Title: OIL-IN-WATER EMULSIONS COMPRISING A BENZODIAZEPINE DRUG

Abstract: There is provided oil-in-water emulsion compositions comprising a benzodiazepine drug, such as midazolam, that is dissolved in an oil phase that comprises 1 to 35% (w/w) vitamin E.
OIL-IN-WATER EMULSIONS COMPRISING A BENZODIAZEPINE DRUG

This invention relates to new oil-in-water emulsion compositions.

Emulsion systems have long been used for pharmaceutical purposes. Such systems include oil-in-water emulsions, water-in-oil emulsions and more complex systems known as multiple emulsions.

Oil-in-water emulsions, in which the continuous phase is aqueous and the dispersed phase is oily in nature, may be used for a variety of purposes and administered via a variety of routes, including injection as well as administration to the eye, nose, lung, gastrointestinal tract or vagina.

Benzodiazepine compounds, which act on the central nervous system to cause sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia and to prevent convulsions, are widely used in medicine. The benzodiazepine drug midazolam (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5α-][1,4]benzodiazepine) is used as a sedative, especially in a hospital setting and particularly as premedication prior to surgery.

The intranasal administration of aqueous solutions of midazolam as a sedative prior to minor invasive surgical and medical procedures has been widely reported (see, for example, S. Björkman et al. *British Journal of Anaesthesia* 79, 575-580 (1997) and N. C. T. Wilton et al. *Anesthesiology* 69, 972-975 (1988)). It has been especially used in the paediatric patient group. Apart from being a patient group in which alleviation of anxiety is particularly beneficial, the use of intranasal midazolam has been largely confined to children because of limited solubility of the drug substance. The aqueous solubility of midazolam is low, and to deliver a therapeutic dose to an adult by the intranasal route would require a prohibitively large
dose volume. An additional drawback of the intranasal administration of midazolam, and which could limit its use (especially in children), is the irritation and stinging that it causes in the nasal cavity. At least part of the cause of this discomfort is thought to be the acidic pH of the simple aqueous solutions of midazolam that are used.

WO 00/24373 describes oil-in-water emulsions of drugs that are poorly soluble in water, especially non-steroidal anti-inflammatory drugs and drugs for the treatment of pain, erectile dysfunction and Parkinson’s disease. Compositions comprising Vitamin E and benzodiazepines are neither disclosed nor suggested.

Compositions comprising benzodiazepines are described in US 4,950,664. The use of vitamin E in such compositions is neither disclosed nor suggested. Further, preferred dosage forms are solutions, suspensions and gels.

A formulation containing 17 mg/mL midazolam, achieved by using sulfobutylether-β-cyclodextrin as a solubilising agent, has been described by Loftsson et al. (Int. J. Pharm. 212, 29-40, (2001)). Penkler et al describes the use of randomly methylated β-cyclodextrin to produce a solution containing 10 mg/mL midazolam (AAPS PharmSci. Supplement 1, S-3642, (1999)).

WO 97/03651 describes emulsion compositions containing vitamin E as a solubilising agent. There is no suggestion in this document of emulsions containing benzodiazepines.
Emulsion formulations of drug compounds are described in US 6,193,985. The compositions comprise active agent dissolved in an oil phase comprising tocopherol (vitamin E), wherein the vitamin E comprises 20 to 95% w/w of the compositions. The second phase of the emulsion comprises vitamin E TPGS as the emulsifying agent. Vitamin E TPGS is a water soluble derivative of vitamin E and consists of tocopherol esterified with succinic acid, the other acidic group of the latter being esterified with polyethylene glycol 1000. Compositions in which the oil phase comprises 1 to 35% (w/w) of vitamin E are neither disclosed nor suggested.

Nonetheless, there is an unmet need for benzodiazepine (and especially midazolam) compositions that contain high concentrations of active agent, that give minimal irritation of the nasal cavity on intranasal administration, and that are stable over prolonged periods.

We have found, surprisingly, that the above-mentioned problems may be solved using an emulsion formulation in which both the amount of oil phase in the emulsion as well as the vitamin E content of that oil phase are carefully selected. We have additionally found that emulsion stability may be further enhanced by addition of a non-ionic surfactant and/or a cellulose-based thickening agent. When administered into the nasal cavity, the emulsion is well tolerated.

