed.

There is a need for sustained or extended contact of the antifungal agent, such as clotrimazole, with the fungal organisms in order to bind with the phospholipids in the fungal cell membrane and thereby alter the cell membrane permeability, with subsequent loss of potassium and other cellular constituents.

Dissolution of a palatable oral preparation over 30 minutes should inhibit most species of candida for up to 3 hours. The long term effective concentration of clotrimazole in saliva appears to be related to the slow release of the drug from the oral mucosa to which the drug is apparently bound.

Thus, a clotrimazole-containing lollipop is an ideal mode of delivery, especially since patient compliance is based on patient acceptance and patient compliance can be directly translated into drug effectiveness. In current practice, the admonition "use till the symptoms are resolved" is questionable, as the candidiasis or monoliasis may not be cured until the underlying cause is resolved. This exposes the patient to a potentially life-threatening systemic fungal infection.

The clotrimazole-containing lollipop provides quick and effective treatment of an oral fungal infection. Elimination of the fungus is significantly fast than under
present treatment methods. Therefore, the patient is not subjected to more medication than is actually necessary to treat the infection. Thus, dose-to-effect drug administration is achieved; the patient receives just enough medication to eliminate the fungus and not any more than is needed.

Examples of compositions and methods of using lollipops containing anti-fungal agents are given herein below.

EXAMPLE 3

A drug-containing lollipop within the scope of the present invention to be used in the treatment of oral candidiasis is made according to the procedure of Example 2, except that the ingredients are combined in the following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotrimazole</td>
<td>1.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>Natural mint</td>
<td>1.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>Ribotide</td>
<td>1.5%</td>
<td>0.3</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2.0%</td>
<td>0.4</td>
</tr>
<tr>
<td>Wild cherry</td>
<td>3.0%</td>
<td>0.6</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>4.0%</td>
<td>0.8</td>
</tr>
<tr>
<td>Artificial vanilla</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Artificial vanilla cream</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Compressed sugar</td>
<td>25.83%</td>
<td>5.17</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>51.67%</td>
<td>10.33</td>
</tr>
</tbody>
</table>

The foregoing procedure results in the preparation of 10 lollipops, each containing 20 milligrams of clotrimazole.

EXAMPLE 4

In the procedure of this example, a patient who is presently experiencing oral candidiasis is given a
clotrimazole-containing lollipop in order to rapidly relieve the oral candidiasis. In this example, clotrimazole in a lollipop dose of 20 milligrams is used. As the patient sucks on the lollipop, regression of the plaque within the oral cavity is observed.

Although the above discussion focused on the antifungal agent clotrimazole, it will be appreciated that other antifungal drugs may also be utilized within the scope of the present invention. What is important is that the antifungal drug be lipophilic, potent, and fast-acting so that the desired effects can be observed by the medical professional or by the patient himself, if the drug is to be self-administered, in sufficient time to remove the lollipop from the patient's mouth in time to prevent overdosing.

B. Antisecretory Agents

Reflux of small amounts of gastric juice into the lower part of the esophagus is a common event. Its frequency is increased by overindulgence. Whether or not reflux occurs and whether it produces symptoms are determined by three factors: (1) the competency of the lower esophageal sphincter, the primary barrier to reflux; (2) the irritant nature of the refluxed material; and (3) the sensitivity of the esophageal mucosa to the refluxed
material. In the past, the symptoms of reflux were attributed to inflammation of the esophagus, i.e., esophagitis. Today, it is clear that esophagitis is a complication of severe reflux of acidic gastric juice rather than being the cause of the symptoms associated with reflux. It appears that the competency of the lower esophageal sphincter correlates well with the presence or absence of reflux.

Heartburn, the typical symptom of reflux, is characterized by a burning epigastric or retrosternal pain which spreads upward. Typically, heartburn appears after meals, especially large meals, and is aggravated by bending over, lying down, or straining. It is relieved by standing up or drinking something, usually antacids.

In the treatment of esophagitis, the medication from a swallowed tablet is expected to be refluxed up into the esophagus and absorbed onto the eroded tissue. However, aluminum sucrose sulfate (a minimally absorbed sulfated disaccharide known as "sucralfate") is essentially insoluble in water, and very little, if any, is refluxed into the esophagus. Aluminum sucrose sulfate suspensions are also used, but because the downward transit time is very short, perhaps three seconds, they are barely more effective than refluxed aluminum sucrose sulfate. Furthermore, in the final phase of swallowing, the
esophagus is swept clean by a peristaltic wave proceeding from the pharynx to the lower esophageal sphincter. Consequently, neither mode of administration is effective in delivering aluminum sucrose sulfate to the eroded tissue areas.

Antisecretory agents such as aluminum sucrose sulfate are used in the treatment of gastric and duodenal ulcers. Although not as lipophilic as some of the other drugs discussed herein, sucralfate exhibits a distinct and unique preferential absorbent action to the protein molecules in damaged esophageal, gastric, and duodenal mucosal wall tissues. It forms an adherent and protective chemical complex with proteins at the site of ulceration which protects the ulcer from pepsin, acid, and bile. Sucralfate also exhibits an ability to absorb bile acids.

The same regimen (a one-gram tablet swallowed four times a day) is commonly used to treat esophagitis, injection sclerosis, and gastroesophageal reflux.

A drug-containing lollipop in accordance with the present invention may effectively treat gastric and duodenal ulcers, as well as esophagitis, injections sclerosis, and gastroesophageal reflux. This modality provides for the gradual dissolution of the agent (aluminum sucrose sulfate), mixed with, and aided by, the viscosity of the saliva, allowing it to slowly but constantly trickle
down the esophagus, and thereby allowing for the adhesion to the eroded tissue. The effectiveness of the therapy can be symptomatically assessed and controlled by the patient thereby providing dose-to-effect modality.

Examples of compositions and methods of using lollipops containing antisecretory agents are given herein below.

**EXAMPLE 5**

A drug-containing lollipop within the scope of the present invention to be used in the treatment of the symptoms of esophagitis is made according to the procedure of Example 2, except that the ingredients are combined in the following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural mint</td>
<td>1.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>Ribotide</td>
<td>1.5%</td>
<td>0.3</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2.0%</td>
<td>0.4</td>
</tr>
<tr>
<td>Wild cherry</td>
<td>3.0%</td>
<td>0.6</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>4.0%</td>
<td>0.8</td>
</tr>
<tr>
<td>Artificial vanilla</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Artificial vanilla cream</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Compressed sugar</td>
<td>9.5%</td>
<td>1.9</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>19.0%</td>
<td>3.8</td>
</tr>
<tr>
<td>Al. sucrose sulfate</td>
<td>50.0%</td>
<td>10.0</td>
</tr>
</tbody>
</table>

The foregoing procedure results in the preparation of 10 lollipops, each containing 1 gram of aluminum sucrose sulfate.
EXAMPLE 6

In the procedure of this example, a patient who is presently experiencing the symptoms of esophagitis is given an aluminum sucrose sulfate-containing lollipop in order to rapidly relieve the symptoms of esophagitis. In this example, aluminum sucrose sulfate in a lollipop dose of 1.0 gram is used. As the patient sucks on the lollipop, the pain associated with esophagitis or heartburn is rapidly relieved.

