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(54) ANTI-HAEMORRHOIDALLY ACTIVE PREPARATIONS FOR LOCAL OR RECTAL ADMINISTRATION

(71) We, CIBA-GEIGY AG (formerly CIBA Limited), a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides anti-haemorrhoidally active preparations for rectal or local administration.

It is known that ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside, marketed under the registered tradename GLYVENOL, has various pharmacological effects that can be utilized in controlling the pathology involved in venous circulation trouble. When administered parenterally or especially orally, it displays specific activities in that it seals off vessels or reduces the capillary permeability and has distinct inhibiting properties for oedemas and inflammations. This substance further antagonizes a variety of endogenic substances that are of importance as mediators in inflamed conditions and in the incidence of pain. Furthermore, it has anti-allergic and anti-anaphylactic properties because it supports the defensive function. It was surprising to observe that this drug, which was recommended for parenteral or especially oral administration for the treatment of venous circulation trouble, of the varicose syndrome and as adjuvant in cases of phlebitis and periphlebitis, can be used with good effects as a rectally or locally applied medicament for the treatment of haemorrhoids.

Accordingly, the present invention provides a pharmaceutical preparation having an anti-haemorrhoidal action and comprising a suppository, cream, or ointment incorporating from 1 to 30% by weight of ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside in admixture or conjunction with a pharmaceutically suitable carrier. The creams, that is to say oil-water emulsions, are preferred over the ointments.

The preparations contain the anti-haemorrhoidal substance in concentrations of from 1 to 30% by weight; for ointments and creams a concentration of from 1 to 10%, especially 5%, and for suppositories (having, for example, the usual weight of 2 g) a concentration from 5 to 30%, especially 15—25% and more especially 20% of the active substance is suitable.

In addition to the said active substance the preparations may contain a local anaesthetic in a concentration from 0.1 to 5% by weight, such as lidocain, piperocain, thesite, 2 - (m - butoxyphenoxy) - diethylamine or especially dibucain. The latter is preferably used in a concentration from 0.1 to 3%, in the first place from 0.25 to 0.5%.

The preparations may be formulated by conventional methods used in the manufacture of ointments, creams or suppositories respectively, with the use of assistants that do not react with the active substances. Thus, for the manufacture of ointments and creams there are preferably used white petroleum jelly, higher aliphatic alcohols, sorbitan esters and their polyalkylene derivatives, polyalkyleneglycols, higher hydrocarbons, vegetable oils, glycerol and isopropyl esters of medium fatty acids. Suppositories are preferably manufactured with cocoa butter, wax, mixtures of mono-, di- and triglycerides of fatty acids containing 12 to 18 carbon atoms, mixtures of saturated fatty acids with 10 to 18 carbon atoms, natural and synthetic fats such as cottonseed oil, palm kernel stearin hydrogenated peanut oil, pork fat, wool fat, coconut fat, aliphatic alcohols, condensation products of polyethylene oxide with fatty acid glycerides or sorbitans, phthalic acid esters with aliphatic alcohols, especially cetyl alcohols.

If desired, further assistants, such as preservatives, colouring matter or perfume may be incorporated with the preparations. They may also contain further therapeutically active substances, such as intibiotics, antimicotics or antiseptics.

[Price 25p]

The invention is also concerned with the manufacture of the pharmaceutical preparations, characterized in that the active substances together with the excipients and, if desired, further active substances are made up in known manner in the desired form of application.

The following non-limiting Examples illustrate the invention.

EXAMPLE 1

Suppositories

Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	400 mg
adeps solidus (mixture of mono-, di- and triglycerides of higher fatty acids) up to	2000 mg

EXAMPLE 2

Suppositories

Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	400 mg
wax	100 mg
cocoa butter, to make	2,000 mg

The suppositories described in Examples 1 and 2 can be manufactured by mixing the active substance with the melted assistants, pouring the melt into suppository moulds and allowing them to cool.

EXAMPLE 3

Suppositories

Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	400 mg
dibucain	5 mg
adeps solidus, to make	2000 mg

EXAMPLE 4

Suppositories

Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	400 mg
dibucain	5 mg
wax	100 mg
cocoa butter, to make	2,000 mg

The suppositories of the compositions shown in Examples 3 and 4 are prepared by dissolving dibucain in the active substance, mixing this solution with the melted assistants, pouring the mixture into suitable suppository moulds and cooling.

EXAMPLE 5

Creams of the following composition:

	grams
Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	5.0
Arlacel 60	1.0
Tween 60	4.0
cetyl alcohol	3.0
stearic acid	9.0
liquid paraffin	12.0
sorbitol 70%	6.0
p-hydroxybenzoic acid ester	0.23
deionized water, to make	100.0

"Arlacel" and "Tween" are Trade Marks.

