Abstract:

This application discloses liquid compositions for administration to a patient comprising midazolam and a pharmaceutically acceptable carrier, wherein the pH of the composition is about 6 or higher and/or an advantageous carrier system is present, the composition comprises less than about 200 mg/ml cyclodextrin, and at least about 50% of the midazolam is present in solution. Uses of these compositions are also disclosed.
This invention relates to a pharmaceutical composition. In particular, it relates to an improved liquid pharmaceutical composition suitable for the treatment of epilepsy. It further relates to a liquid pharmaceutical composition suitable for use as an anaesthetic.

Midazolam, i.e. 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[l,5-a][l,4] is a diazepine of the formula:

![Chemical structure of midazolam](image)

is a well-documented product with sedative, anxiolytic, amnesic and hypnotic properties. It is commercially available in the form of its hydrochloride, for example in the form of a glycerine-based syrup sold under the trade name VERSED®, which contains 2.5 mg/ml of midazolam. It is also sold in the form of its maleate salt, for example in tablets containing 7.5mg or 15mg per tablet under the trade mark DORMICUM®. A product which is formulated for administration via the buccal route is EPISTATUS®. Buccal formulations of midazolam are also disclosed in EP1323422.

It is known that midazolam can exist in solution both in a closed ring form and also in an open ring form. These two forms are in equilibrium with one another:
The amount of the open ring form (la) present in aqueous solution is influenced by pH. A chart showing the effect of pH on the proportion of midazolam present in the open ring form is provided as Figure 1.

One of the factors determining the rate of physiological absorption of midazolam is the proportion of open ring (la) midazolam present in the formulation. The closed ring form (I) of midazolam is lipophilic and is more rapidly absorbed than the open ring form (la). It is therefore desirable to provide a formulation in which the majority of midazolam is present in the closed ring form (I).

While attempts to develop therapeutically effective higher pH formulations of midazolam have been made, these have been unsuccessful due to the inverse relationship between pH and the solubility of midazolam. For example, Olivier et al, International Journal of Pharmaceutics, 2001 (213), pages 187 to 192, concluded the satisfactory solubilisation of midazolam at higher pHs was a problem that remained to be solved.

At pH 8, the solubility of midazolam is just 0.055mg/ml in aqueous solution. To deliver a therapeutically effective amount of such a solution, the volume required would be unacceptably large.

WO01/30391 provides an example of an attempt to formulate midazolam at a higher pH while circumventing the problem of reduced solubility. This is achieved by the use of
cyclodextrin, which forms an inclusion complex with midazolam, retaining it in solution. However, the release of midazolam from cyclodextrin complexes is slow and this increases the time lag between administration and the onset of therapeutic effect.

As a result of the low solubility of midazolam at higher pHs, commercially available liquid formulations of midazolam tend to have pHs of no greater than about 5 as at these pHs, there is a sufficiently high proportion of midazolam in the closed ring form to ensure an acceptable degree of efficacy, while the solubility of midazolam is sufficient to enable a relatively low volume of carrier liquid to be used.

For example, in a typical syrup for oral administration, e.g. VERSED® syrup, the pH ranges from 2.8 to 3.6. Within that range, the solution may contain up to about 40% of midazolam in the open ring form (la). Following administration, the medicament will become exposed to physiologic conditions, including pHs in the range of 5 to 8, and will be absorbed into systemic circulation under those conditions. Thus, the majority of the midazolam present in the open-ring form present in the medicament will be converted to the closed ring form upon absorption. However, this change of pH and absorbance of midazolam will not occur immediately, upon administration, and there is a time lag between administration and the onset of therapeutic activity of approximately 10 to 30 minutes.

The buccally administered form of midazolam, EPISTATUS® is an extremely convenient and straightforward vehicle for delivering midazolam rapidly to patients suffering from epileptic seizures or significant amounts of pain. The pH of the EPISTATUS®, product is around 4.5 to 5.5 and the proportion of midazolam in the open ring form (la) is approximately 1%.

The rate of absorption of midazolam from the EPISTATUS® formulation is sufficiently high to provide a rapid onset of therapeutic effect in patients. However, in view of the importance of the rapid delivery of midazolam to patients in need thereof, it would nevertheless be advantageous if the rate of absorption could be improved.

This is because epileptic seizures are a common cause of neurological medical emergency and may result in brain damage. Failure to relieve the symptoms of an epileptic seizure in
less than about 15 minutes may lead to death. Accordingly, it is extremely desirable to treat a patient suffering from an epileptic seizure as promptly as possible so as to minimise the risk of brain damage or death to the patient. Additionally, when used as an anaesthetic, it is desirable, for obvious reasons, to treat a patient suffering from pain as promptly as possible.

The use of injectable formulations of midazolam is common. While midazolam administered in this way will have a rapid onset of therapeutic effect, it will not be suitable for use in all patient groups. For example, the use of a needled syringe with a patient suffering from an epileptic seizure will be problematic and potentially dangerous to both the patient and the healthcare professional administering the medicament. Additionally, the use of needled syringes is likely to raise anxiety in certain patient groups, such as children.

Accordingly, the administration of midazolam via the mucous membranes of a patient is a desirable route of administration for midazolam. Administration via this route offers the advantages of rapid therapeutic onset as well as the avoidance of needled syringes. Administration of midazolam via the buccal, nasal, rectal and/or sub-lingual mucous membranes is especially desirable.