Although the above discussion focused on the antisecretory agent aluminum sucrose sulfate as a treatment for esophagitis or heartburn, it will be appreciated that other antisecretory drugs may also be utilized within the scope of the present invention. What is important is that the antisecretory agent be lipophilic, potent, and fast-acting so that the desired effects can be observed by the medical professional or by the patient himself, if the drug is to be self-administered, in sufficient time to remove the lollipop from the patient's mouth in time to prevent overdosing.
C. Bronchodilator Agents

Respiratory smooth muscle relaxants are used to produce relief of bronchospasm and increase respiratory flow rates and vital capacity. Theophylline is a typical bronchodilator commonly used for the symptomatic treatment of asthma and reversible bronchospasm that may occur in association with chronic bronchitis or emphysema.

Following oral administration of theophylline capsules or uncoated tablets, peak serum concentrations are usually reached in one to two hours. Peak serum theophylline concentrations are usually obtained after about one hour when theophylline oral solutions or microcrystalline tablets are administered. Absorption of theophyllines may be delayed, but generally not reduced, by the presence of food in the gastrointestinal tract. When administered intramuscularly, theophylline is usually absorbed slowly and incompletely. In addition, rectal suppositories are slowly and erratically absorbed.

In maintenance-dose theophylline schedules, serum concentrations among patients vary at least six-fold and serum half-lives exhibit wide interpatient variation because of differences in the rate of metabolism. (The elimination half-life is the time required for the plasma drug concentration to decrease by one-half.) Serum half-life ranges from about 3 to 12.8 (average 7-9 hours) in
otherwise healthy, nonsmoking asthmatic adults, from about 1.5 to 9.5 hours in children, and from about 15 to 58 hours in premature infants.

When compared with that of otherwise healthy nonsmoking asthmatic adults, the serum half-life of theophylline may be increased and total body clearance decreased in patients with congestive heart failure, chronic obstructive pulmonary disease, cor pulmonale, or liver disease, and in geriatric patients. In cigarette and/or marijuana smokers, theophylline serum half-life averages 4-5 hours and total body clearance is increased compared with nonsmokers.

Therefore, due to the wide variation in patient metabolism of theophylline to administer to proper dose required by each patient. Too much theophylline may result in nausea, vomiting, headache, nervousness, seizures, sinus tachycardia, hypotension, circulatory failure or ventricular arrhythmias. If insufficient theophylline is administered, the respiratory distress continues, which can be as serious as receiving an overdose.

Hence, a theophylline-containing lollipop administered in a dose-to-effect manner would be capable of providing rapid relief of asthma or bronchospasm associated with respiratory distress. The precise dosage necessary to achieve a precise effect in each individual patient could
be provided thereby substantially reducing the risk of
severe consequences associated with an underdose or
overdose. Thus, the wide variation in the rate of
metabolism from patient to patient would be accounted for
by the dose-to-effect modality.

Examples of compositions and methods of using
lollipops containing bronchodilator agents are given herein
below.

EXAMPLE 7

A drug-containing lollipop within the scope of the
present invention to be used in the treatment of
respiratory distress is made according to the procedure of
Example 2, except that the ingredients are combined in the
following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural mint</td>
<td>1.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>Ribotide</td>
<td>1.5%</td>
<td>0.3</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2.0%</td>
<td>0.4</td>
</tr>
<tr>
<td>Wild cherry</td>
<td>3.0%</td>
<td>0.6</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>4.0%</td>
<td>0.8</td>
</tr>
<tr>
<td>Artificial vanilla</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Artificial vanilla cream</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Oxtriphylline</td>
<td>10.0%</td>
<td>2.0</td>
</tr>
<tr>
<td>Compressed sugar</td>
<td>22.83%</td>
<td>4.57</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>45.67%</td>
<td>9.13</td>
</tr>
</tbody>
</table>

The foregoing procedure results in the preparation of 10
lollipops, each containing 200 milligrams of oxtriphylline.
EXAMPLE 8

In the procedure of this example, a patient who is presently experiencing the respiratory distress is given an oxtriphylline-containing lollipop in order to rapidly relieve the respiratory distress. In this example, oxtriphylline in a lollipop dose of 200 milligrams is used. As the patient sucks on the lollipop, the symptoms of respiratory distress are rapidly relieved and the patient returns to more normal respiratory function.

EXAMPLE 9

A drug-containing lollipop within the scope of the present invention to be used in the treatment of respiratory distress is made according to the procedure of Example 1, except that an oxtriphylline solution, in which 4 grams of oxtriphylline is dissolved in 10 cubic centimeters of water, is substituted for the clotrimazole solution. This procedure results in the preparation of 20 lollipops, each containing 200 milligrams of oxtriphylline.

Although the above discussion focused on the bronchodilators theophylline and oxtriphylline, it will be appreciated that other bronchodilators may also be utilized within the scope of the present invention. What is important is that the bronchodilator be lipophilic, potent, and
fast-acting so that the desired effects can be observed by
the medical professional or by the patient himself, if the
drug is to be self-administered, in sufficient time to
remove the lollipop from the patient's mouth in time to
prevent overdosing.

D. Antimigraine Agents

Migraines refer to sudden periodic attacks of
throbbbing headaches which begin in childhood, adolescence,
or early adult life and continue to reoccur with
diminishing frequency during advancing years. A migraine
may last from about five minutes to fifteen minutes,
followed by hemicranial headache, nausea, and vomiting, all
of which last for hours or as long as a day or two.

The drug ergotamine provides symptomatic relief from
the pain of a migraine. Ergotamine is usually administered
orally or sublingually, 2 milligrams taken as soon as the
headache starts, with subsequent doses of 2 milligrams at
intervals of 30 minutes thereafter, if necessary, until a
total of 6 milligrams has been taken. No more than 10
milligrams should be ingested per week. Since overdosage
is the chief cause of untoward effects from ergotamine, the
smallest amount effective for relief of the headache should
be employed.
The speed and thoroughness of the relief from pain are directly proportional to the promptness with which medication is started after the onset of an attack. If the drug is given early, the dose may be decreased considerably. But if the headache has reached its peak, large quantities of ergotamine are needed. Not only is a longer time than required for effective action needed, but also undesirable side effects from this medication are more pronounced.

An ergotamine-containing lollipop administered in a dose-to-effect manner provides the precise dosage necessary to obtain rapid symptomatic relief from migraine pain while at the same time minimizing potential side effects.

Examples of compositions and methods of using lollipops containing antimigraine agents are given herein below.

EXAMPLE 10

A drug-containing lollipop within the scope of the present invention to be used in the treatment of a migraine is made according to the procedure of Example 2, except that the ingredients are combined in the following amounts:
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural mint</td>
<td>1.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>Ribotide</td>
<td>1.5%</td>
<td>0.3</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2.0%</td>
<td>0.4</td>
</tr>
<tr>
<td>Wild cherry</td>
<td>3.0%</td>
<td>0.6</td>
</tr>
<tr>
<td>Propranolol</td>
<td>4.0%</td>
<td>0.8</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>4.0%</td>
<td>0.8</td>
</tr>
<tr>
<td>Artificial vanilla</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Artificial vanilla cream</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Compressed sugar</td>
<td>25.33%</td>
<td>5.07</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>50.67%</td>
<td>10.13</td>
</tr>
</tbody>
</table>

The foregoing procedure results in the preparation of 10 lollipops, each containing 80 milligrams of propranolol.

