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MEDICATED SUPPOSITORIES AND BASES THEREFOR

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This invention relates to medicated suppositories which are stable under high-temperature storage and shipping conditions and yet which are readily disintegrated upon administration. In particular this invention relates to medicated suppositories having bases which are composed of a relatively high-melting, water-soluble or dispersible wax and a wax which melts substantially at body temperature, but does not soften appreciably below its melting temperature, and is substantially insoluble in the relatively high-melting, water-soluble wax. This invention further relates to suppository bases of the foregoing type.

The desirability of administering drugs rectally has long been felt in the medical arts. As one means of accomplishing this, medicated suppositories have frequently been used, though no completely satisfactory product for this purpose has yet been devised. Most medicated suppositories have been prepared by incorporating the therapeutic agent in a base which will melt at substantially body temperature, thereby releasing the medicament. Such suppositories have the obvious disadvantage of melting during storage in warm places where the temperature approaches body temperature, resulting in frequent economic loss, or in the demand for refrigerated storage, which is at best inconvenient. Other suppositories have been made with a base of such nature (as for instance a so-called water-soluble wax) that they are relatively unaffected by temperature changes, but will disintegrate and release their medicament in the presence of moisture. While such a product might appear to be an acceptable answer to the difficulties of rectal administration, in actual fact the rectum is a relatively dry cavity. One of the functions of the lining of the lower part of the large intestine is to absorb water from its contents rather than to secrete it, so that there is actually little moisture present just above the sphincter to bring about the disintegration of such a suppository. While such disintegration might in time occur even in the presence of very limited amounts of moisture, we have found by actual trial on human subjects that such suppositories are in fact undesirable. Among the reasons for this conclusion is the fact that, long before any such slow disintegration can occur, the presence of the solid mass above the sphincter causes a powerful expulsion reflex and the entire medication is lost. It is the object of this invention, therefore, to provide a suppository which can be stored without deterioration under such conditions as are normally encountered, and which when used will disintegrate and liberate its medication without undue delay or discomfort.

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We have found that by using a base which combines the principle of disintegration by moisture with that of disintegration by heat, a suppository can be made which more nearly approaches the desirable characteristics of effective clinical use and reasonable resistance to storage in warm places. For, by choosing a water-soluble or water-dispersible wax whose melting point is appreciably above such temperature as might be encountered during normal storage, a marked degree of resistance to such temperatures is imparted to the mass. By combining with such a substance a waxy ingredient which (1) has a sharp melting point at about body temperature, (2) is relatively hard and does not markedly soften below its melting temperature, and (3) is substantially insoluble in the high-melting water-soluble wax, a base is obtained which is firm at room temperature and becomes appreciably soft at body temperature without completely melting or even losing its shape. Thus it will stand storage indefinitely under any temperature normally encountered, but is able to release its medicament readily under the gentle warmth and peristaltic action of the intestine in the presence of the relatively small amount of moisture occurring therein. By formulating the entire suppository so that the amount of powdered drug (or of inert powdered diluent which may be used with the drug) is relatively large compared to the base, further stability of the entire mass under warm storage conditions is assured, together with an increased tendency to disintegrate when used.

In formulating such bases, we have found the following combinations of commercially available waxes to be satisfactory components. The high-melting water-soluble wax is given first. These examples are representative of the waxes within the scope of the invention. It will be apparent to those skilled in the art that other equivalent materials can be used without departing from the spirit or scope of this disclosure.

A. Polyethylene glycol (molecular weight about 4000, melting point 50–55° centigrade) and propylene glycol monostearate (M. P. 36–37° C.).

B. Polyethylene glycol (molecular weight about 6000, M. P. 58–62° C.) and partially hydrogenated cottonseed oil (M. P. 36–38° C.).

C. Polyethylene glycol and glycerol mono-oleate (M. P. 38° C.). The melting point of the glycerol mono-oleate depends upon its source and purity. The oily commercial products are unsatisfactory for our suppositories. Suitable solid esters melting in the range of 35° to 38° C. can be obtained from purified materials. See Krafft, Berichte, 36, 4343 (1903).