EXAMPLE 6

Creams of the following composition:

	grams
Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	5.0
Cetomacrogol	1.0
isopropyl palmitate	2.0
glycerol monostearate	5.0
cetyl alcohol	6.5
sorbitol 70%	6.0
p-hydroxybenzoic acid ester	0.23
deionized water, to make	100.0

The creams of the compositions shown in Examples 5 and 6 are prepared by melting the fatty ingredients together, mixing in the active substance, on the one hand, and, on the other hand, dissolving the preservative at 80—90°C in water, adding the sorbitol, and mixing the two mixtures together with thorough stirring.

EXAMPLE 7

Creams of the following composition:

	grams
Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	5.0
dibucain HCl	0.25
Arlacel 60	1.0
Tween 60	4.0
cetyl alcohol	3.0
stearic acid	9.0
liquid paraffin	12.0
sorbitol 70%	6.0
p-hydroxybenzoic acid methyl ester	0.23
deionized water, to make	100.0

EXAMPLE 8

Creams of the following composition:

	grams
Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	5.0
dibucain HCl	0.25
Arlacel 60	1.5
Tween 60	6.0
liquid paraffin	10.0
aluminiumpentasilicate	7.5
p-hydroxybenzoic acid methyl ester	0.23
deionized water, to make	100.0

To prepare the creams of the compositions mentioned in Examples 7 and 8 the fatty matter is melted together, the ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside is admixed and, on the other hand, the preservative is dissolved together with dibucain HCl in water, if desired sorbitol is admixed and the two mixtures are mixed together with thorough stirring.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation having an antihaemorrhoidal action and comprising a

of the cap without pressing the same further on to the bottle neck does enable the cap to be removed from it and consequently this arrangement in itself is not entirely safe if young children should have access to the container. A larger indent or cut-away portion 15 (see Figure 2) can be used to remedy this deficiency.

Indent 15 is so dimensioned and positioned in the groove that when the cap is rotated to release the seal on the container, the pins 8 enter this indent as a result of the biasing effect of the pad 12 or its equivalent. Unless a force is applied to keep the pins located in the lower part of the grooves, they become located within indent 15 and the cap cannot be removed unless it is first depressed against the bias force. This depression in combination with rotation of the cap is not at all easy for a child to do. This type of groove configuration will be termed "safety locking configuration" in view of the difficulty in removing the cap.

If required, two sets of grooves longitudinally spaced along the neck of the container may be provided, one set having a safety locking configuration and the other set having the simple sealing construction. An example of this form of groove is shown in Figures 3 and 4. The person sealing the container may choose what sort of sealing is required at any particular time by the choice of cap or the action taken when sealing the container.

In Figures 3 and 4, a single groove has two sealing lock sections, the lower one having a safety locking configuration and the upper a simple sealing construction. For use with this type of groove, a cap having two sets of pins, 18 and 21, as illustrated in Figure 4, may be provided for simple sealing. Each set of pins enters one of the sets of sealing lock sections 19 or 23 of the grooves but the lower pins 21 do not necessarily assist in the sealing of the container since they may be lying clear below indent 24 when the upper pins 18 are held in the small indents of the upper groove. Using the small indents such as 22 at the extreme left of the sealing lock sections, each set of pins is used for sealing and should one pin be broken, effective sealing of the container can still be achieved.

As long as sufficient compressibility of resilient pad 12 (or the alternative spring) is provided, a cap having a single set of pins, as illustrated in Figure 1, will be satisfactory for use with this type of groove; the safety locking will, of course, require a greater manual force to enable the pins to enter the lower locking sections of the grooves. As an alternative to this arrangement, two forms of caps with single pins may be provided, one with high set pins for simple sealing, the other with lower set pins for safety locking. Depending on the contents of the container, an appropriate cap will be chosen.

Yet another form of arrangement where the two types of sealing are provided with a single groove is that where a single downward section of the groove has two sealing lock sections, each extending in opposite directions from the downward section. In one direction, the sealing lock section will have a safety locking configuration and in the other direction, a simple sealing construction. Preferably the two sealing lock sections meet the downward section at different levels to assist in determining when the cap is in a position for removal (i.e., when it has been turned to a point where further rotation of the cap is prevented by the pins bearing against the sides of the downward sections of the grooves).

Yet another possible groove construction is illustrated in Figure 6. This construction is particularly apt for use where safety locking is definitely required, which will be the case with very dangerous substances.

An island 27 is provided in each groove. Island 27 has a tip 28 which may be pointed (typically a downwardly pointing tip) or rounded but is so shaped that it provides a buffer or deflection against re-entry of the pin from the indents section 29 of the groove into channel 26 at the tip 28.