Attempts to prepare formulations of midazolam for nasal administration have been made, for example, as reported by Wilton et al., Anesthesiology 1988, 69, pages 972-5. Most studies on intranasal formulations of midazolam have made use of a dilute aqueous midazolam injection solution that is not suitable for nasal administration because of a low pH (3 or less) which causes intense discomfort to patients and also because they are prone to nasal run-off.

Attempts have been made to overcome these problems. For example, Wermeling et al., Anesthesia & Analgesia, August 2006, volume 103 number 2, pages 344-349, developed a formulation containing midazolam, polyethylene glycol 400, butylated hydroxytoluene, saccharin and propylene glycol. That formulation provided 2.5 mg of midazolam in a 0.1 mL spray delivered using a modified version of a commercially available unit-dose spray pump. However, the formulation was associated with numerous adverse events, including eye
watering (58% of doses), dizziness (17% of doses), bad taste (25% of doses), and nasal congestion/feeling nasopharyngeal irritation (100% of doses).

There is accordingly a need to provide an improved formulation for the administration of midazolam to the mucosal membranes of a patient in need thereof, e.g. a patient suffering an epileptic seizure, or suffering from unacceptable levels of pain.

The present invention seeks to provide a liquid medicament which provides a more rapid onset of therapeutic effect than midazolam-containing formulations of the prior art, that does not raise anxiety levels in patients, which can safely be used with patients suffering from epileptic seizures, which is stable, and/or which can be administered to the mucous membranes of patients without causing discomfort.

According to a first aspect of the present invention there is provided a liquid composition for administration to a patient comprising midazolam and a pharmaceutically acceptable carrier, the composition having a pH of about 6 or higher, the formulation comprising less than 200mg/ml cyclodextrin, and at least 50% of the midazolam being present in solution.

The formulations are suitable for administration to patients via any mucosal membrane. In preferred embodiments, the formulations are suitable for buccal, nasal, rectal and/or sublingual administration.

The possibility of raising the pH of liquid formulations comprising midazolam (and thus the proportion of the lipophilic closed ring form of midazolam) has previously been limited by a simultaneous reduction in solubility of that active. It has surprisingly been found that when the higher pH formulations of the present invention are employed, midazolam is highly, if not totally, soluble. More specifically, in those formulations, at least about 50% of midazolam is retained in solution. In preferred embodiments of the present invention, at least about 60%, 70%, 80%, 90%, 95%, 98% or 99% of midazolam is retained in solution. In especially preferred embodiments, substantially all of the midazolam present is retained in solution.
This is achieved without the need for the use of substantial amounts of cyclodextrin. Although cyclodextrin does aid the solubility of midazolam at higher pHs, it will form inclusion complexes and the release of midazolam from those complexes upon administration will delay the onset of the therapeutic effect. Thus, the formulations of the present invention include less than 200mg/mL of cyclodextrin. The formulations preferably include less than 150mg/mL, 100mg/mL, 50mg/mL, 25mg/mL, 10mg/mL, 5mg/mL, or 2mg/mL of cyclodextrin. In especially preferred embodiments of the present invention, the formulations contain less than 1mg/mL of cyclodextrin or are substantially free of cyclodextrin.

The onset of therapeutic effect of the compositions of the present invention will clearly depend on the rate of their passage across the mucosal membrane. Advantageously, the formulations of the present invention are capable of doing so more rapidly than lower pH counterparts compositions. Thus, in preferred aspects of the present invention, the formulations of the present invention exhibit a flux rate of about 2°Cg/cm²/hour or greater, about 3°Cg/cm²/hour or greater, about 4°Cg/cm²/hour or greater, about 5°Cg/cm²/hour or greater, about 6°Cg/cm²/hour or greater, about 7°Cg/cm²/hour or greater or about 8°Cg/cm²/hour or greater.

For the purposes of the present invention, flux rate is measured at 21°C with an infinite dose of active using a Franz cell (e.g. Rotulex No. 18) with a 250µm membrane and a UV-visible spectrophotometer (Spectronic Biometric, Thermo Electron Limited, Cambridge, UK).

Although the rates of flux measured using this apparatus are not directly comparable with in-vivo flux rates, this system does enable the consistent measurement of flux under conditions which mimic biological conditions.

By providing midazolam in a solution, the drawbacks associated with the use of other types of liquid medication systems, such as emulsions or true suspensions (i.e. those where greater than 50% of medication is suspended therein) can be avoided. More specifically, emulsions are known to be prone to stability problems, especially when stored over extended periods of time as the oil and aqueous phases may separate out into a bilayered
system. Additionally, when suspensions are stored for prolonged periods, the suspended material may settle and agglomerate, making its delivery difficult.

The proportion of midazolam in the closed ring form (I) in the advantageous formulations of the present formulation is at least 99%. More preferably, the proportion of midazolam in the closed ring form (I) is at least 98%, at least 99%, at least 99.5%, at least 99.7% or even at least 99.9%

In prior art formulations having a pH of 4 to 5, approximately 95 to 98% of midazolam was present in the closed ring form. While the therapeutic activity of those medicaments could hypothetically be improved by increasing the pH, and thus the proportion of the closed ring structure present from 95 to 98% to at least 99%, this increase in clinical effect is not justified when weighed against the difficulty of formulating midazolam at higher pHs.

The formulations of the present invention advantageously retain at least 50% of midazolam in solution with the vast majority of the active present in the closed ring form. In addition to improving the efficacy and the speed of onset of therapeutic effect, a further advantage exhibited by those formulations is an improvement in stability.

More specifically, it has been observed that conventional formulations comprising midazolam include certain impurities, which become more prevalent upon extended storage of those products.