D. Polyethylene glycol and cocoa butter (M. P. 30–34° C.).

E. Polyethylene glycol and a paraffin fraction melting at 36–38° C. and being in the main composed of eicosane.

F. Isosorbide monostearate (M. P. 54–58° C.) and propylene glycol monostearate.

G. Sorbitan monostearate (M. P. 47.5–50.5° C.) and propylene glycol monostearate.

H. Isosorbide monostearate and a paraffin wax melting at 36–38° C. and being in the main composed of eicosane.

I. Isosorbide monostearate and cocoa butter.

J. Polyethylene glycol of molecular weight about 4000 with isosorbide monostearate mixed with propylene glycol monostearate.

K. Polyethylene glycol of molecular weight about 6000 mixed with propylene glycol monostearate and glycerol monolaurate (M. P. 28–30° C.).

L. Polyethylene glycol (M. P. 58–62° C.) and anhydrous lanolin U. S. P.

M. Polyethylene glycol and a mixture (M. P. 36° C.) of 7 parts of cocoa butter with 1 part of spermaceti.

It is apparent from the foregoing examples that more than two waxes may also be used in formulating the bases to which this invention relates. For example, two or more high-melting, mutually-miscible, water-soluble bases may be mixed with an immiscible, lower-melting wax, or a high-melting wax may be mixed with two or more waxes which melt near body temperature and which are immiscible in the high-melting wax while miscible with each other.

In practice we prefer to use a suppository base which is composed of a water-soluble polyethylene glycol (also known as polyoxyethylene glycol) and a fatty acid ester of propylene glycol. The polyethylene glycol has a formula

$$HOCH_2—(CH_2OCH_2)_n—CH_2OH$$

in which the value of n is so chosen that the compound is a hard waxy material at room temperature, but melts at 50° to 55° C. Commercially available materials are generally a mixture of homologues; in the mixture preferred by us, the average value of n is about 90. A somewhat harder polyethylene glycol wherein n averages about 135 is also quite satisfactory. While such waxes are completely soluble in water, when formed into a hard suppository they resist the action of the relatively small amount of moisture in the rectum almost indefinitely, and thus are completely useless as suppository bases. As the second ingredient of our base, we prefer to use a fatty acid ester of propylene glycol whose melting point lies between 35° and 37° C. Such esters are not soluble in water. The exact fatty acid mixture used to form the ester is not of critical importance; several such esters are commercially available with appropriate melting points, among which we have found propylene glycol monostearate to be quite satisfactory. Since the fatty acid esters are not miscible with the polyoxyethylene glycol described above, the base is made homogeneous only by vigorous stirring while cooling. As a further result of this immiscibility, when the fatty ester of propylene glycol melts, it does not affect the polyoxyethylene glycol which remains in solid condition.

We have found that higher fatty acid esters of the hexitols obtained by reduction of hexoses are also satisfactory as the relatively high-melting, water dispersible wax. These hexitols exist

as mixtures of the open-chain form with anhydrides formed by the elimination of one or two moles of water. Their esters with fatty acids are either waxy solids or viscous oils, and are all water-dispersible at body temperature. Sorbitan monostearate (prepared from sorbitan by esterification with stearic acid) and isosorbide monostearate (prepared similarly from isosorbide) have been found to be particularly adapted to our novel suppository bases.

The melting point of the relatively high-melting wax should be above the highest temperature to be expected in storing and shipping the suppositories. In general the range should start at about 110° Fahrenheit and 44° centigrade. The upper limit of the melting point should be chosen with regard to the hardness of the waxes and the problem of compounding and pressing or casting the suppositories. The melting point should not be so high that in mixing the melted ingredients the medicament is partly destroyed due to thermal instability. In practice the upper temperature need not exceed 140° F. or 60° C., and for most purposes should not exceed 167° F. or 75° C. The preferred range is about 122–131° F. or 50–55° C. Seldom are temperatures above this range met in shipping or in storage, and the waxes are sufficiently low-melting to afford easy compounding and pressing or casting of the suppositories.