On reversing the movement of the cap, the pin moves back until it reaches tip 28 of the island 27. Because of the shape of the tip 28 and the dimensions of channel 26 at this point, the pin cannot re-enter channel 26 but has to travel along the upper channel 25 until it reaches a stop in the form of the material surrounding the groove at indent 30. From this position, the pin can only be moved into the lead-in of the groove by forcing it past the island in the small passage below indent 30. This passage is dimensioned to be a push fit for a pin. Such an action is an extremely difficult one for a child to master, especially if it is unaware of the nature of the movements required.

To further ensure against a pin re-entering the channel 26, the back edge of the pin (which is the right edge if reference is made to a pin entering the channel of Figure 6) is flat or even diagonally inclined downwardly from right to left as shown by pin 8A in Fig. 6. A wedge-shaped pin, or one having a rounded leading edge, which is capable of expanding the channel 26 at tip 28 would not then be able to pass into channel 26 in the reverse direction. The desired degree of difficulty or complication in removing the cap, particularly aimed at child-resistance, can be obtained by varying the width of the groove below indent 30.

In the case of containers made of non-resilient material, the tip 28 will be positioned so that the pin is a snug fit in the channel 26. This is a sufficient restriction to the path of a pin to make it difficult for the pin to re-enter channel 26 at tip 28 especially if the back edge of the pin is flat or inclined.

Figure 5 illustrates the arrangement of pins and grooves when the pins are incorporated with the bottle while the grooves — having any of the configuration already described — are formed in the inner face of the skirt of the cap.

It will be noted that in the drawings, all the pins in the caps have buttons projecting beyond the outer surface of the cap. This is not necessary but can be useful for location of the pins by a person (for example, a blind or infirm person) wishing to seal a container or as a holding point for the machine filling the containers. They may, therefore, be added to or formed integrally with the exterior of the skirt of the caps.

It should also be realised that while the invention is particularly applicable to containers made of glass or plastics materials and caps made of plastics material, other materials, including metals, can be used for caps or containers where circumstances so require.

WHAT I CLAIM IS:—

1. A container and closure arrangement including a closure member comprising a skirted cap containing a sealing member, and a neck of the container defining an open mouth, said closure member and said container neck cooperating to hold the sealing member over the container mouth, compressible means within the cap to bias the same axially away from said mouth when the closure member is in position on the container, at least one projection on either the closure member or the container neck, and at least the same number of grooves formed in the remaining container neck or closure member, the or each groove comprising an upper downwardly inclined lead-in section for a projection, a sealing lock section having at least one indent within which the projection is located when the container is sealed, said sealing lock section being substantially at or beneath the level of the lower end of the lead-in section so that sealing of the container is effected at substantially the same or a greater degree of compression of the biasing means as, or than, occurs at any position during closing of the seal on the container, and a safety-locking section betwen the lead-in section and the sealing lock section and which includes an indent extending above the level of the lower end of the lead-in section.

2. A container and closure arrangement according to claim 1, wherein said projections are pins and the number of said pins is at least two.

3. A container and closure arrangement in accordance with claim 1 or claim 2, in which the or each sealing lock section extends from said lead-in section at a downward inclination, a plurality of indents being formed in the or each sealing lock section whereby the pins may be located at different distances from said sealing member when said container is sealed by the closure arrangement.

4. A container and closure arrangement in accordance with claim 3, in which the indent of the safety-locking section is deeper than the indents of the sealing lock section, said biasing means being effective to bias the cooperating projection into the deeper indent when said closure members are rotated relative to each other to open a sealed container unless a force is applied to the closure members to overcome the effect of the biasing means until the cooperating projection has reached the lead-in section of the groove.

5. A container and closure arrangement according to any preceding claim, wherein a second sealing lock section is provided above the first-mentioned sealing lock section and is connected to an intermediate point of the lead-in section.

6. A container and closure arrangement according to claim 5, in which two sets of projections are provided, one set of projections moving in the upper sealing lock sections and the other set of projections moving in the lower sealing lock sections.

7. A container and closure arrangement according to claim 5, in which each sealing lock section extends in a different direction away from said lead-in section.

8. A container and closure arrangement according to any preceding claim, in which said projections are provided in the cap and said grooves in the neck of the container.

9. A container and closure arrangement according to any preceding claim, in which said projections are provided in the neck of the container and said grooves are formed in the cap.

10. A container and closure arrangement according to claim 8, in which projections are provided on the outer surface of the skirt of the cap, the positions of these projections being respectively aligned with the positions of the first-mentioned projections.

11. A container and closure arrangement according to any one of claims 1 to 4, in which, in the sealing lock section, each groove is divided into two channels separated by an island, the end of said island remote from the lead-in section forming a restriction in the channel through which the cooperating projection must pass to reach

The invention is also concerned with the manufacture of the pharmaceutical preparations, characterized in that the active substances together with the excipients and, if desired, further active substances are made up in known manner in the desired form of application.