**EXAMPLE 11**

In the procedure of this example, a patient who is presently experiencing the pain associated with a migraine is given an ergotamine-containing lollipop in order to rapidly relieve the pain associated with the migraine. In this example, ergotamine in a lollipop dose of 4 milligrams is used. As the patient sucks on the lollipop, the pain associated with the migraine is rapidly relieved.

Although the above discussion focused on the antimigraine agents ergotamine and propranolol, it will be appreciated that other antimigraine agents may also be utilized within the scope of the present invention. What is important is that the antimigraine agent be lipophilic, potent, and fast-acting so that the desired effects can be observed by the medical professional or by the patient.
himself, if the drug is to be self-administered, in sufficient time to remove the lollipop from the patient's mouth in time to prevent overdosing.

E. Antiemetic Agents

Nausea and vomiting may occur independently of each other, but generally they are so closely related that they can be considered together. Nausea denotes the feeling of the imminent desire to vomit, while vomiting refers to the forceful oral expulsion of gastric contents. Nausea often precedes or accompanies vomiting and is usually associated with diminished functional activity of the stomach and alterations of the motility of the duodenum and small intestine. Increased perspiration, salivation, and the occasional association of hypotension and bradycardia often accompanies severe nausea.

The stomach plays a relatively passive role in the vomiting process, the major ejection force being provided by the abdominal musculature. Repeated emesis (vomiting) may have deleterious effects in a number of ways. The process of vomiting itself may lead to traumatic rupture or tearing of the region of the cardioesophageal junction, resulting in massive hematemesis (the vomiting of blood).

Prolonged vomiting may also lead to dehydration and the loss of gastric secretions, particularly hydrochloric
acid, and metabolic alkalosis and the potentially dangerous loss of potassium. In states of central nervous system depression, such as coma, the gastric contents may actually be aspirated into the lungs, with a resulting aspiration pneumonitis.

The act of vomiting is under the control of two functionally distinct medullary (central nervous system) centers: the vomiting center and the chemoreceptor zone. The vomiting center controls and integrates the actual act of emesis, receiving stimuli from the intestinal tract, the labyrinthine apparatus in the ear, the chemoreceptor zone and other parts of the body. The chemoreceptor trigger zone is also located in the medulla. Activation of this zone initiates impulses to the medullary vomiting center which then initiates the act of emesis. The chemoreceptor trigger zone can be activated by many stimuli, including drugs such as morphine, codeine, cardiac glycosides (digoxin) and ergot alkaloids (ergotamine) and a great many antineoplastic agents. Nausea and vomiting are common manifestations of organic and functional disorders.

Table II provides examples of many disorders which may be accompanied by nausea and vomiting.
Table II

1. acute abdominal emergencies (i.e., acute appendicitis, cholecystitis)
2. chronic indigestion
3. acute infectious diseases accompanied with fever, especially in young children
4. disorders of the nervous system, especially the central nervous system
5. heart diseases such as acute myocardial infarction, especially of the posterior wall of the heart
6. metabolic and endocrine disorders, including diabetic acidosis
7. drugs and chemicals
8. emotional stress may lead to psychogenic vomiting

As described above, nausea and subsequent vomiting is not only an undesirable sensation, it can be severely debilitating and even life threatening in some cases. There are currently only three modalities used to deliver the drugs to ameliorate nausea and vomiting. These are oral (tablets or liquids), intramuscular or intravenous injection, and rectal.

For rapid onset of antiemetic action, the intramuscular or intravenous route is preferred. But it is only rarely available outside of medical facilities, and even then, being an injection, it is the least appealing. The rectal route can be effective, but it is unpredictable at best, due to the variability and placement of the
suppository and subsequent rapid liver metabolism. The oral route is the easiest, but as is usually the case, the antiemetic agent in tablet or solution is expectorated with the emesis before dissolution or absorption can take place.

A lollipop into which a suitable antiemetic agent has been dispersed when administered in a dose-to-effect manner provides a delivery method superior to current methods. Transmucosal administration provides for absorption of the antiemetic agent almost as fast as by the intravenous route. Having a handle, an antiemetic-containing lollipop may be quickly removed from the mouth in the case of unanticipated emesis. Further, transmucosal administration bypasses immediate hepatic metabolism which occurs with oral administration. More importantly, the antiemetic agent cannot be expectorated during transmucosal administration, which usually occurs after oral ingestion of an antiemetic agent. Finally, a drug-containing lollipop administered in a dose-to-effect manner is a highly acceptable mode of delivery.

Examples of compositions and methods of using lollipops containing antiemetic agents are given herein below.

**EXAMPLE 12**
A drug-containing lollipop within the scope of the present invention to be used in the treatment of nausea and vomiting is made according to the procedure of Example 2, except that the ingredients are combined in the following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural mint</td>
<td>1.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>Ribotide</td>
<td>1.5%</td>
<td>0.3</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2.0%</td>
<td>0.4</td>
</tr>
<tr>
<td>Meclizine</td>
<td>2.5%</td>
<td>0.5</td>
</tr>
<tr>
<td>Wild cherry</td>
<td>3.0%</td>
<td>0.6</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>4.0%</td>
<td>0.8</td>
</tr>
<tr>
<td>Artificial vanilla</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Artificial vanilla cream</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Compressed sugar</td>
<td>25.33%</td>
<td>5.07</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>50.67%</td>
<td>10.13</td>
</tr>
</tbody>
</table>

The foregoing procedure results in the preparation of 10 lollipops, each containing 50 milligrams of meclizine.

**EXAMPLE 13**

In the procedure of this example, a patient who is presently experiencing nausea and vomiting is given a meclizine-containing lollipop in order to rapidly relieve the nausea and vomiting. In this example, meclizine in a lollipop dose of 50 milligrams is used. As the patient sucks on the lollipop, the distress associated with nausea and vomiting is eliminated.

Although the above discussion focused on the antiemetic agent meclizine, it will be appreciated that other antiemetic agents may also be utilized within the
scope of the present invention. What is important is that the antiemetic agent be lipophilic, potent, and fast-acting so that the desired effects can be observed by the medical professional or by the patient himself, if the drug is to be self-administered, in sufficient time to remove the lollipop from the patient's mouth in time to prevent overdosing.

F. Antidiuretic Agents

Diabetes insipidus is a chronic symptom complex characterized by the passage of large quantities of pale, dilute urine with secondary excessive thirst. It results from a defect in a chain of events by which vasopressin is released from the neurohypophysis (the posterior part of the pituitary gland) and acts on the cells of the renal tubules. Diabetes insipidus was a rare disease, but with the advent of hypophysectomy in recent years for the treatment of far-advanced breast cancer and other serious disorders, the disease is becoming much more prevalent in the general hospital population.

The chief symptoms of diabetes insipidus are excessive production of urine (polyuria) and excessive thirst. The loss of large quantities of pale, dilute urine, occasionally as much as 15-29 liters per day, results in dehydration and consequently, such related symptoms as dry
skin, constipation, and an intense, almost insatiable thirst. Water deprivation to the limit of tolerance does not prevent polyuria. No consistent physical or chemical changes are noted other than those of dehydration and low urine specific gravity. However, there may be symptoms referable to the localized disease process causing the syndrome.

The role of trauma in the production of diabetes insipidus deserve special comment, since the polyuria that sometimes follows head injury is frequently transient, in contrast with the chronicity of most other forms of the disease. A similar syndrome may develop subsequent to cerebrovascular accidents or intracranial surgery and in association with other forms of cerebral disease. When the full-blown syndrome develops under these conditions, serious dehydration may occur before the diagnosis is suspected.