HPLC traces which confirm the gradual increase of addition products present in prior art formulations of midazolam over time are provided as Figures 2a to 2d. Those traces were obtained from samples of Epistatus which were stored under accelerated conditions (40°C and 75% relative humidity) and tested after 1 month (Figure 2a), 3 months (Figure 2b), 6 months (Figure 2c) and 9 months (Figure 2d).

The broad peak at approximately 24 minutes in all four traces is provided by midazolam. The double peak at approximately 4.5 minutes is provided by two compounds, 3-carboxy-2-(8-chloro-1,6-dimethyl-4/-imidazo[1,5-a][1,4]benzodiazepin-2-ium-2-yl) propanoate and 3-
carboxy-3-(8-chloro-1,6-dimethyl-4H-imidazo[1,5-a][1,4]benzodiazepin-2-ium-2-yl) propanoate, or, for brevity, SMA and SMB. The intensity of that double peak increased over time. While the increase in the amounts of the impurities present was not of sufficient magnitude to contravene the purity and efficacy requirements placed on the Epistatus product, they are nevertheless undesirable.

It has been surprisingly been found that, by formulating midazolam at higher pHs, the amounts of impurities present, especially SMA and SMB, have been significantly reduced.

Without wishing to be bound by theory, it is believed that this advantageous reduction of the amount of impurities is connected to a reduction or elimination of the amount of midazolam present in the open ring form. More specifically, the open ring form of midazolam provides reaction sites at which additive reactions can take place, for example, with counterions from the midazolam salt used to prepare the Epistatus formulation.

Thus, if midazolam is included in a formulation in the form of, for example, its maleate salt, the resultant maleic acid present in solution can degrade the open ring form of midazolam to form succinyl derivatives, such as SMA and SMB. It is envisaged that counterions other than maleate which are used to form salts with midazolam will be involved in analogous unwanted reactions with the open ring form of midazolam.

Initially, there will only be a very small proportion of these derivatives formed, due to the low proportion of the open ring form of midazolam which is present. However, as midazolam in the open ring form is converted to the addition salts mentioned above, this will drive the dynamic equilibrium between the open and closed forms of midazolam to form additional quantities (albeit low) of the open ring form of midazolam which will in turn be converted to form further quantities of the unwanted degradants. It will be appreciated that over time, this effect will cause the proportion of these addition products to increase, while decreasing the amount of midazolam present. It is believed that by maintaining a negligible amount of midazolam in the open ring form, the formation of impurities is reduced.
In preferred embodiments of the present invention, the pH is at least about 7.0, 7.5 or 8.0. In especially preferred embodiments, the pH falls within the range of about 8 to about 11.0, about 8 to about 10.5 or most preferably about 8 to about 10.

A further advantage of the use of higher pH formulations of midazolam is that they are more suitable for nasal and buccal administration than prior art, low-pH formulations. Those acidic prior art formulations, when administered nasally, cause discomfort as the acidic medicament acts as an irritant to the nasal mucosa, causing stinging of the nasal membrane. Further, the use of formulations having a pH of 3 or less via the buccal route will be damaging to buccal mucosa and also to dental enamel. These problems are avoided through the use of the formulations of the present invention.

Excessively high pHs, for example, above 11.0 are generally avoided as the rate of degradation of midazolam is increased and also because formulations at such high pHs will have an unacceptable 'soapy' taste.

The pH of the formulation may be inherently provided by the excipients present in the formulation or a pH adjustment agent may be employed. The pH adjustment agent may comprise a simple base or acid, or may additionally or alternatively comprise a buffer.

The use of a buffer is preferred as, once the formulation is administered to the mucous membranes, especially those in the buccal cavity, the buffer will maintain the desired pH of the formulation whereas the pH of a simple basified formulation will be adjusted to a mildly acidic pH by saliva once administered. Any pharmaceutically acceptable buffer may be employed, although buffers which maintain the pH of the formulation at a basic pH are preferred. Examples of such buffers include phosphate buffers, glycine/NaOH buffers, carbonate or bicarbonate buffers.

The compositions of the present invention preferably comprise about 5mg/ml to about 100mg/ml of midazolam. In preferred embodiments, the compositions comprise about 5 to 80mg/ml, about 5 to 60mg/ml, 5 to 30mg/ml, 5 to 20mg/ml, 6mg/ml to about 15mg/ml or most preferably from about 7.5mg/ml to about 12.5mg/ml of midazolam.
The compositions of the present invention preferably have a viscosity of about 500 CP or lower when measured at 22°C. In preferred embodiments, the viscosity may be about 200 to 400CP, about 250 CP to 350 CP, or most preferably, about 270 CP to 330 CP.

Viscosity may be measured using any apparatus known to those skilled in the art, for example, Brookfield LVDV +/-.

The use of a formulation having a viscosity of from about 200CP to about 400 CP is advantageous as when it is administered to the mucous membranes of a patient, the liquid will be less mobile and will remain localised in the desired position while midazolam is absorbed. For example, if the compositions are administered into the buccal cavity of a patient, there is a low degree of circulation of the formulation throughout the mouth, meaning that the risk of a quantity of the formulation trickling down the patient's throat is minimised, if not eliminated.

The viscosity of the formulation may inherently be provided by the other excipients included therein, or a viscosity enhancing component may additionally be present. Preferred viscosity enhancing components include glycerol, carrageen, quince seed, casein, dextrin, gelatin, carboxy vinyl polymer, hydrogenated starch hydrolysate, maltitol syrup, sugar (dextrose, glucose and sucrose), cellulose derivatives such as sodium or calcium carboxymethylcellulose, hydroxy ethyl cellulose and hydroxypropyl cellulose, a polysaccharide, a pectin, agar, a hydrophilic gum such as acacia gum, guar gum, arabic gum and xanthan gum, tragacanth gum, alginic acid, an alginate, dextran, a carbomer resin or mixtures thereof.