Thus, according to the invention there is provided oil-in-water emulsion compositions for the delivery of a benzodiazepine drug to a patient comprising:

(a) an oil phase, which phase comprises 10 to 60% (w/v) of the emulsion, and which phase comprises vitamin E in an amount 1 to 35% (w/w of that phase) and a benzodiazepine drug;

(b) an aqueous phase; and
(c) an emulsion stabiliser,
which compositions are referred to hereinafter as "the emulsions according to the invention".

5 It is preferred that the emulsions according to the invention are adapted for intranasal administration.

When used herein, the term "vitamin E" includes all tocol and tocotrienol derivatives that exhibit vitamin E activity. It is preferred that the vitamin E is water insoluble and/or non-water dispersible. The nomenclature for vitamin E and related compounds is unclear in current practice and can vary when used by different compendia and organisations. The United States Pharmacopoeia describes vitamin E as a form of \( \alpha \)-tocopherol. This includes D- or D\(_{L}\)-\( \alpha \)-tocopherol, D- or D\(_{L}\)-\( \alpha \)-tocopherol acetate and D- or D\(_{L}\)-\( \alpha \)-tocopherol succinate. The Association of Official Analytical Chemists (AOAC) states that the term vitamin E should be used as a generic description for all tocol and tocotrienol derivatives that exhibit vitamin E activity. Thus the term tocopherols is synonymous with vitamin E but also for methyl tocols. \( \alpha \)-Tocopherol is a trivial name without defined stereochemistry.

The vitamin E is preferably in the form of the free alcohol, but suitable tocopherol derivatives include esters of tocopherol such as the linoleate, nicotinate, acetate or acid succinate ester.

25 The emulsions according to the invention have an oil phase that comprises one or more pharmaceutically acceptable oils. These oils are preferably non-hydroxylated (i.e. they have a hydroxyl value of less than 20) and as such they include vegetable oils such as soybean oil, sesame oil, safflower
oil, canola oil, corn oil, cottonseed oil and olive oil as well as marine oils such as cod liver oil and sardine oil. Preferred oils are sesame oil, canola oil, corn oil, cottonseed oil, and, especially, soybean oil.

The emulsions according to the invention preferably have an oil phase that represents 12 to 50% (w/v) and more preferably 15 to 40% (w/v) of the total emulsion. Further, the emulsions according to the invention preferably have an oil phase that comprises 2.5 to 30% (w/w) (such as 5 to 25% (w/w)) vitamin E.

When used herein, the term “benzodiazepine drug” will be understood by those skilled in the art to include all pharmacologically active compounds that possess the benzodiazepine (sub-)structure, and which may act on the central nervous system. See also the definition provided in Goodman & Gilman’s “The Pharmacological Basis of Therapeutics”, 9th Edition (1996), McGraw-Hill at pages 363 and 364, the relevant disclosure in which document is hereby incorporated by reference. Examples of suitable benzodiazepine drugs include alprazolam, bentazepam, bromazepam, brotizolam, camazepam, chlordiazepoxide, cinolazepam, clobazam, clonazepam, clorazepic acid, clorazepate, clotiazepam, clozapine, delorazepam, diazepam, estazolam, ethyl loflazepate, etizolam, fludiazepam, flunitrazepam, flurazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, metaclazepam, mexazolam, midazolam, nimetazepam, nitrazepam, oxazepam, pinazepam, prazepam, quazepam, temazepam, tetrazepam and triazolam. Preferred benzodiazepine drugs include alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, nitrazepam, oxazepam, prazepam, quazepam, temazepam, triazolam and, especially, midazolam.
The benzodiazepine drug content of the emulsions according to the invention is dependent upon the solubility of the benzodiazepine drug in question and the dose that needs to be delivered to the patient. For an intranasal formulation delivered as a liquid, the typical dose volume is in the range 0.1 to 0.4 mL although smaller or larger volumes may also be given. The benzodiazepine drug may be incorporated into the emulsions according to the invention by being dissolved into the oil phase prior to emulsification. The benzodiazepine drug content of the oil phase prior to preparation of the emulsions according to the invention is preferably in the range 1 to 1000 mg/mL, more preferably 2 to 800 mg/mL and most preferably 4 to 600 mg/mL. The benzodiazepine drug content of the final oil-in-water emulsion is preferably in the range 0.1 to 300 mg/mL, more preferably 0.5 to 250 mg/mL and most preferably 1 to 200 mg/mL.