Treatment of diabetes insipidus may be divided into two phases: (1) correction of the underlying intracranial difficulty, if present; and (2) replacement therapy with vasopressin, which usually must be continued throughout life. Current treatment consists of intranasal administra-

Desmopressin acetate or lypressin solution should be administered intranasally with care to insure that the drug
is deposited high in the nasal cavity and yet does not pass either down the throat or too high into the sinuses. Although intranasal administration of the drug is preferred for chronic therapy, parenteral administration of the drug may be necessary when other factors make nasal administration ineffective or inappropriate. Such factors may include poor intranasal absorption, nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. In addition, parenteral administration is also necessary when the patient has an impaired level of consciousness, during recovery from surgery, or when nasal packing is present.

The lowest effective intranasal or parenteral dosage should always be given. Adverse effects of this nasal delivery system include rhinorrhea, nasal congestion, irritation with a burning sensation, and pruritus of the nasal passages, nasal ulceration, headache, and dizziness.

A lollipop into which a suitable antidiuretic has been dispersed administered in a dose-to-effect manner provides an ideal method for treating polyuria. In particular, an antidiuretic-containing lollipop administered in a dose-to-effect manner rapidly introduces the antidiuretic into the bloodstream yet avoids the inconvenience and adverse consequences associated with nasal delivery.
Dose-to-effect administration permits the patient to receive just enough of the antidiuretic to decrease the patient's urine output while avoiding an overdose with its serious side effects.

Examples of compositions and methods of using lollipops containing antidiuretic agents are given herein below.

**EXAMPLE 14**

A drug-containing lollipop within the scope of the present invention to be used in the treatment of the symptoms associated with polyuria is made according to the procedure of Example 2, except that the ingredients are combined in the following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmopressin</td>
<td>0.001</td>
<td>0.0002</td>
</tr>
<tr>
<td>Natural mint</td>
<td>1.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>Ribotide</td>
<td>1.5%</td>
<td>0.3</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2.0%</td>
<td>0.4</td>
</tr>
<tr>
<td>Wild cherry</td>
<td>3.0%</td>
<td>0.6</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>4.0%</td>
<td>0.8</td>
</tr>
<tr>
<td>Artificial vanilla</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Artificial vanilla cream</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Compressed sugar</td>
<td>26.17%</td>
<td>5.234</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>52.33%</td>
<td>10.47</td>
</tr>
</tbody>
</table>

The foregoing procedure results in the preparation of 10 lollipops, each containing 20 micrograms of desmopressin.

**EXAMPLE 15**
In the procedure of this example, a patient who is presently experiencing the symptoms of polyurea is given a desmopressin-containing lollipop in order to rapidly relieve the symptoms of polyuria. In this example, desmopressin in a lollipop dose of 20 micrograms is used. As the patient sucks on the lollipop, a rapid decrease in urine output is observed.

Although the above discussion focused on the antidiuretics desmopressin and lypressin, it will be appreciated that other antidiuretic drugs may also be utilized within the scope of the present invention. What is important is that the antidiuretic drug be lipophilic, potent, and fast-acting so that the desired effects can be observed by the medical professional or by the patient himself, if the drug is to be self-administered, in sufficient time to remove the lollipop from the patient's mouth in time to prevent overdosing.

G. Anti-Parkinsonian Agents

The therapeutic management of Parkinson's disease is a complex problem in which drug therapy plays a major role. In Parkinson's disease, the lenticular nuclei and globus pallidus have a reduced content of dopamine, serotonin, and norepinepherine. The quantity of L-dopa (levodopa) in the striatum and substantia nigra is also decreased, lending
support to the idea that Parkinson's disease is a disorder of a particular neuronal (central nervous system) system.

In its fully developed form, Parkinson's disease cannot be mistaken for any other. The victim exhibits stooped posture, stiffness and slowness of movement, a fixed facial expression, and rhythmic tremor of the limbs which subsides on active willed movement or complete relaxation.

Also typical are more or less general hypokinesia (slow reflexes) and stiffness of the musculature. Even where tremor is inapparent, the disease may still be indicated by a staring and immobile facial expression, a monotonous voice, a general slowness and decrease of all motor activity, and a curious lack of the little spontaneous movements of postural change that are characteristic of the normal individual.

When tremor is minimal, patients often are able to alleviate it by resting their hands on a table or on the arms of a chair or by keeping them in their pockets. The tremor is generally most pronounced in the hands but may involve also the legs, lips, tongue, and neck muscles, and is easily seen in the eyelids when they are lightly closed.

There is no total paralysis, although general enfeeblement of voluntary movement is characteristic of the fully developed disorder. Together with the stooped
attitude, there is the typical gait, whereby the patient, prevented by the abnormality of postural tone from making the appropriate reflex adjustments required for effective walking, progresses with the quick, shuffling steps at an accelerating pace as if to catch up with the center of gravity. Intellectual deterioration is not a consistent feature of Parkinsonism, but it must be conceded that in the very advanced stages of the condition, dementia may be encountered.

Although there is no treatment that is known to halt or reverse the neuronal degeneration that presumably underlies Parkinson's disease, current methods do attempt to bring about a considerable degree of relief from symptoms in many patients.

At the present, levodopa is unquestionably the most effective method available. Although rapidly absorbed from the gastrointestinal tract, less than one percent of absorbed levodopa penetrates into the central nervous system (the site of action) where it is converted to dopamine (which does not cross the blood-brain barrier). It is then metabolized such that 85% of the dose is excreted as dopamine metabolites in the urine within 24 hours. The plasma half-life of levodopa is approximately one hour.
The adverse reactions are usually dose-related and included: nausea, vomiting, involuntary movement, gastrointestinal bleeding, duodenal ulcers, epigastric abdominal distress, and mild to severe central nervous system disturbances. The dosage requirement of levodopa can be reduced with simultaneous administration of carbidopa. Levodopa, with or without carbidopa, completely or partially relieves akinesia, rigidity, and tremor in about 80% of patients treated.

Akinesia paradoxica, a sudden hypnotic freezing in which the patient frequently falls because he becomes akinetic just as he starts to walk, may be relieved by reducing the dosage of levodopa. Although the cause of these episodes has not been precisely determined, it appears that they may result from a combination of progression of the disease and excessive levodopa dosage.

The "on-off" phenomenon is a sudden loss of effectiveness of levodopa with an abrupt onset of akinesia ("off" effect) which may last from one minute to an hour, followed by an equally sudden return to effectiveness ("on" effect); this may occur many times daily. At present, this can occasionally be minimized by increasing the number of doses per day.

A levodopa-containing lollipop administered in a dose-to-effect manner reduces the total dose of levodopa
required and minimizes related side effects. In addition, a lower but effective dose of levodopa can protect against potentially compromised renal and hepatic functions, particularly in the geriatric patient. Furthermore, the patient can be instructed to optimally utilize the dose-to-effect modality in order to avoid the "on-off" effect, or use the dose-to-effect modality during the "on-off" experiences.

Examples illustrating compositions and methods of using lollipops containing levodopa and carbidopa are given herein below.