To increase shelf-life, the formulation may include a microbial preservative. Any preservative which does not adversely interact with midazolam or any of the excipients may be employed. Preferred preservatives include alcohol, benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, bronopol, butyl-paraben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethanol, ethylparaben, glycerin, imidurea, methylparaben, phenol, phenoxyethanol, phenylethyl alcohol, phenyl mercuric acetate,
phenyl mercuric borate, phenylmercuric nitrate, potassium sorbate, propylene glycol, propyl-paraben, sodium benzoate, sodium propionate, sorbic acid and thiomersal or a mixture thereof. The amount of preservative may range, for example, from about 0.5 to about 10mg/ml of the composition, preferably from about 1 to about 5mg/ml of the formulation.

Shelf life may also be increased by preventing the oxidation of midazolam. This may be achieved by limiting exposure of the formulation to light. For example, if the formulation of the present invention is provided as a bulk solution, it would be preferable for that solution to be packaged in a dark-coloured glass bottle. Alternatively, if the formulation is to be provided in unit dosage form, then the dosage forms are preferably overwrapped with an opaque packaging material.

Additionally, antioxidants, such as sodium metabisulphite, ascorbic acid, or chelating agents, such as sodium edetate, may be employed. Glycerine may also be used to act as a stabilising agent. The amount of antioxidant and stabilising agent may range, for example, from about 0.5 to about 10mg/ml of the composition, preferably from about 1 to about 5mg/ml of the formulation.

The formulation may also contain an antifungal agent. Typical antifungal agents include alkali metal salts of an alkyl hydroxybenzoate, such as sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, or mixtures thereof. The amount of antifungal agent may range for example, from about 0.5 to about 1mg/ml of the composition, preferably from about 1 to about 5mg/ml of the formulation.

A sweetening agent may be employed in the formulations of the present invention. Preferred sweetening agents include sugar, acesulfame, sucralose, high fructose corn syrup, maltitol syrup, cyclamates, saccharins and aspartame. However, in the case of formulations intended for administration via the buccal cavity, as the formulation will be held in the buccal cavity, adjacent to the teeth, the sweetening agent is preferably a synthetic sweetening agent.
A flavour enhancer may also be employed in the formulations of the present invention. The flavour enhancer may impart any flavour to the formulations which improves their acceptance by patients. Preferred flavours include strawberry, raspberry, cranberry, banana, peach, mango, passion fruit, apple, grape, caramel, watermelon, chocolate, coffee, yoghurt, vanilla, ice cream or bubblegum.

The amount of sweetening agent and/or flavour enhancer preferably ranges from about 10mg/ml to about 100mg/ml of the formulation.

Any pharmaceutically acceptable carrier which is capable of retaining midazolam in solution at higher pHs may be included in the formulation of the present application. The carrier is preferably one which is miscible with water. The carrier may comprise alcohols (including lower molecular weight alcohols e.g., ethanol and polyhydric alcohols, e.g., glycerine, glycerol, glycerol tri-esters with carboxylic acids having 1 to 6 carbon atoms, maltitol, non-toxic glycols such as polyethylene glycol or propylene glycol, especially propylene glycol 200 to 400) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil) or mixtures thereof. In preferred arrangements of the present invention, the carrier is present in an amount which retains midazolam in solution at a pH greater than 6. Around 5 to 75, 15 to 60, or 25 to 50 percent carrier may be employed in preferred embodiments of the present invention.

In especially preferred embodiments, the carrier system comprises glycerol and / or a glycol (preferably either or both of polyethylene glycol and/or propylene glycol) and optionally other excipients such as water, maltitol or any of the other potential carriers outlined above. In such a carrier system, the weight ratio of glycerol:glycol preferably ranges from about 0:100, about 1:99, about 10:90, about 15:85, or about 20:80 to about 50:50, to about 45:55, or to about 40:60.

According to a further aspect of the present invention, there is provided a liquid composition for administration to a patient comprising midazolam and a pharmaceutically acceptable carrier, the composition comprising less than about 200mg/ml cyclodextrin, the carrier comprising a glycol and optionally glycerol, wherein the weight ratio of
glyceroglycerol ranges from about 0:100 to about 50:50 and at least about 50% of the midazolam is present in solution.

The compositions of this aspect of the present invention may be used in the treatment of epilepsy or in inducing anaesthesia.

In the compositions of the present invention, the amount of ethanol present is preferably less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than 10%, less than 5%, or less than 1%, all by weight of the composition. In certain embodiments, the compositions of the present invention are essentially free of ethanol.

Any pharmaceutically acceptable and effective form of midazolam may be included in the formulations of the present invention. For example, the free molecule of midazolam may be employed. Alternatively, a salt may be used. In preferred embodiments of the present invention, the hydrochloride, maleate, sulphate, tartrate, acetate, or citrate salt is used. The hydrochloride and maleate salts are the most commonly used forms of midazolam. Additional pharmaceutically acceptable salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulphate, besylate, bisulphate, phosphate, acid phosphate, propionate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bicarbonate, bitartrate, ascorbate, succinate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

The formulations of the present invention may be administered sequentially or simultaneously with other therapeutic agents selected from (but not limited to) corticosteroids, cytotoxics, antibiotics, immunosuppressants, nonsteroidal antiinflammatory drug, other narcotic analgesics, local anaesthetics, NMDA antagonists, neuroleptics, anticonvulsants, antispasmodics, antiemetics, antidepressants or muscle relaxants. The agents can be administered separately or in combination.
The formulations of the present invention may be provided as a bulk solution, from which doses can be removed. However, in a preferred embodiment, the formulation is provided as a unit dose. The unit dose is preferably provided in a single-use means of administration, most preferably a dropper, such as that disclosed in UK Patent Application No. 0922357.9, the contents of which are incorporated by reference.