When used herein, the term “emulsion stabiliser” refers to agents that, when present in emulsions according to the invention, either prevent or retard phase separation (i.e. the formation of distinct oil and/or water layers) in the emulsions. The term therefore includes agents that prevent phase separation in the emulsions according to the invention for one or more hours or, preferably, for one or more days (e.g. 3 or more days, such as one or more weeks, and, particularly, one or more months).

The emulsion stabiliser is preferably incorporated into the emulsions according to the invention via the aqueous phase. Preferred emulsion stabilisers include one or more thickening and/or, particularly, emulsifying agents. Suitable thickening agents include cellulose-based thickening agents such as methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Suitable emulsifying agents include:

(a) ionic surfactants (e.g. phospholipids such as lecithin); and
(b) non-ionic surfactants (e.g. polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polyoxyethylene castor oil derivatives and polyoxyethylene alkyl ethers).


Principal sources of lecithin are eggs and soybeans. Synonyms for lecithin include egg lecithin; mixed soybean phosphatides; ovolecithin; egg yolk phospholipids; soybean lecithin; soybean phospholipids; vegetable lecithin.

Preferred emulsions according to the invention include those that include an emulsion stabiliser that is an emulsifying agent (e.g. an ionic surfactant such as lecithin). In this respect, preferred emulsions according to the invention also include those in which lecithin is employed as an emulsion stabiliser, and a non-ionic surfactant and/or a thickening agent, as hereinbefore defined, is/are optionally employed as (a) further emulsion stabiliser(s).

The amount of emulsion stabiliser (e.g. lecithin) used in the emulsion according to the invention is preferably in the range 0.01 to 15% (w/v), more preferably 0.05 to 10% (w/v) and most preferably 0.1 to 5% (w/v).

When present in the emulsions according to the invention, the non-ionic surfactant may have a concentration that is preferably in the range 0.01 to 25% (w/v), more preferably 0.05 to 20% (w/v) and most preferably 0.1 to 15% (w/v).
When present in the emulsions according to the invention, the thickening agent may have a concentration that is dependent upon its molecular weight. However, its concentration in an emulsion according to the invention is preferably in the range 0.01 to 20% (w/v), more preferably 0.05 to 15% (w/v) and most preferably 0.1 to 10% (w/v).

The pH of the emulsions according to the invention is an important determinant of how well they are tolerated when administered into the nasal cavity. The emulsion may cause irritation and stinging if the pH is too high or low. Further, when the emulsion according to the invention comprises midazolam, it is also preferable to avoid a low pH in order to minimise drug partitioning from the oil phase into the aqueous phase. High concentrations of midazolam in the aqueous phase may exacerbate irritation.

Measuring accurately the pH of an oil-in-water emulsion may be problematic. Indeed, it may be more convenient to measure the pH of the aqueous phase of the emulsion. This measurement may be performed by centrifugation of the emulsion at a force adequate to separate the oil and aqueous phases into separate layers. The aqueous layer may then be removed and the pH measured. The pH of the aqueous phase of an emulsion according to the invention is preferably in the range pH 5.0 to 8.0, more preferably 5.25 to 7.8 and most preferably pH 5.5 to 7.6.

The pH of the aqueous phase of the emulsions according to the invention may be adjusted and controlled by means well known to those skilled in the art, such as buffer salts, acids and bases. Thus, the aqueous phase may contain one or more of the following pH controlling agents: organic acids (e.g. citric acid and the like) or alkali metal (e.g. sodium) salts thereof, pharmaceutically acceptable salts (e.g. sodium, magnesium or calcium salts) of inorganic acids (such as carbonic acid or phosphoric acid), oxides of
magnesium, as well as alkali, and alkaline earth, metal (e.g. sodium, calcium, potassium and the like) sulphates, metabisulphates, propionates and sorbates. The aqueous phase may, in particular, comprise a buffered aqueous solution, such as phosphate-buffered saline, that has a pH within any of the above-mentioned ranges (e.g. pH 7.4).

The emulsions according to the invention may, if necessary, be adjusted to approximately the same osmotic pressure as that of the body fluids. This may be desirable where a composition is to be applied to delicate tissue membranes, such as those found in the nasal cavity. A composition that has been adjusted in this manner is said to be isotonic and will not tend to swell or contract the tissues with which it comes into contact and will result in minimal discomfort on application. The formation of isotonic preparations may be achieved by adding an ionic compound, such as sodium chloride, or a non-ionic compound to the composition. Suitable non-ionic compounds include glycerol and mannitol.

