Exhibit 1004

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Klokkers-Bethke et al.

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[54] **PHARMACEUTICAL HYDROPHILIC SPRAY CONTAINING NITROGLYCERIN FOR TREATING ANGINA**

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[21] Appl. No.: **989,987**

[22] Filed: **Dec. 11, 1992**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 709,581, Jun. 3, 1991, abandoned.

[30] **Foreign Application Priority Data**

Jun. 13, 1990 [DE] Germany 4018919

[51] **Int. Cl.**[5] **A61K 9/12**

[52] **U.S. Cl.** **424/47;** 128/200.13; 128/200.14; 141/20; 215/247; 222/394; 424/45

[58] **Field of Search** 424/45, 47; 128/200.13, 128/200.14; 215/247; 141/20; 222/394

[56] **References Cited**

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Assistant Examiner—Robert H. Harrison
Attorney, Agent, or Firm—Marshall, O'Toole, Gerstein, Murray & Borun

[57] **ABSTRACT**

A pharmaceutical aerosol spray for treating an angina attack including a container having a liquid composition therein comprising 0.1 to 2 weight percent of nitroglycerin, 2 to 60 weight percent of ethanol, 2 to 60 weight percent of propylene glycol, 10 to 50 weight percent of dichlorodifluoromethane and 30 to 70 weight percent of dichlorotetrafluoroethane, the container having a valve assembly sealed to the container around an opening in the container by a sealant material which has a nitroglycerin absorption value less than 10 mg/1 g of sealant material.