The following non-limiting Examples illustrate the invention.

EXAMPLE 1

Suppositories

Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	400 mg
adeps solidus (mixture of mono-, di- and triglycerides of higher fatty acids) up to	2000 mg

EXAMPLE 2

Suppositories

Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	400 mg
wax	100 mg
cocoa butter, to make	2,000 mg

The suppositories described in Examples 1 and 2 can be manufactured by mixing the active substance with the melted assistants, pouring the melt into suppository moulds and allowing them to cool.

EXAMPLE 3

Suppositories

Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	400 mg
dibucain	5 mg
adeps solidus, to make	2000 mg

EXAMPLE 4

Suppositories

Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	400 mg
dibucain	5 mg
wax	100 mg
cocoa butter, to make	2,000 mg

The suppositories of the compositions shown in Examples 3 and 4 are prepared by dissolving dibucain in the active substance, mixing this solution with the melted assistants, pouring the mixture into suitable suppository moulds and cooling.

EXAMPLE 5

Creams of the following composition:

	grams
Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	5.0
Arlacel 60	1.0
Tween 60	4.0
cetyl alcohol	3.0
stearic acid	9.0
liquid paraffin	12.0
sorbitol 70%	6.0
p-hydroxybenzoic acid ester	0.23
deionized water, to make	100.0

"Arlacel" and "Tween" are Trade Marks.

EXAMPLE 6

Creams of the following composition:

	grams
Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	5.0
Cetomacrogol	1.0
isopropyl palmitate	2.0
glycerol monostearate	5.0
cetyl alcohol	6.5
sorbitol 70%	6.0
p-hydroxybenzoic acid ester	0.23
deionized water, to make	100.0

The creams of the compositions shown in Examples 5 and 6 are prepared by melting the fatty ingredients together, mixing in the active substance, on the one hand, and, on the other hand, dissolving the preservative at 80—90°C in water, adding the sorbitol, and mixing the two mixtures together with thorough stirring.

EXAMPLE 7

Creams of the following composition:

	grams
Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	5.0
dibucain HCl	0.25
Arlacel 60	1.0
Tween 60	4.0
cetyl alcohol	3.0
stearic acid	9.0
liquid paraffin	12.0
sorbitol 70%	6.0
p-hydroxybenzoic acid methyl ester	0.23
deionized water, to make	100.0

EXAMPLE 8

Creams of the following composition:

	grams
Ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside	5.0
dibucain HCl	0.25
Arlacel 60	1.5
Tween 60	6.0
liquid paraffin	10.0
aluminiumpentasilicate	7.5
p-hydroxybenzoic acid methyl ester	0.23
deionized water, to make	100.0

To prepare the creams of the compositions mentioned in Examples 7 and 8 the fatty matter is melted together, the ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside is admixed and, on the other hand, the preservative is dissolved together with dibucain HCl in water, if desired sorbitol is admixed and the two mixtures are mixed together with thorough stirring.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation having an antihaemorrhoidal action and comprising a

* C L M S *

suppository, cream, or ointment incorporating from 1 to 30% by weight of ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside in admixture or conjunction with a pharmaceutically suitable carrier.

2. A preparation as claimed in claim 1, which also incorporates a local anaesthetic.

3. A suppository having an antiheamorrhoidal action as claimed in claim 1 or claim 2, which incorporates ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside in a concentration of from 5 to 30% by weight.

4. A suppository as claimed in claim 3, which incorporates ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside in a concentration of from 15 to 25% by weight.

5. A suppository as claimed in claim 4, which incorporates ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside in a concentration of 20% by weight.

6. A suppository as claimed in any one of claims 3 to 5, which incorporates a local anaesthetic in a concentration of from 0.1 to 5% by weight.

7. A suppository as claimed in claim 6, wherein the local anaesthetic comprises dibucain.

8. A suppository as claimed in claim 7, which incorporates dibucain in a concentration of from 0.1 to 3% by weight.

9. A suppository as claimed in claim 8, which incorporates dibucain in a concentration of from 0.25 to 0.5% by weight.

10. An ointment or cream as claimed in claim 1, which incorporates from 1 to 10% by weight of ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside and also incorporates a local anaesthetic.

11. An ointment or cream as claimed in claim 10, which incorporates dibucain or a salt thereof in a concentration of from 0.1 to 3% by weight.

12. An ointment or cream as claimed in claim 11, which incorporates dibucain or a salt thereof in a concentration of from 0.25 to 0.5% by weight.

13. A suppository substantially as described in any one of Examples 1 to 4 herein.

14. A cream substantially as described in any one of Examples 5 to 8 herein.

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