The unit dose may comprise between about 0.1 to about 20ml of medicament. In more preferred embodiments, the unit dose comprises about 0.2 to about 10ml, about 0.25 to about 5ml, or more preferably, about 0.5 to about 2ml of the formulation. In a most preferred arrangement, the unit dose comprises 1ml of medicament. The use of a unit dose of medicament is advantageous as the risk of administering an incorrect dose is eliminated.

Compositions of this aspect of the present invention include midazolam as the principle active agent. However, analogous compositions may be used to formulate alternative active ingredients in place of or in addition to midazolam, for example benzodiazepines, including alprazolam, bretazenil, bromazepam, brotizolam, chlordiazepoxide, cinolazepam, clonazepam, clorazepate, cloxazolam, delorazepam, diazepam, estazolam, etizolam, etizolam, flunitrazepam, flurazepam, flutoprazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, nimetazepam, nitrazepam, nordazepam, oxazepam, phenazepam, pinazepam, prazepam, premazepam, quazepam, temazepam, tetrazepam and triozolam.

Alternative active ingredients which may be formulated in the compositions of the present invention in place of or in addition to midazolam include nicotine and derivatives thereof and / or opioids, including codeine, morphine, diacetylmorphine, dihydrocodeine, hydrocodone, oxycodone, hydromorphone, nicomorphine, oxymorphone, fentanyl, methylfentanyl, alfentanil, sufentanil, remifentanil, pethidine, methadone, buprenorphine, tramadol.

The formulation of the present invention may be provided as part of a kit. The kit may also comprise instructions to administer the formulation to the buccal, nasal, sub-lingual and/or
rectal cavity of a patient in need thereof. The formulation is preferably included in the kit in the form of at least one unit dose of the formulation of the present invention. The kit may also comprise one or more doses of a further therapeutic agent.

According to a third aspect of the present invention, there is provided the use of midazolam in the manufacture of a liquid medicament having a pH of about 6.0 or greater and comprising less than 200mg/ml cyclodextrin for administration to a patient to treat epileptic seizures and/or induce a degree of anaesthesia in the patient, wherein at least 50% of the midazolam is present in solution.

According to a fourth aspect of the present invention, there is provided the use of midazolam to treat epileptic seizures and/or induce a degree of anaesthesia, wherein the midazolam is administered as a liquid medicament having a pH of about 6.0 or higher and comprising less than 200mg/ml of cyclodextrin to a patient, and at least 50% of the midazolam is present in solution.

According to a fifth aspect of the present invention, there is provided a method of treating epileptic seizures and/or inducing a degree of anaesthesia in a patient by administering the formulations discussed above to a patient.

In these third, fourth and fifth aspects of the present invention, the midazolam is preferably administered in the formulations described above.

The formulations of the present invention are suitable for use with all patient groups. However, certain advantages are especially apparent when the formulations are used with paediatric patients. For example, administration of midazolam via the buccal route avoids causing anxiety to patients through the use of a needled syringe, which will be especially acute for such younger patients. Additionally, the use of formulations having acceptable flavour profiles will be especially important for such patients.
The term 'paediatric patient' covers all children and adolescents below the age of 18. The formulations of the present invention are especially suitable for younger patients, e.g. pre-term infants to children of 12 to 14 years of age.

For the avoidance of any doubt, where the concentration of midazolam is provided, e.g. the formulation has a concentration of 5mg/ml of midazolam, it is the concentration of free midazolam which is provided and not the concentration of any salt of midazolam that may be employed unless otherwise specified.

Where reference is made to the proportion of the open or closed ring forms of midazolam, e.g. the proportion of the closed ring form present is 99%, the percentage given is a proportion of the total amount of midazolam present.

Where 'mg/ml' units are used to define the concentrations of midazolam and excipients, the concentrations are provided as a proportion of the total formulation.

The invention is further illustrated in the following Examples.

**Example 1**

A range of formulations were prepared which had the following composition:

<table>
<thead>
<tr>
<th>Material</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam Maleate</td>
<td>13.60mg (equivalent to 10.00mg midazolam)</td>
</tr>
<tr>
<td>Saccharin Sodium</td>
<td>40.00mg</td>
</tr>
<tr>
<td>Purified Water</td>
<td>0.06ml</td>
</tr>
<tr>
<td>Ethanol</td>
<td>197.250mg</td>
</tr>
<tr>
<td>Glycerol</td>
<td>220.500mg</td>
</tr>
<tr>
<td>Lycasin\textsuperscript{TM} 80/55</td>
<td>To 1.0ml</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>QS to appropriate pH</td>
</tr>
</tbody>
</table>
The formulations had pHs of 3.4, 4.1, 4.8, 5.5, 6.2, 6.9, 7.5, 8.0, 8.5, 9.0, 10.0. Once prepared, the formulations were stored at 40°C and at a relative humidity of 75%. After one month of storage, the impurity profile of the samples was measured and the following results were observed:

<table>
<thead>
<tr>
<th>pH of Formulation</th>
<th>Amount of SMA (%)</th>
<th>Amount of SMB (%)</th>
<th>Total Impurities (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4</td>
<td>0.54</td>
<td>0.61</td>
<td>2.12</td>
</tr>
<tr>
<td>4.1</td>
<td>0.62</td>
<td>0.71</td>
<td>1.70</td>
</tr>
<tr>
<td>4.8</td>
<td>0.61</td>
<td>0.70</td>
<td>1.56</td>
</tr>
<tr>
<td>5.5</td>
<td>0.56</td>
<td>0.64</td>
<td>1.45</td>
</tr>
<tr>
<td>6.2</td>
<td>0.49</td>
<td>0.57</td>
<td>1.31</td>
</tr>
<tr>
<td>6.9</td>
<td>0.37</td>
<td>0.42</td>
<td>1.04</td>
</tr>
<tr>
<td>7.5</td>
<td>0.19</td>
<td>0.33</td>
<td>0.91</td>
</tr>
<tr>
<td>8.0</td>
<td>0.10</td>
<td>0.12</td>
<td>0.61</td>
</tr>
<tr>
<td>8.5</td>
<td>0.08</td>
<td>0.09</td>
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<td>9.0</td>
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<td>0.07</td>
<td>0.55</td>
</tr>
<tr>
<td>10.0</td>
<td>0.05</td>
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</table>

These results are presented on the chart provided as Figure 3. As can be seen, formulations having increased pH benefitted from a reduction in the amount of impurities observed after storage at 40°C and at a relative humidity of 75% relative humidity. Thus, by increasing the pH of those formulations, the stability of the midazolam in those formulations is advantageously and unexpectedly improved.

Figure 4 is a chart showing the extrapolated impurity contents of the formulations. Assuming that the formation of the degradant by-products is relatively constant, the formulations having pHs of 8 to 10 will have an impurity content of only about 5% following storage under accelerated conditions for 9 months.

**Example 2**
To further investigate the effects of pH on stability, an alternative series of formulations to those discussed in Example 1 were prepared. A range of compositions comprising midazolam in solution at pH 8.5 were produced according to the following two processes:

**Process 1.** All of the excipients (except the 10% sodium hydroxide) were blended as a single premix, with the order of addition being water, glycerol, Lycasin™, propylene glycol/PEG 200/400, and ethanol. Once these excipients were mixed to a final homogenous solution, midazolam maleate was added.

**Process 2.** Midazolam maleate was firstly added to the mixture vessel. The excipients were then sequentially added in the following order: water, glycerol, Lycasin™, propylene glycol/PEG 200/400, ethanol. Midazolam was allowed to undergo boundary layer pH-induced dissolution and precipitation in the water-glycerol premix, with a ten minute delay between the addition of glycerol and Lycasin™. After addition of the remaining excipients, the vessel (a screw top glass bottle) is sealed and shaken vigorously until the solution is clear by eye, after approximately 10 to 15 minutes.

The solutions which were prepared had the compositions set out below. Also provided in the following tables is an indication of the appearance of the solutions following short term storage in a freezer, to promote crystallisation. The clarity of the obtained solutions confirm that crystallisation did not occur and that midazolam is stable therein.

**Glycerol/Propylene Glycol Carrier System:**

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<tr>
<th>Ingredient</th>
<th>Glycerol 40 (PG 60)</th>
<th>Glycerol 25 (PG 75)</th>
<th>Glycerol 0 (PG 100)</th>
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<tr>
<td>Midazolam maleate</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
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<tr>
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<td>Glycerol</td>
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<td>4.4025</td>
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<td>17.61</td>
</tr>
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<td>Glycerol 0 (PEG 200) 100</td>
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<td>1.1</td>
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<td>15.77</td>
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<tr>
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<td>4.4025</td>
<td>0.00</td>
</tr>
<tr>
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<td>13.2075</td>
<td>17.61</td>
</tr>
<tr>
<td>Lycasin 80/85</td>
<td>57.53</td>
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</tr>
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<td>Deionised water</td>
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</tr>
<tr>
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**Glycerol/PEG 400 Carrier System**

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<th>Glycerol 25 (PEG 400) 75</th>
<th>Glycerol 0 (PEG 400) 100</th>
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<tr>
<td><strong>Appearance</strong></td>
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</table>

**Example 3**

The stability of a number of the formulations discussed in Example 2 was compared against two samples of the commercially available Epistatus product (comparative) which has a pH of 4.5 to 5.5. The samples were stored for three months at a temperature of 40% and at a relative humidity of 75%. Following storage, the samples were analysed and the % concentration of succinyl midazolam (SMA, SMB) impurities and total impurities are provided as Figures 5a and 5b, respectively. As can be seen, the higher pH formulations of the present invention contained far lower quantities of impurities following storage for three months at a temperature of 45°C and at a relative humidity of 75%.

The analytical method used to determine the impurity content of the formulations discussed in Example 2 differed from and had a higher level of sensitivity than the analytical method used to determine the impurity content of the formulations discussed in Example 1. Thus, the results obtained in Example 1 are not directly comparable with the results discussed in this example and illustrated in Figures 5a and 5b.

**Example 4**
The rate of flux of a composition of the present invention versus a lower pH (about 5) comparative formulation was determined using a Franz cell. Flux rate was measured at 21°C using a Rotulex No. 18 Franz cell with an infinite dose of active and a 250 μm membrane with a UV-visible spectrophotometer (Spectronic Biomate, Thermo Electron Limited, Cambridge, UK).

