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(54) Titre : COMPLEXES D'INCLUSION D'ALPRAZOLAME ET COMPOSITIONS PHARMACEUTIQUES LES
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(54) Title: ALPRAZOLAM INCLUSION COMPLEXES AND PHARMACEUTICAL COMPOSITIONS THEREOF

(57) Abrégé/Abstract:

Pharmaceutical composition for transmucosal delivery contains an inclusion complex of alprazolam and a water soluble unsubstituted or substituted beta- or gamma-cyclodextrin such as 2-hydroxypropyl beta-cyclodextrin, and a pharmaceutically acceptable carrier therefor. The pharmaceutical composition is of particular application in the treatment of Generalised Anxiety Disorder or for the management of panic disorders.



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(54) Title: ALPRAZOLAM INCLUSION COMPLEXES AND PHARMACEUTICAL COMPOSITIONS THEREOF

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ALPRAZOLAM INCLUSION COMPLEXES AND PHARMACEUTICAL COMPOSITIONS THEREOF

BACKGROUND OF THE INVENTION

This invention relates to an inclusion complex of alprazolam and an unsubstituted or substituted beta- or gamma-cyclodextrin, and to pharmaceutical compositions containing such a complex, particularly for oral, nasal or rectal mucosal delivery, for the treatment of anxiety and panic attack.

Alprazolam is also known as 8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine.

Alprazolam is indicated for the short term treatment of Generalised Anxiety Disorder (GAD) and has particular utility as an agent for the management of panic disorders (with or without agoraphobia).

In an acute state such as a panic attack, a rapid onset of action is desirable. Although alprazolam is well absorbed from a tablet formulation after conventional orogastric administration, maximum plasma levels occur between

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0,7 to 1,8 hours post-dose. The onset of anxiolysis correlates with attainment of maximum plasma levels. The absorption rate is therefore often not sufficiently rapid to provide immediate symptomatic relief in an anxiety crisis. Absorption of alprazolam from the stomach is further adversely affected by the presence of food and antacids, the use of the latter being frequently associated with stress related syndromes. Rapid absorption of alprazolam in a manner which would avoid these complications and avoid the need for administration of the dosage form with a liquid would have distinct advantages.

The mucosal route of drug delivery, in particular the sublingual or nasal mucosal routes, offer a useful alternative to parenteral delivery where a rapid therapeutic effect is desired. Sublingual use of the commercially available oral tablet dosage forms of alprazolam offers no significant benefit over conventional orogastric administration in terms of speed of onset [see J.M. Scavone et al, J. Clin. Psychopharmacol., 1987, 7, 332-335]. Formulation of alprazolam in a manner which permits rapid uptake from the sublingual, nasal or rectal mucosa would have distinct utility in the emergency relief of anxiety symptoms.

The oral, nasal and rectal cavities have several advantages as sites for systemic drug delivery, particularly avoidance of pre-systemic metabolism. However, the low permeability of the membranes that line the oral and nasal cavities result in a low flux of drug. There is therefore a need to enhance drug solubility and penetration to improve bioavailability following oral or nasal mucosal drug delivery.

There are several methods known in the art to deliver drugs to the oral, nasal and rectal mucosae. These include buccal and sublingual tablets or lozenges, adhesive patches, gels, solutions or sprays (powder, liquid or aerosol) for the oral cavity and solutions or sprays (powder, liquid or aerosol) for the nasal cavity and suppositories for rectal administration.

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The absorption of drugs from mucosal membranes may be enhanced by (i) increasing drug solubility, (ii) pH modification to favour the unionised form of the drug, (iii) addition of mucoadhesive agents to improve contact between the delivery system and the membrane and (iv) incorporation of so-called penetration enhancers.

There are a number of penetration enhancers known to influence the permeability of drugs across epithelial membranes (for a recent review see Walker, R.B. and Smith, E.W. *Advanced Drug Delivery Reviews* 1996, 18, 295 - 301).