The melting point of the low-melting wax should be substantially that of body temperature, which is 37° C. In actual practice it has been found that the melting point can range from about 30° C. to about 38° C. The preferred melting range is from 35–38° C. In practice it is difficult to obtain accurate melting points of substances melting in the range of 30–38° C. Generally the solidification point is the one actually determined. It is usually observed that the solidification point of a given substance is a few degrees lower than the melting point of the substance, due undoubtedly to superheating during the melting point determination. For example, the solidification points of samples of propylene glycol monostearate, which have melting points in the range of 35–37° C., are generally in the range of 33–35° C. Similarly, the polyethylene glycol of melting point 50–55° C. commonly has solidification points in the range of 47–52° C.

In order that the finished suppository be stable in warm climates it is important that the quantity of this low-melting ingredient in the base be small enough so that when it has melted, the finished suppository will not lose its shape, but there must at the same time be sufficient present so that when it does melt after being used, the finished suppository is softened sufficiently that disintegration may start. We have found that a proportion of 20 to 80% by weight in the base of the wax which melts substantially at body temperature is satisfactory and desirable in preparing a suppository according to this invention. With fatty esters of propylene glycol and polyethylene glycols, it has been found that 20 to 60% by weight of the lower melting wax is preferred.

We have found that the ratio of drug (including inert powdered diluent thereof) to base is also important in formulating a suppository which will achieve the object of this invention. The upper limit is determined by the readiness with which the mass can be mixed and shaped, either by casting, molding, compression or otherwise. Since the presence of powdered drug or diluent aids disintegration of the suppository, the lower

limit is that point at which disintegration becomes unsatisfactory. We have found that as a practical expedient, suppositories which contain from 20 to 85% by weight of powdered drug or its diluent are satisfactory in fulfilling the object of this invention. When polyethylene glycols form the relatively high-melting wax we have found that about 35 to 70% by weight of powdered drug and/or diluent are the preferred proportions. It is generally desirable that the powdered diluent be mainly water-soluble, in order that it may be absorbed with the drug and thus removed. It is not necessary that all the diluent be water-soluble since starch and gelatin, which are only partly soluble, are quite satisfactory as part of the inert powder. These materials swell with water and are useful in aiding the disintegration of the suppository.

While our suppository bases as herein disclosed are made up of a relatively high-melting water-soluble wax or mixture of such waxes and a wax or mixture of waxes melting at substantially body temperature and substantially insoluble in the higher-melting wax or waxes, other components may be incorporated into our bases. Among such components are lubricants like castile or soft soap, gelatine, oleic acid, stearic acid and glycerol. For ease of removal from molds, substances such as lycopodium powder or talc may be used. Coatings of gelatine or flexible collodion may be applied. It is to be understood that such additions or modifications are not outside the scope of this invention. Other additives will be apparent to those skilled in the art without departing from the spirit or scope of our disclosure and claims.

This application is a continuation-in-part of our prior, copending application Serial No. 605,836, filed July 18, 1945, now abandoned.

Our invention is further disclosed by the following examples, which are illustrative only and in no way limit the scope of our invention. The relative amounts are given in parts by weight.

Example 1

As an example of a suppository which has the properties desired to be furnished by this invention, the following composition may be used:

	Parts
Aminophyllin (finely powdered)	50
Polyoxyethylene glycol (M. P. 50–55° C.)	25
Propylene glycol fatty acid ester (M. P. 35–37° C.)	25

The glycol and ester are melted together, the aminophyllin added and the whole vigorously stirred or kneaded while cooling. When molded into suppositories of 1 gram each, a dose of 500 milligrams of aminophyllin is present in each suppository.

Example 2

In the event a larger suppository, or a smaller dose, is desired, the following illustrates the use of a diluent:

	Parts
Aminophyllin (finely powdered)	25
Sodium chloride (finely powdered)	25
Polyoxyethylene glycol (M. P. 50–55° C.)	25
Propylene glycol fatty acid ester (M. P. 35–37° C.)	25

The glycol and ester are melted together, and the aminophyllin and sodium chloride added and the whole stirred vigorously during cooling. A 2 gm. suppository will contain 500 mg. of aminophyllin, or a 1 gm. suppository will have a dose of 250 mg. of the drug. The diluent used in this example may be replaced by other suitable diluents, certain of which are mentioned in the other examples.