The lower pH comparative formulation had the following composition:

<table>
<thead>
<tr>
<th>Material</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam Maleate</td>
<td>13.60 mg (equivalent to 10.00 mg midazolam)</td>
</tr>
<tr>
<td>Purified Water</td>
<td>0.06 ml</td>
</tr>
<tr>
<td>Ethanol</td>
<td>197.250 mg</td>
</tr>
<tr>
<td>Glycerol</td>
<td>220.500 mg</td>
</tr>
<tr>
<td>Lycasin® 80/55</td>
<td>To 1.0 ml</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>QS to appropriate pH</td>
</tr>
</tbody>
</table>

The flux rate of that comparative formulation and also of the Glycerol 40 : (PEG 200) 60 formulation were determined using the apparatus outlined above. The results obtained are presented graphically as Figure 6. The upper line, with square points, are the results obtained for the inventive composition and the lower line, with diamond points, are the results obtained for the comparative composition.

As can be seen from that figure, the absorbance of the inventive composition peaked at 232 nm. The average cell volume of the comparative formulation was 2.93 ml and the average cell volume of the inventive formulation was 3.13 ml. The absorbance of 25 μg/ml standard of midazolam maleate is 1.455 at 232 nm.

Thus, the calculated flux rate of the inventive composition was 88.67 μg/cm²/hour whereas the calculated flux rate of the comparative composition was only 8.12 μg/cm²/hour. In other words, the inventive composition exhibited a flux rate in the Franz cell which is over ten times greater than that of the comparative composition.
This strongly suggests that the formulations of the present invention will be absorbed via the buccal cavity more rapidly than conventional compositions and thus, exhibit a faster onset of therapeutic activity.

**Example 5**

Additional Franz cell testing was performed using the comparative formulation discussed in Example 4 and several of the compositions prepared in Example 2.

The results obtained are presented as Figures 7a and 7b. As can be seen from Figure 7a, the transfer of midazolam when formulated in an inventive composition was significantly higher than the comparative formulation, and the difference between them increased as time progressed. As is clear from Figure 7b, the advantageous results observed in Figure 7a were not limited to the PEG 200:GLY (60:40) formulation, but were also exhibited by other formulations of the present invention.
1. A liquid composition for administration to a patient comprising midazolam and a pharmaceutically acceptable carrier, wherein the pH of the composition is about 6 or higher, the composition comprises less than about 200mg/ml cyclodextrin, and at least about 50% of the midazolam is present in solution.

2. The liquid composition of Claim 1, wherein the composition is for administration via the buccal, nasal, rectal and/or sub-lingual routes.

3. The liquid composition of Claim 1 or 2, wherein the pH of the composition is about 7 or higher.

4. The liquid composition of any one of Claims 1 to 3, wherein the pH of the composition is about 8 or higher.

5. The liquid composition of any one of Claims 1 to 4, wherein the pH of the composition is about 8 to about 11.

6. The liquid composition of any one of Claims 1 to 5, wherein the pH of the composition is about 8 to about 10.5.

7. The liquid composition of any one of Claims 1 to 6, wherein the pH of the composition is about 8 to about 10.

8. The liquid composition of any one of Claims 1 to 7, wherein at least about 90% of the midazolam is present in solution.

9. The liquid composition of any one of Claims 1 to 8, wherein at least about 98% of the midazolam is present in solution.
10. The composition of any one of Claims 1 to 9, wherein the concentration of midazolam is about 5mg/ml to about 20mg/ml.

11. The composition of any one of Claims 1 to 10, wherein the concentration of midazolam is about 6mg/ml to about 15mg/ml.

12. The composition of any one of Claims 1 to 11, wherein the concentration of midazolam is about 7.5mg/ml to about 12.5mg/ml.

13. The composition of any one of Claims 1 to 12, wherein the viscosity of the composition is about 250 CP to about 350 CP.

14. The composition of any one of Claims 1 to 13, wherein the viscosity of the composition is about 270 CP to about 330 CP.

15. The composition of any one of Claims 1 to 14, wherein the composition further comprises a viscosity enhancing component.

16. The composition of any one of Claims 1 to 15, wherein the composition comprises about 50mg/ml or less of cyclodextrin.

17. The composition of any one of Claims 1 to 16, wherein the composition is substantially free of cyclodextrin.

18. The composition of any one of Claims 1 to 14, wherein the composition further comprises a buffer.

19. The composition of Claim 18, wherein the buffer is a phosphate buffer, a glycine/NaOH buffer or a carbonate or bicarbonate buffer or a mixture thereof.

20. The composition of any one of Claims 1 to 19, wherein the composition additionally comprises a sweetener, a flavour enhancer, a preservative and/or an antifungal agent.
21. The composition of any one of Claims 1 to 20, wherein the carrier comprises water, ethanol, maltitol, glycerine, glycerol, polyethylene glycol, propylene glycol or mixtures thereof.

22. The composition of any one of Claims 1 to 21, further comprising an additional therapeutic agent.

23. A liquid composition for administration to a patient comprising midazolam and a pharmaceutically acceptable carrier, the composition comprising less than about 200mg/ml cyclodextrin, the carrier comprising a glycol and optionally glycerol, wherein the weight ratio of glycerol:glycol ranges from about 0:100 to about 50:50 and at least about 50% of the midazolam is present in solution.

24. The liquid composition of Claim 23, wherein the weight ratio of glycerol:glycol is 10:90 to 45:55.

25. The composition of any one of Claims 1 to 24, wherein the composition exhibits a flux rate of about 20µm/cm²/hour or greater.

26. The composition of any one of Claims 1 to 25, wherein the composition exhibits a flux rate of about 20µm/cm²/hour or greater.