Cyclodextrins and their derivatives have found extensive application as solubilizers and stabilizers due to their ability to form inclusion complexes with a wide variety of compounds (see J. Szejtli, *Cyclodextrin Technology*, Kluwer Academic Press) and (J. Szejtli & K-H Fromming, *Cyclodextrins in Pharmacy*, Kluwer Academic Press). Cyclodextrins have been used to enhance intestinal absorption of drugs primarily through increasing solubility. Recently, cyclodextrins have been shown to have positive and negative effects on transdermal penetration of drugs (see Loftsson, T. et al *International Journal of Pharmaceutics* 1995, 115, 255 - 258), (Vollmer, U. et al. *International Journal of Pharmaceutics* 1993, 99, 51 - 58), (Legendre, J.Y. et al. *European Journal of Pharmaceutics* 1995, 3, 311 - 322) and (Vollmer, U. et al *Journal of Pharmacy and Pharmacology* 1994, 46, 19 - 22). Cyclodextrins may improve nasal absorption of drugs (see Merkus, F.W. et al. *Pharmaceutical Research* 1992, 9, 1157 - 1163) and enhance absorption from sublingual administration of drug / cyclodextrin complexes. Cyclodextrins also protect nasal mucosal damage by penetration enhancers (see Jabbal.Gill, I. et al. *European Journal of Pharmaceutical Sciences* 1994, 1 (5), 229 - 236).

Cyclodextrins are water soluble cone-shaped cyclic oligosaccharides containing 6, 7 or 8 glucopyranose units. The interior or "cavity" of the cone is

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hydrophobic whilst the exterior is hydrophilic. The size of the cavity increases with increasing number of glucose units. Several cyclodextrin derivatives such as alkyl, hydroxyalkyl and sulfoalkyl ethers have been prepared with improved solubility (see J. Szejtli & K-H Fromming, *Cyclodextrins in Pharmacy*, Kluwer Academic Press) and (Stella, V.J. et al. *Pharmaceutical Research* 1995, 12 (9) S205). Suitably sized hydrophobic "guest" molecules may enter the "host" cavity to form a classical host-guest "inclusion compound" or "inclusion complex" with either the entire guest molecule included or only a portion thereof. The driving mechanism for cyclodextrin inclusion complexation is the affinity of the hydrophobic guest molecule for the cavity of the cyclodextrin host molecule with displacement of cavity water molecules to a thermodynamically more stable state. The term "complex stability" or stability of a given inclusion complex refers to the association / dissociation equilibrium of host and guest in solution. Complex stability depends on the number of intermolecular bonding interactions between the host and guest. Van der Waals forces and hydrophobic interactions are the main interactions stabilising inclusion complexes (Bergeron, R.J. et al. *Journal of the American Chemical Society* 1977, 99, 5146). Depending on the nature and position of hydrogen bonding functionalities on a given guest, there may be hydrogen bonding between the guest and hydroxyl groups of the cyclodextrin or other hydrogen bonding groups in the case of cyclodextrin derivatives. Ionic interactions between the host and guest are also possible in the case of ionic cyclodextrins such as sulfobutyl ethers (Stella, V.J. et al. *Pharmaceutical Research* 1995, 12 (9), S205).

Cyclodextrin inclusion complexes may be prepared on the basis of liquid state, solid state or semi-solid state reaction between the components (J. Szejtli, *Cyclodextrin Technology*, Kluwer Academic Press). The first is accomplished by dissolving the cyclodextrin and guest in a suitable solvent or mixture of solvents and subsequently isolating the solid state complex by crystallisation, evaporation, spray drying or freeze drying. In the solid state method, the two

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components may be screened to uniform particle size and thoroughly mixed whereafter they are ground in a high energy mill with optional heating, screened and homogenised. In the semi-solid state, the two components are kneaded in the presence of small amounts of a suitable solvent, and the complex so-formed, is dried, screened and homogenised.

The liquid state reaction generally provides optimum conditions for completeness of reaction. Depending on solvent conditions, the dissolved inclusion complex exists in equilibrium between uncomplexed host and guest and complexed host / guest.

The use of cyclodextrins to increase the solubility of alprazolam has been described. In an article in *Acta Pharm. Nord.* 3(4), 1991, 215-217, Loftsson et al describe the effect of the cyclodextrin derivative, 2-hydroxypropyl- β -cyclodextrin, on the aqueous solubility of 13 different drugs, including alprazolam. A 16-fold solubility enhancement for alprazolam in a 20% solution of 2-hydroxypropyl- β -cyclodextrin is reported. No solid complex is described.