Example 3

Similarly suppositories may be made using drugs requiring much smaller doses by increasing the diluent used:

	Parts
Phenobarbital	3
Dextrose	33
Polyoxyethylene glycol (M. P. 50–55° C.)	32
Propylene glycol fatty acid ester (M. P. 35–37° C.)	32

When made into 1 gm. suppositories, each will contain a dose of 30 mg. of phenobarbital.

Example 4

	Parts
Morphine sulfate	0.266
Sodium sulfate	60
Polyoxyethylene glycol (M. P. 50–55° C.)	20
Propylene glycol fatty acid ester (M. P. 35–37° C.)	20

Example 5

According to the method of Example 1, a suppository is made of the following components:

	Parts
Isosorbide monostearate	50
Propylene glycol monostearate	50
Aminophyllin	50
Sucrose	10
Starch	40

The resulting composition is easily pressed, does not stick to the die and is firm and stable at temperatures up to 56° C.

Example 6

A suppository is made of the following composition:

	Parts
Sorbitan monostearate	80
Cocoa butter	20
Aminophyllin	50
Sucrose	10
Starch	40

The product is firm and not sticky.

Example 7

A satisfactory suppository is compounded of the following ingredients according to the method of Example 1:

	Parts
Polyethylene glycol (M. P. 50–55° C.)	286
Propylene glycol monostearate	433
Aminophyllin powder	500
Potato starch	358
Powdered sugar	358
Sodium phenobarbital	100

Example 8

A satisfactory suppository has the following formula:

	Parts
Polyethylene glycol (M. P. 50–55° C.)	28
Propylene glycol monostearate	42
Aminophyllin	50
Sucrose	40
Starch	40

Example 9

A satisfactory suppository is compounded as follows:

	Parts
Polyethylene glycol (M. P. 58–62° C.)	40
Propylene glycol monostearate	20
Glycerol monolaurate	10
Powdered medicament and diluent	130

Example 10

The following formulation gives an excellent suppository having all the desired properties of firmness, heat resistance and ease of compounding:

	Parts
Polyethylene glycol (M. P. 50–55° C.)	20
Propylene glycol monostearate	30
Isosorbide monostearate	50
Aminophyllin	50
Sucrose	10
Starch	40

Example 11

A suppository is made according to the following formulation.

	Parts
Aminophyllin powder	2,780
Potato starch	2,038
Powdered sugar	2,038
Sodium pentobarbital	569
Polyethylene glycol of M. P. 50–55° C.	812
Propylene glycol monostearate	1,232

The waxes are melted and filtered through a No. 30 screen. The powdered drugs and excipients are thoroughly mixed and added with vigorous stirring to the wax melt in a power agitator. The stirring is continued until the mass reaches a semi-solid state. The mixture is removed from the agitator, allowed to cool and pressed into 2-gram suppositories.

Example 12

A suppository made according to the following formula is stable and easily compounded and pressed:

	Parts
Aminophyllin powder	25
Sodium pentobarbital	5
Starch	20
Sugar, powdered	20
Polyethylene glycol of M. P. 50–55° C.	18
Propylene glycol monostearate	12

Example 13

A satisfactory suppository can be made according to the following formula:

	Parts
Aminophyllin powder	25
Sodium 5-allyl-5-(1-methylbutyl) barbiturate	5
Starch	20
Sugar, powdered	20
Polyethylene glycol of M. P. 50–55° C.	3
Propylene glycol monostearate	27

Example 14

The following formula gives a satisfactory suppository:

	Parts
Aminophyllin powder	25
Sodium phenobarbital	5
Starch	20
Sugar, powdered	20
Polyethylene glycol of M. P. 50–55° C.	27
Propylene glycol monostearate	3

Example 15

A stable suppository can be formulated as follows:

	Parts
Aminophyllin powder	500
Sodium pentobarbital	100
Starch	500
Powdered sucrose	500
Polyethylene glycol of M. P. 50–55° C.	200
Propylene glycol monostearate	200

Example 16

A cast suppository can be produced in accordance with the following formula:

	Parts
Aminophyllin powder	40
Polyethylene glycol of M. P. 50–55° C.	80
Propylene glycol monostearate	80

In practice it is advisable to use heated dies with this formulation.