27. The composition of any one of Claims 1 to 26 for use in the treatment of an epileptic seizure and/or to induce a degree of anaesthesia.

28. The composition as hereinbefore described in the accompanying description.

29. A unit dose of the composition of any one of Claims 1 to 28.

30. The unit dose of Claim 29, comprising about 0.1 to about 10ml of the formulation.
31. The unit dose of Claim 29 or 30, comprising about 0.2 to about 5ml of the formulation.

32. The unit dose of any one of Claims 29 to 31, comprising about 0.5 to about 2ml of the formulation.

33. The unit dose of any one of Claims 29 to 32, wherein the unit dose is contained within a single-use means of administration.

34. The unit dose of any one of Claims 29 to 33, wherein the single-use means of administration is a dropper.

35. A kit comprising the composition of any one of Claims 1 to 28 or the unit dose of any one of Claims 29 to 34 and instructions to administer the formulation into the buccal, rectal, nasal and/or sub-lingual cavity of a patient.

36. The kit of Claim 35, further comprising an additional therapeutic agent.

37. The kit of Claim 33, wherein the additional therapeutic agent is provided as a unit dose.

38. The use of midazolam in the manufacture of a liquid medicament having a pH of about 6 or higher and comprising less than about 200mg/ml of cyclodextrin for administration to a patient to treat an epileptic seizure and/or to induce a degree of anaesthesia in the patient, wherein at least about 50% of the midazolam is present in solution.

39. The use of midazolam to treat an epileptic seizure and/or to induce a degree of anaesthesia in a patient, wherein the midazolam is administered in a liquid medicament to a patient, the medicament has a pH of about 6 or higher and comprises less than about 200mg/ml of cyclodextrin and at least about 50% of the midazolam is present in solution.

40. The use of Claim 38 or 39, wherein the medicament comprises the formulation of any one of Claims 1 to 24.
41. The use of any one of Claims 38 to 40, wherein the patient is 14 years of age or under.

42. The use of any one of Claims 38 to 41, wherein the patient is simultaneously or sequentially administered an additional therapeutic agent.

43. The use of Claim 42, wherein the medicament comprises the additional therapeutic agent.

44. The use of Claim 42 or 43, wherein the additional therapeutic agent is selected from the group consisting of corticosteroids, cytotoxics, antibiotics, immunosuppressants, nonsteroidal antiinflammatory drug, narcotic analgesics, local anaesthetics, NMDA antagonists, neuroleptics, anticonvulsants, antispasmodics, antiemetics, antidepressants and muscle relaxants.

45. A method of treating an epileptic seizure and/or inducing a degree of anaesthesia in a patient by administering midazolam formulated in a liquid medicament to a patient, wherein the medicament has a pH of 6 or higher and comprises less than 200mg/ml of cyclodextrin and at least 50% of the midazolam is present in solution.

46. The method of Claim 45, wherein the medicament comprises the formulation of any one of Claims 1 to 28.

47. The method of Claim 45 or 46 wherein the patient is 14 years of age or younger.

48. The method of any one of Claims 45 to 47, wherein the patient is simultaneously or sequentially administered an additional therapeutic agent.

49. The method of Claim 48, wherein the medicament comprises the additional therapeutic agent.

50. The method of Claim 48 or 49 wherein the additional therapeutic agent is selected from the group consisting of corticosteroids, cytotoxics, antibiotics, immunosuppressants,
nonsteroidal antiinflammatory drug, narcotic analgesics, local anaesthetics, NMDA antagonists, neuroleptics, anticonvulsants, antispasmodics, antiemetics, antidepressants and muscle relaxants.
Figure 1

Effect of pH on Proportion of Midazolam Present in the Open Ring Form Percentage of Midazolam Present in the Open Ring Form

- pH
- Percentage of Midazolam Present in the Open Ring Form

Figure 1
Effect of pH on Impurity Content

Extrapolation of Impurity Content Over Time

Figure 3

Figure 4
Figure 6

Flux of Comparative Formulation vs Inventive Composition (PEG200:Glycerol 60:40)

Figure 7a

Midazolam Transfer with Time

UV Absorbance (@230nm)

- Comparative
- PEG 200:GLY (60:40)
Midazolam Transfer After 1 Hour

UV Absorbance (@230nm)

- Comparative
- PG:GLY (100:0)
- PG:GLY (60:40)
- PEG 200:GLY (100:0)
- PEG 200:GLY (60:40)

Formulations

Figure 7b
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/GB2011/051146

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### A. CLASSIFICATION OF SUBJECT MATTER


ADD.

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

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### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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

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### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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**Further documents are listed in the continuation of Box C.**

**See patent family annex.**

* Special categories of cited documents :

  - **A** document defining the general state of the art which is not considered to be of particular relevance
  - **E** earlier document but published on or after the international filing date
  - **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - **D** document referring to an oral disclosure, use, exhibition or other means
  - **P** document published prior to the international filing date but later than the priority date claimed

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**Date of the actual completion of the international search**

19 September 2011

**Date of mailing of the international search report**

27/09/2011

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**Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016**

**Authorized officer**

Rodriguez-Palmero, M
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<td>&quot;Midazolam hydrochloride 1-mg/mL oral 1/p, i.e. d&quot;, INTERNATIONAL JOURNAL OF PHARMACEUTICAL COMPOUNDING, IJPC, EDMOND, OK, US, vol. 10, no. 5, 1 September 2006 (2006-09-01), page 387, XP009152262, ISSN: 1092-4221 page 387, column 1, last paragraph</td>
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