**EXAMPLE 16**

A drug-containing lollipop within the scope of the present invention to be used in the treatment of the symptoms of Parkinson's disease is made according to the procedure of Example 2, except that the ingredients are combined in the following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural mint</td>
<td>1.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>Carbidopa</td>
<td>1.25%</td>
<td>0.25</td>
</tr>
<tr>
<td>Ribotide</td>
<td>1.5%</td>
<td>0.3</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2.0%</td>
<td>0.4</td>
</tr>
<tr>
<td>Wild cherry</td>
<td>3.0%</td>
<td>0.6</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>4.0%</td>
<td>0.8</td>
</tr>
<tr>
<td>Artificial vanilla</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Artificial vanilla cream</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Levodopa</td>
<td>12.5%</td>
<td>2.5</td>
</tr>
<tr>
<td>Compressed sugar</td>
<td>21.58%</td>
<td>4.32</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>43.17%</td>
<td>8.63</td>
</tr>
</tbody>
</table>
The foregoing procedure results in the preparation of 10 lollipops, each containing 25 milligrams of carbidopa and 250 milligrams of levodopa.

EXAMPLE 17

In the procedure of this example, a patient who is presently inflicted with Parkinson's disease is given a levodopa/carbidopa-containing lollipop in order to rapidly relieve the symptoms of Parkinson's disease. In this example, levodopa in a lollipop dose of 250 milligrams and carbidopa in a lollipop dose of 25 milligrams is used. As the patient sucks on the lollipop, the symptoms associated with Parkinson's disease are rapidly reduced.

Although the above discussion focused on the anti-Parkinsonian drugs levodopa and carbidopa, it will be appreciated that other anti-Parkinsonian drugs may also be utilized within the scope of the present invention. What is important is that the anti-Parkinsonian drug be lipophilic, potent, and fast-acting so that the desired effects can be observed by the medical professional or by the patient himself, if the drug is to be self-administered, in sufficient time to remove the lollipop from the patient's mouth in time to prevent overdosing.

H. Oxytocic Agents
The dramatic effect of ergot (a drug obtained from a species of rye fungus) ingested during pregnancy has been recognized for over two thousand years, and it was first used by physicians as an oxytocic agents almost four hundred years ago. All the natural alkaloids of ergot markedly increase the motor activity of the uterus. The character of the changes elicited is related to the dose administered. After small doses, contractions are increased in force or frequency, or both, but are followed by a normal degree of relaxation. After larger doses, contractions become forceful and prolonged and resting tonus is increased. Very high doses can cause sustained contracture.

The sensitivity of the uterus to ergot alkaloids varies, especially with the degree of maturity and the stage of gestation, but even an immature uterus is stimulated. The gravid uterus, however, is very sensitive. Even small doses of ergot alkaloids can be given at term or immediately post partum to obtain a marked uterine response. The mechanism of activation is one of direct stimulation.

All natural ergot alkaloids have qualitatively the same effect on the uterus, but they exhibit important differences in potency. Ergonovine is the most active of all. Among the amino acid alkaloids, ergotamine is by far
the most potent. However, when ergotamine is used clinically, there is an appreciable latent period between its intravenous administration and the onset of uterine activity. This is not true for ergonovine, which manifests its activity almost immediately. Furthermore, ergonovine is active after oral administration, whereas ergotamine is not. Finally, ergonovine is much less toxic than ergotamine.

Oxytocin is an octapeptide hormone secreted by the neurons of the supraoptic and paraventricular nuclei of the hypothalamus and is stored in the posterior pituitary (neurohypophysis) in mammals. Oxytocin indirectly stimulates contraction of uterine smooth muscle by increasing the sodium permeability of uterine myofibrils.
Uterine response to oxytocin increases with the duration of pregnancy and is greater in patients who are in labor than in those not in labor. Only very large doses elicit contractions in early pregnancy. Contractions produced in the term uterus by oxytocin are similar to those occurring during spontaneous labor. In the term uterus, oxytocin increases the amplitude and frequency of uterine contractions which in turn tends to decrease cervical activity producing dilation and effacement of the cervix and also tends to transiently impede uterine blood flow. In addition oxytocin contracts myoepithelial cells surrounding the alveoli of the breasts, forcing milk from the alveoli into the larger ducts and thus facilitating milk ejection. Oxytocin is destroyed by chymotrypsin in the gastrointestinal tract.

Uterine response occurs almost immediately and subsides within one hour following intravenous administration of oxytocin. Following intramuscular injection of the drug, uterine response occurs within three to five minutes and persists for two to three hours. Following intranasal application of oxytocin, contractions of the myoepithelial tissue surrounding the alveoli of the breasts begin within a few minutes and continue for twenty minutes. Intravenous oxytocin produces the same effect as intranasal oxytocin, but with a dose one hundred times less. Intranasal
Oxytocin may also be of some value in cases of post partum breast engorgement. Oxytocin has a plasma half-life of about three to five minutes, since most of the drug is rapidly destroyed in the liver and kidneys. Only small amounts of oxytocin are excreted in the urine unchanged.

Incorporating an oxytocin drug into a lollipop for transmucosal dose-to-effect administration can be used to produce controlled contractions of the uterus for the induction of labor. The drug-containing lollipop could also augment contractions if labor is prolonged during the first and second stages of labor, or it may be used to shorten the third stage of labor immediately following delivery of the infant.

Importantly, the drug-containing lollipop administered in a dose-to-effect manner would provide just enough oxytocin agent at critical stages of labor to facilitate proper childbirth. Too much oxytocin agent could be dangerous to both mother and child.

Examples of compositions and methods of using lollipops containing oxytocin agents are given herein below.

EXAMPLE 18

A drug-containing lollipop within the scope of the present invention to be used in order to induce labor or
reduce postpartum hemorrhage is made according to the procedure of Example 2, except that the ingredients are combined in the following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocin</td>
<td>0.001%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Natural mint</td>
<td>1.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>Ribotide</td>
<td>1.5%</td>
<td>0.3</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2.0%</td>
<td>0.4</td>
</tr>
<tr>
<td>Wild cherry</td>
<td>3.0%</td>
<td>0.6</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>4.0%</td>
<td>0.8</td>
</tr>
<tr>
<td>Artificial vanilla</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Artificial vanilla cream</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Compressed sugar</td>
<td>26.17%</td>
<td>5.234</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>52.33%</td>
<td>10.466</td>
</tr>
</tbody>
</table>

The foregoing procedure results in the preparation of 10 lollipops, each containing 20 micrograms of oxytocin.

**EXAMPLE 19**

In the procedure of this example, a patient is given an oxytocin-containing lollipop in order to induce labor or induce postpartum hemorrhage. In this example, oxytocin in a lollipop dose of 20 micrograms is used. As the patient sucks on the lollipop, labor is induced or postpartum hemorrhaging is stopped.

Although the above discussion focused on the oxytocic agents ergonovine and oxytocin, it will be appreciated that other oxytocic drugs may also be utilized within the scope of the present invention. What is important is that the oxytocic drug be lipophilic, potent, and fast-acting so
that the desired effects can be observed by the medical professional or by the patient himself, if the drug is to be self-administered, in sufficient time to remove the lollipop from the patient's mouth in time to prevent overdosing.