The emulsions according to the invention may also contain other ingredients in the oil and/or aqueous phases such as antioxidants, chelating agents, preservatives or other agents generally used in pharmaceutical liquid or emulsion formulations. Such agents are well known to those skilled in the art.

Preferred emulsions according to the invention include those that are stable with respect to phase separation for one or more days (e.g. 3 or more days, such as one or more weeks, and, particularly, one or more months). When used herein, the term “stable with respect to phase separation” includes compositions that, on storage, either do not form a distinct oil layer or form a distinct layer of non-coalesced oil droplets that may be redispersed by
gentle shaking (e.g. shaking by hand) alone. The latter process, by which a layer of stabilised oil droplets separates, is known as “creaming”.

In their simplest form, the emulsions according to the invention are prepared by dissolving or dispersing emulsion stabiliser in the aqueous phase. The aqueous phase is then mixed with the oil phase (comprising vitamin E, oil and the benzodiazepine drug) to form a dispersion of oil droplets.

Thus, according to a further aspect of the invention, there is provided a process for the preparation of an emulsion according to the invention, which process comprises:
(i) addition of an emulsion stabiliser, as hereinbefore defined, to an aqueous component (e.g. water) to form the aqueous phase;
(ii) addition of vitamin E, and of a benzodiazepine drug, as hereinbefore defined, to an oil to form the oil phase; and
(iii) mixing the oil phase and the aqueous phase together.

The size and size distribution of the oil droplets in the emulsions according to the invention will depend on the method of mixing. In stable emulsions, the droplet size, as measured by techniques such as light microscopy or laser diffraction, generally lies in the range 0.1 to 10 μm. High shear mixing using equipment such as a homogeniser or a microfluidiser is the preferred method of preparing pharmaceutical emulsions.

According to a further aspect of the invention, there is provided the use of an emulsion according to the invention for the manufacture of a medicament for the administration of a benzodiazepine drug (e.g. midazolam) to a patient in need of such administration.
Similarly, another aspect of the invention provides a method of administering a benzodiazepine drug (e.g. midazolam) to a patient, which method comprises administering to the patient an emulsion according to the invention.

In another aspect of the invention, there is provided the use of an emulsion according to the invention in the manufacture of a medicament for the treatment of a condition in which benzodiazepine drug treatment is indicated.

Particular conditions where benzodiazepine drug treatment may be indicated include anxiety disorders, convulsive disorders (e.g. febrile convulsions and convulsions from status epilepticus), disturbed behaviour, parasomnias (e.g. insomnia, restless leg syndrome, sleepwalking or night terrors), dyspnœa, muscle spasm (e.g. from spasticity, dystonias, stiff-man syndrome, cerebral palsy, poisoning or tetanus), emesis (e.g. nausea and vomiting associated with, for example, cancer chemotherapy), schizophrenia, vertigo and withdrawal syndromes (e.g. alcohol or opioid withdrawal).

Benzodiazepine drugs may also be given for premedication (e.g. before general anaesthesia or to provide sedative cover for minor surgical or investigative procedures) and/or to induce sedation, hypnosis and/or anterograde amnesia. Preferred indications include the provision of sedative cover for minor surgical or investigative procedures.

The emulsions according to the invention may be administered orally or parenterally. When used herein, the term “parenterally” includes administration to the muscles, subcutaneous tissue, peritoneal cavity, venous system, arterial system, lymphatic system, spinal fluid (intrathecal,
epidural) and joint cavities. Parenteral formulations will be sterile and usually pyrogen-free.

The emulsions according to the invention may also be administered to the gastrointestinal tract or other mucosal surfaces, such as the eye, nose, vagina or rectal cavity.

It is preferred that the emulsions according to the invention are administered intranasally. When adapted for intranasal administration, the emulsions according to the invention may be administered to the nasal cavity in forms including drops or sprays. Spray devices can be single ("unit") dose or multiple dose systems and are available from various commercial sources, including Pfeiffer, Valois, Bespak and Becton-Dickinson.

Emulsions according to the invention have the advantage that they may be more stable than (particularly with respect to phase separation), be better tolerated than, be less toxic than, have fewer side effects than, have better pharmacokinetic properties than, be more easily prepared than, or have any other useful properties over, compositions known in the prior art.