In a subsequent article published in *Int. J. Pharm.*, 1994, 110, 169-177, Loftsson et al describe the effect of 2-hydroxypropyl- β -cyclodextrin on the water solubility of alprazolam in the presence and absence of water soluble polymers. Enhanced solubility of alprazolam is obtained following heating of a solution of 2-hydroxypropyl- β -cyclodextrin and a water soluble polymer in a sealed container at 120°C for 20 minutes. No solid complex is described.

JP 07165616 to Hisamitsu Pharmaceutical Company, Japan similarly claims the formation of inclusion complexes of drugs with cyclodextrin in the presence of water soluble polymers to improve solubility and stability.

Loftsson et al [see *Int. J. Pharm.*, 1998, 162(2), 115-121] have also reported an enhancement in the solubility and have demonstrated improved complexing

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ability for β -cyclodextrin in solutions of drugs containing water soluble polymers, including the drug alprazolam. No solid complex is described.

DE 44 28 986 A1 to KRKA, Slovenia teaches the formulation of rapidly dissolving solid dosage forms for orogastric administration of alprazolam containing alpha-, beta-, or gamma cyclodextrin when employed as water soluble carriers. Alprazolam is deposited on the carrier by spray drying prior to incorporation into a tablet.

US Patents Nos 5 288 497 and 5 785 989 to Stanley, T.H. et al (The University of Utah) entitled "Compositions of Oral Dissolvable Medicaments" and "Compositions and Methods of Manufacturing of Oral Dissolvable Medicaments", respectively, recite in their claims a drug-containing dosage form (where the drug is a benzodiazepine) which permits absorption through the mucosal tissues of the mouth. The dosage form is referred to as an "appliance or holder" containing drug dispersed into a carbohydrate, fat, protein, wax or other dissolvable matrix.

SUMMARY OF THE INVENTION

According to one aspect of the invention there is provided an inclusion complex of (a) alprazolam and (b) a water soluble 2-hydroxypropyl-beta-cyclodextrin with a degree of substitution between 3.9 and 5.1 hydroxypropyl groups per cyclodextrin molecule.

A pharmaceutical composition may comprise the inclusion complex and a pharmaceutically acceptable carrier suitable for transmucosal delivery of the inclusion complex.

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The inclusion complex preferably has a stoichiometry of (a) to (b) from 1 : 1 mol / mol to 1 : 10 mol / mol inclusive and more preferably 1:7 mol / mol inclusive.

The pharmaceutical composition is preferably for use in the treatment of Generalised Anxiety Disorder (GAD) and has particular utility as an agent for the management of panic disorders.

The pharmaceutical composition is preferably adapted for oral, nasal or rectal mucosal delivery.

BRIEF DESCRIPTION OF THE DRAWINGS

- Figure 1** represents the effect of varying concentrations of beta-cyclodextrin (BCD) on the aqueous solubility of alprazolam at 25°C.
- Figure 2** represents the effect of methyl-beta cyclodextrin (squares) and 2-hydroxypropyl-beta-cyclodextrin (triangles) on the aqueous solubility of alprazolam at 25°C.

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Figure 3 represents the dissolution rate of alprazolam from a physical mixture (solid squares) of alprazolam and 2-hydroxypropyl-beta-cyclodextrin and the corresponding complex (open diamonds) obtained from Example 3 and performed according to Example 5.

Figure 4 represents the dissolution rate of alprazolam from a physical mixture (solid squares) of alprazolam and methyl-beta-cyclodextrin and the corresponding complex (open diamonds) obtained from Example 4 and performed according to Example 5. The powder samples were compressed into disks using a single punch and die.

DESCRIPTION OF EMBODIMENTS

The crux of the invention is an inclusion complex of (a) alprazolam and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin, and pharmaceutical compositions containing the inclusion complex for transmucosal delivery.

The second component of the inclusion complex is an unsubstituted or substituted beta- or gamma-cyclodextrin.