G. Hypoglycemic Agents

Insulin is a hormone produced by the beta cells of the pancreatic Islets of Langerhans. The diabetic syndrome is characterized by an absolute or relative lack of circulating insulin. It develops as a consequence of in imbalance between insulin production and release on the one hand, and hormonal or tissue factors modifying the insulin requirement on the other hand. Insulin is absolutely lacking in those forms of secondary diabetes in which destruction or removal of the pancreas has taken place. Similarly, overt growth-onset diabetes is characterized by insulin deficiency. Regardless of the type of diabetes, by definition the cardinal sign is hyperglycemia, frequently associated with glycosuria (glucose in the urine).

Exogenous insulin elicits all the pharmacological responses usually produced by endogenous insulin. Insulin stimulates carbohydrate metabolism in skeletal and cardiac muscle and adipose tissue by facilitating transport of glucose into these cells. In the liver, insulin
facilitates phosphorylation of glucose to glucose-D6-phosphate which is converted to glycogen or further metabolized.

Insulin also has a direct effect on fat and protein metabolism. The hormone stimulates lipogenesis and inhibits lipolysis and releases the free fatty acids from disposed cells. Insulin also stimulates protein synthesis. In addition, insulin promotes an intracellular shift of potassium and magnesium, thereby temporarily decreasing elevated blood concentrations of these ions.

Administration of suitable doses of insulin to patients with insulin-dependent (type 1) diabetes mellitus temporarily restores their ability to metabolize carbohydrates, fats, and proteins, to store glucose in the liver, and to convert glycogen to fat. When insulin is given in suitable doses at regular intervals to a patient with diabetes mellitus, blood glucose is maintained at a reasonable concentration, the urine remains relatively free of glucose and ketone bodies and diabetic acidosis and coma are prevented.

Because of its protein nature, insulin is destroyed in the gastrointestinal tract and must be administered parenterally. Following subcutaneous or intramuscular administration, insulin is absorbed directly into the blood. The rate of absorption depends on many factors,
including the route of administration, site of injection, volume and concentration of the injection, and the type of insulin.

Hyperinsulinism, resulting in hypoglycemia, may occur in patients with brittle diabetes or in patients who have received an overdose of insulin, a decreased or delayed food intake, or an excess amount of exercise in relation to the insulin dose. Mild hypoglycemia may be relieved by oral administration of carbohydrates such as orange juice. Insulin is usually administered by subcutaneous injection and is preferred to intramuscular administration because it provides more prolonged absorption and is less painful.

An insulin-containing lollipop within the scope of the present invention would be capable of rapid action and would provide a precise dosage necessary to lower the blood glucose level in every patient. Importantly, the insulin could be delivered painlessly without the need of multiple daily injections.

Furthermore, if administered after a meal, the insulin level could reach a peak level within approximately fifteen minutes and then slowly diminish over the next hour, analogous to the normal physiological response to rising blood sugar levels following a meal.

With the recent advent of noninvasive continuous monitoring of blood glucose level, the precise insulin dose
necessary to normalize the patient's blood glucose level may be given. Thus, the serious risk of hypoglycemia or hyperglycemia can be avoided.

Examples of compositions and methods of using lollipops containing hypoglycemic agents are given herein below.

**EXAMPLE 20**

A drug-containing lollipop within the scope of the present invention to be used in the treatment of the symptoms associated with diabetes is made according to the procedure of Example 2, except that the ingredients are combined in the following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>0.05%</td>
<td>0.01</td>
</tr>
<tr>
<td>Natural mint</td>
<td>1.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>Ribotide</td>
<td>1.5%</td>
<td>0.3</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2.0%</td>
<td>0.4</td>
</tr>
<tr>
<td>Wild cherry</td>
<td>3.0%</td>
<td>0.6</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>4.0%</td>
<td>0.8</td>
</tr>
<tr>
<td>Artificial vanilla</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Artificial vanilla cream</td>
<td>5.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Compressed sugar</td>
<td>26.15%</td>
<td>5.23</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>52.3%</td>
<td>10.46</td>
</tr>
</tbody>
</table>

The foregoing procedure results in the preparation of 10 lollipops, each containing the equivalent of 30 units of insulin.

**EXAMPLE 21**
In the procedure of this example, a patient who is presently experiencing the symptoms of diabetes is given an insulin-containing lollipop in order to rapidly relieve the achieve a more normal blood glucose level. In this example, insulin in a lollipop dose of 1 milligram, equal to about 30 units, is used. As the patient sucks on the lollipop, the patient's blood sugar level normalizes.

Although the above discussion focused on the hypoglycemic agent insulin, it will be appreciated that other hypoglycemic drugs may also be utilized within the scope of the present invention. What is important is that the hypoglycemic drug be lipophilic, potent, and fast-acting so that the desired effects can be observed by the medical professional or by the patient himself, if the drug is to be self-administered, in sufficient time to remove the lollipop from the patient's mouth in time to prevent overdosing.

From the foregoing, it will be appreciated that the present invention allows great flexibility and permits physician control on a case-by-case basis with respect to the dose given to a particular patient, and the rate at which that dose is given.

The use of a drug-containing lollipop for administration of antimigraine, antiemetic, bronchodilator, oxytocic, anti-Parkinsonian, antidiuretic, hypoglycemic,
antifungal, or antisecretory agents is much faster acting than oral administration, and also avoids unacceptable loss of the drug on a first pass through the liver before systemic distribution. Further, the use of a lollipop in accordance with the present invention provides for a relatively level drug plasma concentration, which is preferable when dealing with potent drugs.

Further, a physician can easily monitor a patient's condition to ensure the patient receives a dose adequate to evoke a desired physiological state. If necessary, the physician can instruct the patient to alter the aggressiveness with which he sucks the lollipop, or he can take the lollipop from the patient.

A patient can also self-administer suitable antimigraine, antiemetic, hypoglycemic, bronchodilator, anti-Parkinsonian, antidiuretic, antifungal, or antisecretory medication using a lollipop in accordance with the present invention. Thus, a patient can place a drug-containing lollipop passively in his mouth for continuous low-level administration of a drug, or can take a lick of the lollipop from time to time as it may be needed to reduce his own subjective experience of pain or physical discomfort.

Although the method and compositions of the present invention have been described with reference to specific
examples, it is to be understood that the method and compositions of the present invention may be practiced in other forms without parting from its spirit or essential characteristics. Described methods and compositions are considered in all respects only as illustrative, and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

What is claimed is:
1. A method for administering a drug in a dose-to-effect manner to a patient experiencing a migraine, the method comprising the steps of:

obtaining a soluble matrix material in the form of a lollipop into which the drug has been dispersed, said soluble matrix material being capable of releasing the drug for absorption through mucosal tissues of the mouth, pharynx, and esophagus;

providing the drug-containing lollipop to the patient to whom the drug is to be administered in order to produce relief from the pain associated with the migraine;

administering the drug-containing lollipop to the patient in a manner such that the lollipop is dissolved so that the drug is absorbed through the mucosal tissues of the mouth, pharynx, and esophagus, thereby entering the patient's bloodstream, said administering step being accomplished in a dose-to-effect manner; and

controlling the rate of dissolution of the drug-containing lollipop in a dose-to-effect manner in order to obtain relief from the pain associated with the migraine while accounting for the patient's susceptibility to the drug and the patient's individual subjective experience of the pain associated with the migraine.
2. A method for administering a drug as defined in claim 1, wherein the drug is ergotamine and the dosage of ergotamine dispersed in the matrix is in the range of from about 2 milligrams to about 4 milligrams of ergotamine equivalent.