10 Claims, 1 Drawing Sheet

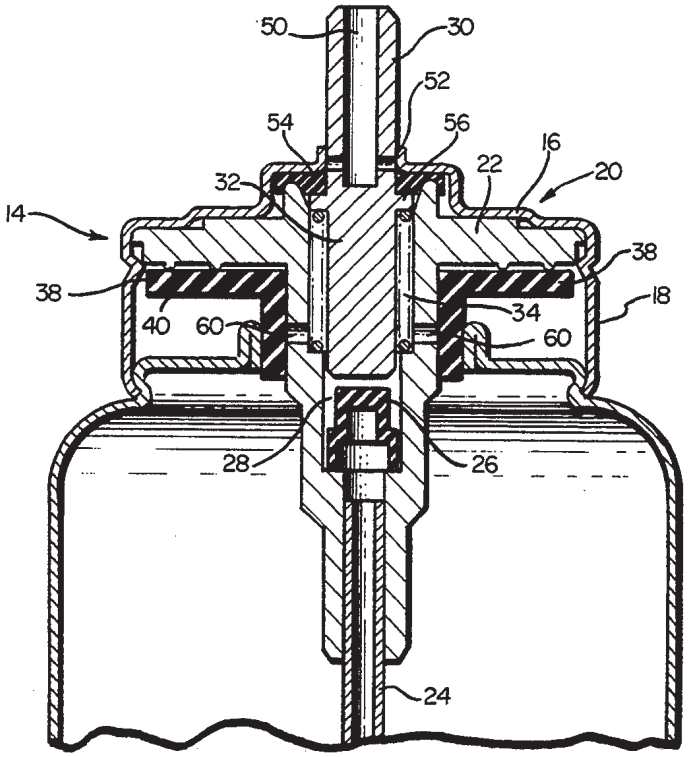


FIG. 1

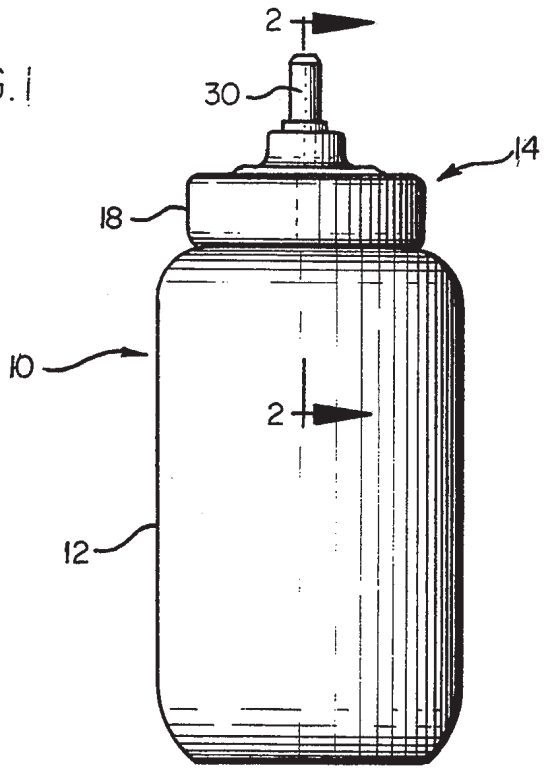
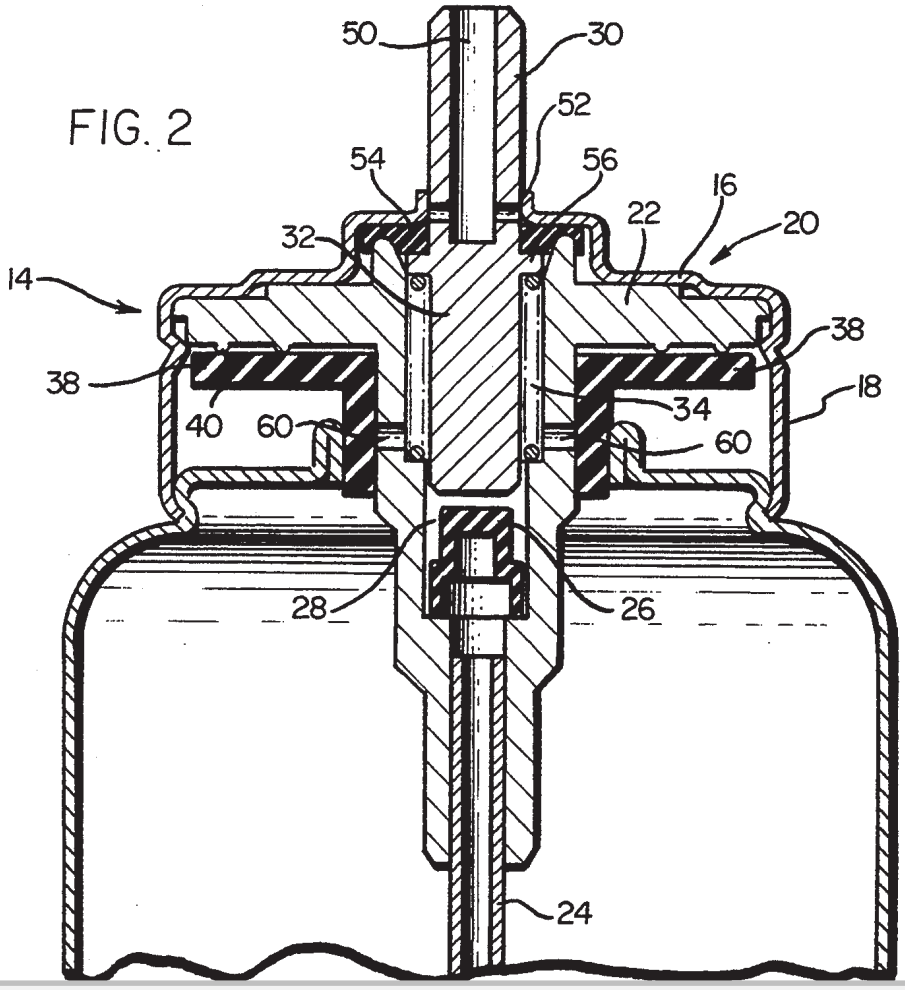


FIG. 2



PHARMACEUTICAL HYDROPHILIC SPRAY CONTAINING NITROGLYCERIN FOR TREATING ANGINA

This application is a continuation-in-part, of application Ser. No. 07/709,581, filed Jun. 3, 1991, abandoned.

This invention pertains to a liquid nitroglycerin spray, desirably having a hydrophilic base, and a sealant material for a container having the spray composition therein and which sealant contacts the spray composition, the nitroglycerin absorption value of the sealant being less than 10 mg of nitroglycerin per one gram of sealant material.

BACKGROUND OF THE INVENTION

Nitroglycerin, also called glycerol trinitrate or GTN, is an active substance for the treatment of angina pectoris attacks. Among other things, it is used in emergencies when the medication should be fast acting.

The pharmaceutical agents used for this specific purpose, such as sublingual tablets or crunchable capsules, have disadvantages. A disadvantage, amongst others, is that after intake the active agent in these pharmaceutical agents must first be released and dispersed prior to being available for resorption in dissolved form. Furthermore, the loss of time needed to take the pharmaceutical agent out of a blister package can be critical during an acute angina attack.

To avoid the disadvantages of the described pharmaceutical forms, nitroglycerin-containing sprays have been developed. By spraying a dose of the active agent into the buccal area of the mouth, a direct and rapid dispersion of a solution of the active agent over as large a portion as possible of the oral mucosa, which absorbs the active agent nitroglycerin was to be achieved. In this way, a large area was to be reached, thereby accelerating absorption of the active agent.