Moreover, emulsions according to the invention also have the advantage that they may be prepared using established pharmaceutical processing methods and employ materials that are approved for use in food or pharmaceuticals or are of like regulatory status.

The invention is illustrated, but in no way limited, by the following examples.
Examples

Example 1
Placebo emulsion comprising 25% w/v oil phase in which oil phase comprises 40% w/w vitamin E

The oil phase was prepared by mixing 10 g of vitamin E (Sigma, Poole, UK) with 15 g of soybean oil (Oleificio SABO, Manno, Switzerland). Into 50 mL of phosphate buffered saline solution (PBS; Sigma) was dispersed 1.2 g of egg yolk phospholipid (lecithin; Kabi Pharmacia, Sweden), followed by the addition of 2.2 g of glycerol (Sigma). A coarse emulsion was prepared by mixing the oil and aqueous phases using a Silverson L4R homogeniser. The coarse emulsion was adjusted to a 100 mL volume with PBS and further emulsified by passing through a Rannie Mini-Lab high pressure valve homogeniser set at 1000 bar pressure.

Example 2
Placebo emulsion comprising 25% w/v oil phase in which oil phase comprises 20% w/w vitamin E

The oil phase was prepared by mixing 5 g of vitamin E with 20 g of soybean oil. The emulsion was then prepared in an identical manner to Example 1.
Example 3
Placebo emulsion comprising 33.3% w/v oil phase in which oil phase comprises 20% w/w vitamin E

The oil phase was prepared by mixing 6.66 g of vitamin E with 26.64 g of soybean oil. The emulsion was then prepared in an identical manner to Example 1.

Example 4
Placebo emulsion comprising 40% w/v oil phase in which oil phase comprises 20% w/w vitamin E

The oil phase was prepared by mixing 8 g of vitamin E with 32 g of soybean oil. The emulsion was then prepared in an identical manner to Example 1.

Example 5
Stability of emulsions prepared in Examples 1-4

Samples of the emulsions prepared in Examples 1-4 were sealed into 50 mL clear glass injection vials and stored at room temperature. The appearance of the emulsions was recorded over a 7-day period. The results are provided in the table below. Examples 2, 3 and 4 showed good physical stability over the test period. Although there was some separation of the two phases (creaming), the uniform appearance of the emulsions could be restored with gentle shaking.

Example 1, with an oil phase comprising 40% w/w vitamin E, had poor stability and the oil phase readily separated. It was not possible to restore the emulsion to its original uniform state by means of shaking.
<table>
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<tr>
<th>Sample</th>
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<th>3 hours</th>
<th>1 day</th>
<th>3-4 days</th>
<th>7 days</th>
</tr>
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<tbody>
<tr>
<td>Ex. 1</td>
<td>Stable</td>
<td>Stable</td>
<td>Slight separation, easily redispersed</td>
<td>Separation</td>
<td>Separation</td>
</tr>
<tr>
<td>Ex. 2</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Slight separation, easily redispersed</td>
</tr>
<tr>
<td>Ex. 3</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Slight separation, easily redispersed</td>
<td>Slight separation, easily redispersed</td>
</tr>
<tr>
<td>Ex. 4</td>
<td>Stable</td>
<td>Stable</td>
<td>Slight separation, easily redispersed</td>
<td>Slight separation, easily redispersed</td>
<td>Slight separation, easily redispersed</td>
</tr>
</tbody>
</table>

**Example 6**

Emulsion containing 10 mg/mL midazolam and 25% w/v oil phase

Vitamin E (5 g) and 20 g of soybean oil were weighed into a 50 mL beaker. Midazolam (1 g; R. W. Unwin, Welwyn, UK) was added to the vitamin E/soybean oil and the mixture was warmed and stirred at 30-40°C until the drug had dissolved. Egg yolk phospholipid (1.2 g; lecithin) was weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40°C. Glycerol (2.2 g) was added to the lecithin dispersion. The oil phase was added to the aqueous phase and the two were mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed was made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product was a milky white to off-white emulsion.
Example 7

Emulsion containing 10 mg/mL midazolam and 33% w/v oil phase
Vitamin E (6.66 g) and 26.64 g of soybean oil were weighed into a 50 mL beaker. Midazolam (1 g) was added to the vitamin E/soybean oil and the mixture was warmed and stirred at 30-40°C until the drug had dissolved. The emulsion was then prepared according to Example 6.