3. A method for administering a drug as defined in claim 1, wherein the drug is propranolol and the dosage of propranolol dispersed in the matrix is in the range from about 80 milligrams to about 160 milligrams of propranolol equivalent.

4. A method for administering a drug as defined in claim 1, wherein the drug is methysergide and the dosage of methysergide dispersed in the matrix is in the range of from about 2 milligrams to about 4 milligrams of methysergide equivalent.

5. A method for administering a drug as defined in claim 1, wherein the drug is suloctidil and the dosage of suloctidil dispersed in the matrix is in the range of from about 200 milligrams to about 300 milligrams of suloctidil equivalent.
6. A method for administering a drug as defined in claim 1, wherein the patient is initially caused to suck on the drug-containing lollipop in a manner capable of effecting rapid dissolution thereof, such that relatively high quantities of drug are absorbed into the patient's bloodstream in order to rapidly produce relief from the pain associated with the migraine, and wherein the patient thereafter caused to suck on the drug-containing lollipop only as needed to maintain such desired effect.

7. A method for administering a drug as defined in claim 2, wherein the drug-containing lollipop is maintained relatively passively in the patient's mouth after the desired effect is obtained in order to maintain such desired effect.

8. A method for administering a drug as defined in claim 1, wherein the soluable matrix material in the drug-containing lollipop is a carbohydrate mass.

9. A method for administering a drug as defined in claim 1, wherein the soluble matrix material is a compressed carbohydrate mass.
10. A method for administering a drug as defined in claim 1, wherein the drug-containing lollipop is intermittently removed from the patient's mouth in order to prevent an excessive amount of drug from being absorbed through the mucosal tissues into the patient's bloodstream.

11. A method for administering a drug as defined in claim 1, wherein the drug-containing lollipop includes an inner matrix containing the drug in a suitable concentration for maintaining the desired relief from the pain associated with the migraine, and an outer matrix covering the inner matrix, said outer matrix containing the drug in a suitable concentration for rapidly producing the desire relief from the migraneous pain.

12. A method for administering a drug as defined in claim 1, wherein a first drug-containing lollipop is initially administered to the patient in order to rapidly produce relief from the pain associated with the migraine, and thereafter a second drug-containing lollipop is administered that is suitable for use in maintaining the desired relief from the migraneous pain.

13. A method for administering a drug as defined in claim 46, wherein the first drug-containing lollipop and
the second drug-containing lollipop are of different colors in order to be easily distinguished from one another.

14. A method for administering an antiemetic drug in a dose-to-effect manner to a patient experiencing nausea and vomiting, the method comprising the steps of:

obtaining a soluble matrix material in the form of a lollipop into which the drug has been dispersed, said soluble matrix material being capable of releasing the drug for absorption through mucosal tissues of the mouth, pharynx, and esophagus;

providing the drug-containing lollipop to the patient to whom the drug is to be administered in order to produce systemic relief from nausea and vomiting;

administering the drug-containing lollipop to the patient in a manner such that the lollipop is dissolved so that the drug is absorbed through the mucosal tissues of the mouth, pharynx, and esophagus, thereby entering the patient's bloodstream, said administering step being accomplished in a dose-to-effect manner; and

controlling the rate of dissolution of the drug-containing lollipop in a dose-to-effect manner in order to obtain relief from nausea and vomiting while accounting for the patient's susceptibility to the drug and the
patient's individual subjective experience of nausea and vomiting.

15. A method for administering an antemetic drug as defined in claim 14, wherein the antiemetic drug is meclizine and the dosage of meclizine dispersed in the matrix is in the range of from about 25 milligrams to about 100 milligrams of meclizine equivalent.

16. A method for administering an oxytocic drug in a dose-to-effect manner to a patient in order to induce labor or reduce post partum hemorrhage, the method comprising the steps of:

obtaining a soluble matrix material in the form of a lollipop into which the drug has been dispersed, said soluble matrix material being capable of releasing the drug for absorption through mucosal tissues of the mouth, pharynx, and esophagus;

providing the drug-containing lollipop to the patient to whom the drug is to be administered in order to induce labor or reduce post partum hemorrhage;

administering the drug-containing lollipop to the patient in a manner such that the lollipop is dissolved so that the drug is absorbed through the mucosal tissues of the mouth, pharynx, and esophagus, thereby entering the
patient's bloodstream, said administering step being accomplished in a dose-to-effect manner; and

controlling the rate of dissolution of the drug-containing lollipop in a dose-to-effect manner in order to obtain increased uterine tone or cervical effacement while accounting for the patient's susceptibility to the drug.

17. A method for administering an oxytocic drug as defined in claim 16, wherein the oxytocic drug is oxytocin and the dosage of oxytocin dispersed in the matrix is in the range of from about 5 units to about 20 units of oxytocin equivalent.

18. A method for administering a bronchodilator drug in a dose-to-effect manner to a patient experiencing a respiratory distress, the method comprising the steps of:

obtaining a soluble matrix material in the form of a lollipop into which the drug has been dispersed, said soluble matrix material being capable of releasing the drug for absorption through mucosal tissues of the mouth, pharynx, and esophagus;
providing the drug-containing lollipop to the patient to whom the drug is to be administered in order to restore more normal respiratory functions of the patient;

administering the drug-containing lollipop to the patient in a manner such that the lollipop is dissolved so that the drug is absorbed through the mucosal tissues of the mouth, pharynx, and esophagus, thereby entering the patient's bloodstream, said administering step being accomplished in a dose-to-effect manner; and

controlling the rate of dissolution of the drug-containing lollipop in a dose-to-effect manner in order to restore more normal respiratory functions of the patient while accounting for the patient's susceptibility to the drug and the patient's individual subjective experience of respiratory distress.

19. A method for administering a bronchodilator as defined in claim 18, wherein the bronchodilator drug is oxtriphylline and the dosage of oxtriphylline dispersed in the matrix is in the range of from about 50 milligrams to about 400 milligrams of oxtriphylline equivalent.

20. A method for administering a bronchodilator as defined in claim 18, wherein the bronchodilator drug is theophylline and the dosage of theophylline dispersed in
the matrix is in the range of from about 50 milligrams to about 400 milligrams of theophylline equivalent.

21. A method for administering a drug in a dose-to-effect manner to a patient experiencing the symptoms of Parkinson's disease, the method comprising the steps of:

obtaining a soluble matrix material in the form of a lollipop into which the drug has been dispersed, said soluble matrix material being capable of releasing the drug for absorption through mucosal tissues of the mouth, pharynx, and esophagus;

providing the drug-containing lollipop to the patient to whom the drug is to be administered in order to reduce the symptoms of Parkinson's disease;

administering the drug-containing lollipop to the patient in a manner such that the lollipop is dissolved so that the drug is absorbed through the mucosal tissues of the mouth, pharynx, and esophagus, thereby entering the patient's bloodstream, said administering step being accomplished in a dose-to-effect manner; and

controlling the rate of dissolution of the drug-containing lollipop in a dose-to-effect manner in order to reduce the symptoms of Parkinson's disease while accounting for the patient's susceptibility to the drug.
and the patient's individual subjective experience of the symptoms of Parkinson's disease.

22. A method for administering a drug as defined in claim 21, wherein the drug is a combination of carbidopa and levodopa and the dosage of carbidopa dispersed in the matrix is in the range of from about 10 milligrams to about 50 milligrams of carbidopa equivalent, and the dosage of levodopa dispersed in the matrix is in the range of from about 100 milligrams to about 750 milligrams of levodopa equivalent.