The previously known nitroglycerin pharmaceutical solutions are characterized by high vapor pressure, solution properties, and an explosive nature which have limited their use and acceptance. Therefore, a desensitized active agent—supplementary agent mixture has to be used for safety reasons during the formulation of the pharmaceutical agent spray.

Based on its lipophilic characteristics, nitroglycerin is readily soluble in solvents such as ether, acetone, ethylacetate, benzol, chloroform and triglycerides. On the other hand, the solubility of nitroglycerin in hydrophilic solvents, such as water, is limited. The solubility of nitroglycerin in water amounts to merely about 1.1 mg/ml.

Because of the low solubility of nitroglycerin in water the solvents used in the customary spray formulations are lipophilic, i.e. oils or triglycerides. However, the lipophilic solvents prevent dispersion of the active agent nitroglycerin into the hydrophilic mucosa with the desired speed during acute angina pectoris attacks.

Previously, if it was desired to increase the availability of an active agent, the amount of the lipophilic solvent was reduced. However, the nitroglycerin surge duration, measurable via the maximum plasma nitroglycerin glycerin concentration (C_{max}) and the time of the maximum concentration (t_{max}), was only insignificantly affected.

It is reported that P.M. Dewland et al [Heart and Vessels, 7, 536–544 (1987)] obtained higher C_{max} values (Table 1) for three nitroglycerin sprays, manufactured with lipophilic solutions, by decreasing the amount of the lipophilic formulation portions; however, the t_{max} is not significantly different.

Another way to increase the availability of the active agent is described in the DE-A 32 46 081. That reference discloses increasing the propellant portion to 60–95% by weight of the formulation. The increased propellant portion effects a higher concentration of the active agents in non-volatile oily solvents. Furthermore, the active agent must first diffuse in the mucosa from the oily active agent solution. However, the surge of the active agent, which is important when the angina attack occurs, cannot be significantly shortened. Also, for reasons of increased environmental consciousness, it is undesirable to increase the amount of propellant, so this should be avoided.

A qualitatively significant improvement in treating an angina attack is not possible if lipophilic solvents are retained in the spray.

Another starting point for quickly dispersing the active agent in the hydrophilic mucosa, is the use of a solution with dissolving characteristics which are as small as possible for the active agent nitroglycerin. In this regard, it is necessary to take into consideration that the spray formulation solution or solution mixture desensitizes the active agent nitroglycerin sufficiently and also that the solution be technically easy to handle with respect to production requirement.

U.S. Pat. No. 3,155,574 describes a nitroglycerin spray formulation-for inhalation using a hydrophilic solution base containing the active agent nitroglycerin, 1,2-propanediol and ethanol free of water, but actual exemplified embodiments of the primary packaging means are missing. However, inhalation is rather detrimental to a patient during the occurrence of an angina attack since it is more difficult to carry out. More desirable are nitroglycerin-containing sprays in which the active agent is sufficiently absorbed through the oral mucosa, so that inhalation of the active agent is not necessary.

Investigations by H. Laufen et al, reported in Therapy Week, 34, 963–970 (1984) indicated that when a hydrophilic formulation, as compared to nitroglycerin-containing sprays using a lipophilic base, is used the amount of the active agent in the blood, as well as the amount of the absorbed substance, is faster and greater than when a lipophilic base is used. The authors report use of a pump spray for dosing the solution. We know from general experience that pump sprays presently do not meet the requirements for administering pharmaceutical agents so that the formulation or composition of Laufen et al having the described therapeutically beneficial effect cannot be converted into a useful pharmaceutical agent.

The EP-A 0 310 910 describes a nitroglycerin-containing spray formulation which, besides the active agent, contains only ethanol and water as a solvent and is adjusted to a pH value of 2.4 to 6.7. However, during evaporation of the ethanol the active agent in this formulation experiences a phase separation from the water and thus is not present in a desensitized form, even though desensitization actually is desirable for safety reasons.

The present state of technology with respect to sprays having a hydrophilic base, as compared to those having a lipophilic base, reveals shortcomings, such as an absorption of nitroglycerin in the valve component parts and a reduction of the dosage amount of the active

agent nitroglycerin during each new or individual spray puff or shot.

SUMMARY OF TEE INVENTION

According to the invention it has been discovered that the concentration of nitroglycerin in a liquid composition can be maintained substantially steady or constant even if placed in contact with a sealant material by selecting a sealant material which has a nitroglycerin absorption value of less than 10 mg of nitroglycerin per one gram of sealant material.