Example 8

Emulsion containing 10 mg/mL midazolam with polyoxyethylene 20 sorbitan monooleate as additional emulsifier
Vitamin E (5 g) and 20 g of soybean oil are weighed into a 50 mL beaker. Midazolam (1 g) is added to the vitamin E/soybean oil and the mixture is warmed and stirred at 30-40°C until the drug has dissolved. Egg yolk phospholipid (1.2 g; lecithin) and 0.5 g of polyoxyethylene 20 sorbitan monooleate (Sigma) is weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40°C. Glycerol (2.2 g) is added to this aqueous phase. The oil phase is added to the aqueous phase and the two are mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed is made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product will be a milky white to off-white emulsion.

Example 9

Emulsion containing 10 mg/mL midazolam with methylcellulose as thickening agent
Vitamin E (6.66 g) and 26.64 g of soybean oil are weighed into a 50 mL beaker. Midazolam (1 g) is added to the vitamin E/soybean oil and the mixture is warmed and stirred at 30-40°C until the drug has dissolved. Egg yolk phospholipid (1.2 g; lecithin) and 0.5 g of methylcellulose (Methocel®...
A15LV; Colorcon, Orpington, UK) are weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40°C. Glycerol (2.2 g) is added to the lecithin dispersion. The oil phase is added to the aqueous phase and the two are mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed is made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product will be a milky white to off-white emulsion.

**Example 10**

Emulsion containing 10 mg/mL midazolam with polyoxyl 40 stearate as additional emulsifier and hydroxypropyl methylcellulose as thickening agent

Vitamin E (6.66 g) and 26.64 g of soybean oil are weighed into a 50 mL beaker. Midazolam (1 g) is added to the vitamin E/soybean oil and the mixture is warmed and stirred at 30-40°C until the drug has dissolved. Egg yolk phospholipid (1.2 g; lecithin), 0.5 g of polyoxyl 40 stearate (polyoxyethylene (40) stearate; Sigma) and 0.5 g of hydroxypropyl methylcellulose (Methocel® K4M; Colorcon) are weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40°C. Glycerol (2.2 g) is added to the lecithin dispersion. The oil phase is added to the aqueous phase and the two are mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed is made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product will be a milky white to off-white emulsion.
Example 11
Tolerability of midazolam emulsion in sheep

The sheep is an excellent animal model for nasal pharmacokinetic studies with a large nasal cavity and the ability to receive human-sized doses of drugs and formulations. If an irritant drug or formulation is administered intranasally to the sheep, it may cause the animal to sneeze and snort and the extent of sneezing and snorting may be related to the irritancy of the formulation. A group of five sheep were each administered with a midazolam emulsion formulation of identical composition to Example 7 as part of a pharmacokinetic study. Each animal, weighing approximately 55 kg, was administered intranasally with the emulsion at a dose volume of 0.02 mL/kg divided equally between both nostrils i.e. a 55 kg sheep received 0.55 mL of emulsion per nostril. In the 60 minutes following dosing, any incidences of sneezing or snorting were recorded. There were no incidences in any of the five animals during this period, indicating that the formulation was extremely well tolerated.
Claims

1. An oil-in-water emulsion composition for the delivery of a benzodiazepine drug to a patient comprising:
   (a) an oil phase, which phase comprises 10 to 60% (w/v) of the emulsion, and which phase comprises vitamin E in an amount 1 to 35% (w/w of that phase) and a benzodiazepine drug;
   (b) an aqueous phase; and
   (c) an emulsion stabiliser.

2. A composition as claimed in Claim 1, wherein the benzodiazepine drug is alprazolam, benzepam, bromazepam, brotizolam, camazepam, chlordiazepoxide, cinolazepam, clobazam, clonazepam, clorazepic acid, clorazepate, clotidezepam, clozapine, delorazepam, diazepam, estazolam, ethyl loflazepate, etizolam, fludiazepam, flunitrazepam, flurazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, metaclazepam, mexazolam, midazolam, nimetazepam, nitrazepam, oxazepam, pinazepam, prazepam, quazepam, temazepam, tetrazepam or triazolam.

3. A composition as claimed in Claim 2, wherein the benzodiazepine drug is alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, oxazepam, prazepam, quazepam, temazepam or triazolam.