23. A method for administering an antidiuretic drug in a dose-to-effect manner to a patient experiencing polyuria, the method comprising the steps of:

   obtaining a soluble matrix material in the form of a lollipop into which the drug has been dispersed, said soluble matrix material being capable of releasing the drug for absorption through mucosal tissues of the mouth, pharynx, and esophagus;

   providing the drug-containing lollipop to the patient to whom the drug is to be administered in order to decrease the patient's urine output;

   administering the drug-containing lollipop to the patient in a manner such that the lollipop is dissolved
so that the drug is absorbed through the mucosal tissues of the mouth, pharynx, and esophagus, thereby entering the patient's bloodstream, said administering step being accomplished in a dose-to-effect manner; and

controlling the rate of dissolution of the drug-containing lollipop in a dose-to-effect manner in order to decrease the patient's urine output while accounting for the patient's susceptibility to the drug and the patient's individual urine output.

24. A method for administering an antidiuretic drug as defined in claim 23, wherein the antidiuretic drug is desmopressin and the dosage of desmopressin dispersed in the matrix is in the range of from about 10 micrograms units to about 50 micrograms of desmopressin equivalent.

25. A method for administering a hypoglycemic drug in a dose-to-effect manner to a patient experiencing the symptoms of diabetes, the method comprising the steps of:

obtaining a soluble matrix material in the form of a lollipop into which insulin has been dispersed, said soluble matrix material being capable of releasing the insulin for absorption through mucosal tissues of the mouth, pharynx, and esophagus;
providing the insulin-containing lollipop to the patient to whom the hypoglycemic drug is to be administered in order to restore to more normal the blood sugar concentration of the patient;

administering the insulin-containing lollipop to the patient in a manner such that the lollipop is dissolved so that the insulin is absorbed through the mucosal tissues of the mouth, pharynx, and esophagus, thereby entering the patient's bloodstream, said administering step being accomplished in a dose-to-effect manner; and

controlling the rate of dissolution of the insulin-containing lollipop in a dose-to-effect manner in order to restore to more normal the blood sugar concentration of the patient while accounting for the patient's susceptibility to the drug.

26. A method for administering a hypoglycemic drug as defined in claim 25, wherein the hypoglycemic drug is insulin and the dosage of insulin dispersed in the matrix is in the range of from about 5 units to about 20 units of insulin equivalent.

27. A method for administering an antifungal drug in a dose-to-effect manner to a patient experiencing oral candidiasis, the method comprising the steps of:
obtaining a soluble matrix material in the form of a lollipop into which the drug has been dispersed, said soluble matrix material being capable of releasing the drug for absorption into mucosal tissues of the oral cavity;

providing the drug-containing lollipop to the patient to whom the drug is to be administered in order to induce rapid regression of the plaque in the oral cavity and restore normal oral flora balance;

administering the drug-containing lollipop to the patient in a manner such that the lollipop is dissolved so that the drug is absorbed into the mucosal tissues of the oral cavity, thereby entering the patient's bloodstream, said administering step being accomplished in a dose-to-effect manner; and

controlling the rate of dissolution of the drug-containing lollipop in a dose-to-effect manner in order to induce rapid regression of the plaque in the oral cavity, reduce the pain and distress associated with oral candidiasis, and restore normal oral flora balance while accounting for the patient's susceptibility to the drug.

28. A method for administering an antifungal drug as defined in claim 27, wherein the antifungal drug is clotrimazole and the dosage of clotrimazole dispersed in
the matrix is in the range of from about 10 milligrams to
about 20 milligrams of clotrimazole equivalent.

29. A method for administering an antisecretory drug
in a dose-to-effect manner to a patient experiencing
heartburn or the symptoms of esophagitis, the method
comprising the steps of:

obtaining a soluble matrix material in the form
of a lollipop into which the drug has been dispersed, said
soluble matrix material being capable of releasing the
drug for adsorption onto mucosal tissues of the esophagus;

providing the drug-containing lollipop to the patient
to whom the drug is to be administered in order to reduce
the discomfort and pain associated with heartburn or
esophagitis;

administering the drug-containing lollipop to the
patient in a manner such that the lollipop is dissolved
so that the drug is adsorbed onto the mucosal tissues of
the esophagus, thereby entering the patient's bloodstream,
said administering step being accomplished in a dose-to-
effect manner; and

controlling the rate of dissolution of the drug-
containing lollipop in a dose-to-effect manner in order
to reduce the discomfort and pain associated with
heartburn or esophagitis while accounting for the
patient's susceptibility to the drug and the patient's individual subjective experience of the discomfort and pain associated with heartburn or esophagitis.

30. A method for administering an antisecretory drug as defined in claim 29, wherein the antisecretory drug is aluminum sucrose sulfate and the dosage of aluminum sucrose sulfate dispersed in the matrix is in the range of from about 1 grams to about 2 grams of aluminum sucrose sulfate equivalent.

31. A composition for use in treating in a dose-to-effect manner a patient experiencing pain associated with a migraine, said composition comprising:

   an effective dose of a drug capable of being absorbed through mucosal tissues of the mouth, pharynx, and esophagus, and capable of rapidly relieving the pain associated with a migraine;

   a soluble matrix material, the drug being dispersed substantially uniformly within the matrix so that the drug is released in a dose-to-effect manner for absorption through mucosal tissues of the mouth, pharynx, and esophagus as the matrix dissolves when placed in a patient's mouth; and
holder means secured to the drug-containing matrix, said holder means being configured so as to permit convenient insertion of the drug-containing matrix into the mouth of a patient and convenient removal thereof while accounting for the patient's susceptibility to the drug and the patient's individual subjective experience of the pain associated with the migraine.

32. A composition as defined in claim 31, wherein the holder means is a stick with an enlarged end to prevent it from getting caught in the patient's mouth.

33. A composition as defined in claim 31, wherein the dosage of drug dispersed in the soluble matrix material is in the range of from about 1 to about 50 times greater than the dosage that would be given by intravenous injection.

34. A composition as defined in claim 48, wherein the drug is ergotamine and the dosage of ergotamine dispersed in the matrix is in the range from about 2 milligrams to about 4 milligrams of ergotamine equivalent.
INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) 4

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 9/20

II. FIELDS SEARCHED

Minimum Documentation Searched 7

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<th>Classification System</th>
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<td>U.S.</td>
<td>424/440</td>
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Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched 6

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

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<tr>
<th>Category</th>
<th>Citation of Document, 11 with indication, where appropriate, of the relevant passages 12</th>
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<tr>
<td>Y</td>
<td>US, A, 3,943,928 (LARICIA et al) 16 March 1976 (See entire document)</td>
<td>1 to 34</td>
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<tr>
<td>Y</td>
<td>US, A, 4,551,329 (HARRIS et al) 5 November 1985 (See entire document)</td>
<td>1 to 34</td>
</tr>
<tr>
<td>X</td>
<td>US, A, 4,671,953 (STANLEY et al) 9 June 1987 (Column 8, lines 38 to 41)</td>
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* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search
10 April 1990

Date of Mailing of this International Search Report
25 MAY 1990

International Searching Authority
ISA/US

Signature of Authorized Officer
Shep Rose

Form PCT/ISA/210 (second sheet) (Rev.11-87)