Example 17

A medicated suppository can be made according to the following formula:

	Parts
Tannic acid	20
Iodoform	20
Cocoa butter	80
Polyethylene glycol of M. P. 58–62° C.	80

The iodoform is dissolved in the melted cocoa butter and the tannic acid and polyethylene glycol are thoroughly mixed with the melt. The warm mixture is then cast into molds to form 2-gram suppositories.

Example 18

A medicated suppository compounded according to the following formula is stable and satisfactory:

	Parts
Aminophyllin powder	250
Potato starch	275
Powdered sucrose	275
Sodium pentobarbital	50
Polyethylene glycol of M. P. 50–55° C.	75
Cocoa butter	75

We claim:

1. A medicated suppository comprising a base which consists of not less than 20% and not more than 60% by weight of a relatively high-melting, water-soluble polyethylene glycol wax, the balance of the base being a fatty acid ester of propylene glycol which melts substantially at body temperature but does not soften appreciably below its melting temperature.

2. A medicated suppository in which the base consists of not less than 20% and not more than 60% by weight of a polyethylene glycol whose melting point lies between 50° and 55° C., the balance of the base being a fatty acid ester of propylene glycol whose melting point lies between 35° and 37° C., and which does not soften appreciably below its melting temperature.

3. A medicated suppository in which the base consists of not less than 20% and not more than 60% by weight of a polyethylene glycol whose melting point lies between 50° and 55° C., the balance of the base being a fatty acid ester of propylene glycol and whose melting point lies between 35° and 37° C., and which does not soften appreciably below its melting temperature, and in which suppository the proportion of powdered drug, including inert diluents thereof, lies be-

tween 20 and 85% by weight of the total suppository.

4. A medicated suppository comprising a base which consists of not less than 20% and not more than 60% by weight of a polyethylene glycol whose melting point lies between 50° and 55° C. and whose average molecular weight is about 4000, the balance of the base being propylene glycol monostearate.

5. A medicated suppository comprises aminophyllin and a base which consists of not less than 20% and not more than 60% by weight of a polyethylene glycol whose melting point lies between 50° and 55° C. and whose average molecular weight is about 4000, the balance of the base being propylene glycol monostearate.

6. A medicated suppository comprising aminophyllin, a barbiturate and a base which consists of not less than 20% and not more than 60% by weight of a polyethylene glycol whose melting point lies between 50° and 55° C. and whose average molecular weight is about 4000, the balance of the base being propylene glycol monostearate.

7. A medicated suppository comprising aminophyllin, sodium pentobarbital and a base which consists of not less than 20% and not more than 60% by weight of a polyethylene glycol whose melting point lies between 50° and 55° C. and whose average molecular weight is about 4000, the balance of the base being propylene glycol monostearate.

8. A suppository base comprising not less than 20% and not more than 60% by weight of a relatively high melting water soluble polyethylene glycol wax and a fatty acid ester of a polyhydric saturated aliphatic alcohol which melts substantially at body temperature, but does not soften appreciably below its melting temperature.

9. A suppository base comprising not less than 20% and not more than 60% by weight of a polyethylene glycol, the melting point of which is in the range of 50–55° centigrade, and a fatty acid ester of a polyhydric saturated aliphatic alcohol which has a melting point in the range of 35–37° C. and which does not soften appreciably below its melting point.

10. A suppository base comprising not less than 20% and not more than 60% by weight of a polyethylene glycol, the melting point of which lies between 50–55° C. and which has an average molecular weight of about 4000, and propylene glycol monostearate.

11. A medicated suppository comprising a base as defined in claim 8 and 20–85% by weight of powdered drug and inert diluents.

12. A medicated suppository comprising a base as defined in claim 9 and 20–85% by weight of powdered drug and inert diluents.

13. A medicated suppository comprising a base as defined in claim 10 and 20–85% by weight of powdered drug and inert diluents.

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