4. A composition as claimed in Claim 3, wherein the benzodiazepine drug is midazolam.

5. A composition as claimed in any one of the preceding claims, wherein the oil phase comprises a non-hydroxylated oil.
6. A composition as claimed in Claim 5, wherein the non-hydroxylated oil is soybean oil, sesame oil, safflower oil, canola oil, corn oil, cottonseed oil, olive oil, cod liver oil or sardine oil.

7. A composition as claimed in Claim 6, wherein the non-hydroxylated oil is soybean oil, sesame oil, canola oil, corn oil or cottonseed oil.

8. A composition as claimed in Claim 7, wherein the non-hydroxylated oil is soybean oil.

9. A composition as claimed in any one of the preceding claims, wherein the oil phase represents 12 to 50% (w/v) of the emulsion.

10. A composition as claimed in Claim 9, wherein the oil phase represents 15 to 40% (w/v) of the emulsion.

11. A composition as claimed in any one of the preceding claims, wherein the oil phase comprises 2.5 to 30% (w/w) vitamin E.

12. A composition as claimed in Claim 11, wherein the oil phase comprises 5 to 25% (w/w) vitamin E.

13. A composition as claimed in any one of the preceding claims, wherein the benzodiazepine drug content of the oil-in-water emulsion is in the range 0.1 to 300 mg/mL.

14. A composition as claimed in any one of the preceding claims, wherein the emulsion stabiliser is one or more thickening and/or emulsifying agents.
15. A composition as claimed in Claim 14, wherein the emulsion stabiliser is an emulsifying agent.

16. A composition as claimed in Claim 15, wherein the emulsifying agent is an ionic surfactant.

17. A composition as claimed in Claim 16, wherein the ionic surfactant is a phospholipid.

18. A composition as claimed in Claim 17, wherein the phospholipid is lecithin.

19. A composition as claimed in any one of Claims 15 to 18, wherein a non-ionic surfactant and/or a thickening agent is/are optionally employed as (a) further emulsion stabiliser(s).

20. A composition as claimed in Claim 19, wherein the non-ionic surfactant is selected from the group consisting of a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene stearate, a polyoxyethylene castor oil derivative and a polyoxyethylene alkyl ether.

21. A composition as claimed in Claim 19 or Claim 20, wherein the thickening agent is cellulose-based.

22. A composition as claimed in Claim 21, wherein the thickening agent is methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose or hydroxypropyl methylcellulose.
23. A composition as claimed in any one of the preceding claims, wherein the pH of the aqueous phase is in the range pH 5.0 to 8.0.

24. A composition as claimed in any one of the preceding claims, wherein the emulsion is stable with respect to phase separation for one or more days.

25. The use of a composition as defined in any one of Claims 1 to 24 for the manufacture of a medicament for the administration of a benzodiazepine drug to a patient in need of such administration.

26. Use as claimed in Claim 25 wherein the benzodiazepine drug is midazolam.

27. A method of administering a benzodiazepine drug to a patient, which method comprises administering to the patient a composition as defined in any one of Claims 1 to 24.

28. A method as claimed in Claim 27, wherein the emulsion is administered intranasally.

29. The use of a composition as defined in any one of Claims 1 to 24 in the manufacture of a medicament for the treatment of a condition in which benzodiazepine drug treatment is indicated.

30. The use as claimed in Claim 29, wherein the condition to be treated is an anxiety disorder, a convulsive disorder, disturbed behaviour, a parasomnia, dyspnoea, muscle spasm, emesis, schizophrenia, vertigo or a withdrawal syndrome.
31. The use as claimed in Claim 29, wherein the benzodiazepine drug is given for premedication and/or to induce sedation, hypnosis and/or anterograde amnesia.

32. A process for the preparation of a composition as defined in any one of Claims 1 to 24, which process comprises:

(i) addition of an emulsion stabiliser to an aqueous component to form the aqueous phase;

(ii) addition of vitamin E, and of a benzodiazepine drug, to an oil to form the oil phase; and

(iii) mixing the oil phase and the aqueous phase together.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER


According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

| IPC | A61K |

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, PASCAL, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

Date of the actual completion of the international search: 26 September 2002

Date of mailing of the international search report: 07/10/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HN Rijswijk
Tel.: (+31-70) 340-2040, Fax: 340-3016

Authorized officer

Zimmer, B
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