More specifically, the invention provides a product comprising a container having a liquid composition therein containing nitroglycerin, said container including a sealant material which absorbs less than 10 mg of nitroglycerin per one gram of sealing material. The container can include a valve assembly, the valve assembly including sealant means which has a nitroglycerin absorption value of less than 10 mg of nitroglycerin per one gram of sealant material. The container can include a suitable propellant which is effective for producing an aerosol spray of the liquid composition for medicinal purposes. The valve assembly can be of the type which provides a metered aerosol dose of the nitroglycerin in the form of a puffer shot. The liquid composition desirably is hydrophilic.

The sealant material is desirably a resilient polymeric material, and preferably a synthetic material. A sealant material which absorbs less than 10 mg of nitroglycerin per one gram of sealing material can be use in this invention as a monolithic sealing material, meaning that it has essentially solid uniformity and constitutes one undifferentiated whole mass which may be a single polymeric material or a mixture of two or more closely related or different polymeric materials. Thus, it need not be coated with, or covered by, some other material before it is acceptable for use in the invention. Specifically undesirable as a sealant are TEFLON-type polymers used alone, or as a coating on some other sealant material, because TEFLON-type polymers absorb nitroglycerin and swell when in contact with it.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side elevational view of one embodiment of container which can contain a hydrophilic liquid composition including nitroglycerin and which container includes a conventional valve assembly capable of dispensing a metered aerosol puff or spray of the nitroglycerin active agent; and

FIG. 2 is a vertical sectional view taken along the line 2—2 of FIG. 1 and shows the valve assembly included in the container illustrated in FIG. 1.

DETAILED DESCRIPTION OF THE INVENTION

According to a specific embodiment of the invention, a nitroglycerin aerosol spray is provided comprising a container having therein nitroglycerin, ethanol, 1,2-polyethyleneglycol, dichlorodifluoromethane and dichlorotetrafluoroethane, present in certain weight ratios to one another and which is in essentially constant contact with a container sealant material, desirably a synthetic material, the absorption value of which for nitroglycerin is less than 10 mg/1 g of sealant material.

The nitroglycerin spray according to this invention is desirably in the form of a nitroglycerin dosing pressurized aerosol-forming hydrophilic liquid, desirably composed of 0.73 weight-% nitroglycerin in a hydrophilic solution of 13.83 weight-% ethanol and 7.28 weight-% 1,2-propyleneglycol and a propellant portion of 78.16 weight-%, and with this composition being in essentially constant contact with a container sealant material, the absorption value of which is less than 10 mg of nitroglycerin per one gram of sealant material, and particularly is in the range of 0.1 to 9.9 mg of nitroglycerin per one gram of sealant material.

Besides the previously mentioned main component parts, the nitroglycerin spray according to this invention may contain the customary additives such as, for example, a nitroglycerin desensitization agent selected from the group consisting of a water soluble alcohol, glycerin and diethyleneglycol, flavoring and/or fragrance materials, which are well known to those skilled in the art.

The nitroglycerin spray according to this invention is manufactured by preparing a homogeneous one-phase solution of nitroglycerin, ethanol and 1,2-propyleneglycol and filling it into an open mouth aerosol spray container, i.e. can or bottle, at a weight-% ratio such as stated in Table 2, a suitable dosing valve assembly is crimped or swaged on and the completed closed container is then charged with a mixture of dichlorodifluoromethane and dichlorotetrafluoroethane at a weight-% ratio such as also stated in Table 2. The sealant materials in the completed product have a nitroglycerin absorption value of less than 10 mg per one gram of sealant material. The container has a height of about 63 mm and a diameter of about 22 mm. It provides about 150 puffs. Table 1 provides pharmacokinetic parameters of various prior art nitroglycerin-containing sprays, as well as of a spray (Formula XS) according to the invention, following sublingual application.

Table 2 sets forth prior art spray formulations and a spray formulation according to this invention.

The composition of a specific hydrophilic liquid spray according to this invention is as follows:

SPECIFIC FORMULA XS

COMPONENT	AMOUNT IN GRAMS IN 100 G OF SOLUTION
Nitroglycerin	0.73
Ethanol	13.83
1,2-Propyleneglycol	7.28
Dichlorodifluoromethane	31.26
Dichlorotetrafluoroethane	46.90
Sealant material with an absorption value for nitroglycerin below 10 mg/1 g of sealant material	

Hydrophilic liquid spray compositions provided by the invention will usually be within the following formulas:

BROAD FORMULA XB

COMPONENT	AMOUNT IN GRAMS IN 100 G OF SOLUTION
Nitroglycerin	0.1 to 2
Ethanol	2 to 20
1,2-Propyleneglycol	2 to 30
Dichlorodifluoromethane	10 to 40
Dichlorotetrafluoroethane	30 to 50
Sealant material with an absorption value for nitroglycerin below 10 mg/1 g of sealant material	

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