Highly water soluble cyclodextrins such as 2-hydroxypropylated or randomly methylated or sulfoalkylated derivatives of beta-cyclodextrin are the preferred cyclodextrins of the invention. Gamma-cyclodextrin or 2-hydroxypropylated or randomly methylated or sulfoalkylated derivatives of gamma-cyclodextrin may also be used in the same manner as the corresponding preferred beta-cyclodextrin derivatives. The degree of substitution of the cyclodextrin derivatives may vary between 1 to 20 substituents per cyclodextrin molecule, but more preferably between 3 to 15 substituents per cyclodextrin molecule.

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When the cyclodextrin is 2-hydroxypropyl-beta-cyclodextrin, the preferred degree of substitution is between 3,9 and 5,1 hydroxypropyl groups per cyclodextrin molecule. When the cyclodextrin is a randomly methylated-beta-cyclodextrin, the preferred degree of substitution is between 1,8 and 2 methyl groups per glucose unit. When the cyclodextrin is sulfobutyl ether-beta-cyclodextrin, the preferred degree of substitution is between 1 and 7 sulfobutyl ether groups per cyclodextrin molecule.

The inclusion complex of the invention may be prepared from aqueous solutions, slurries or pastes of alprazolam and cyclodextrin according to conventional methods. The molar ratio of alprazolam to cyclodextrin may vary between 1 : 1 to 1 : 10 inclusive, but more preferably between 1 : 1 to 1:7 inclusive. Solutions are prepared by dissolving the cyclodextrin in a sufficient quantity of purified deionised water. Alprazolam is added to the solution with stirring until dissolved. The solution may be used in the preparation of liquid delivery systems such as drops, sprays or aerosols. Where a solid inclusion complex is desired, the solution or slurry may be dried by spray drying or freeze drying.

Alternatively, alprazolam and cyclodextrin are mixed. The powder mixture is wetted with water while mixing vigorously until a paste is formed. The paste is mixed for 0,25 to 2 hours and dried in an oven or in vacuo at elevated temperature. The dried complex is crushed and sieved to the desired particle size.

The particle size of the complex is preferably 95% less than 100 microns and most preferably 95% less than 50 microns, to facilitate wetting of a solid formulation.

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The second aspect of the invention is a pharmaceutical composition which comprises as an active ingredient an inclusion complex as described above.

The pharmaceutical composition of the invention is of particular application in the treatment of GAD and for the management of panic disorders.

Further, the pharmaceutical composition of the invention is preferably adapted for oral, nasal, or rectal mucosal delivery.

The administration of an anxiolytic drug through the mucosal tissue of the nose, mouth or rectum avoids the problems associated with oral administration of alprazolam (i.e. slow onset of action, low bio-availability and associated poor compliance).

Absorption of the drug from the pharmaceutical composition of the invention is rapid such that the drug reaches the systemic circulation almost as fast as through injection and appreciably faster than oral administration, which is highly advantageous for the rapid relief of anxiety.

Further, the unpleasant taste and irritant properties of the active principle are reduced by presenting the drug to the nasal or rectal oral mucosal membranes in the form of a cyclodextrin inclusion complex.

The present invention achieves these advantages by molecular encapsulation of the drug in a cyclodextrin, so forming a molecular inclusion complex which may be used in the solid form for the preparation of sublingual or buccal tablets, buccal patches, nasal inhalation powders (insufflations), suppositories, or powder aerosols for nasal or pulmonary application. The inclusion complex may be used in the liquid state for the preparation of metered dose sprays, drops or pressurised aerosols for nasal or oral administration. The complex according to the invention may be incorporated into a shearform matrix

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designed for immediate release as described in Fuisz Technologies Ltd. patents (Eur. Pat. Appl. EP 95-650038 and PCT Int. Appl. WO 95/34293).

The water soluble complexes of alprazolam according to the invention may be incorporated into controlled release matrices for sustained release following oral administration of a matrix tablet. The matrix may be composed of any suitable erodible matrix such as substituted celluloses and the like. Alternatively the complexes may be applied to non-pareil spheres by coating methods known in the art. The coated spheres may be optionally coated with controlled release polymers such as polyacrylates and the like.

According to the invention, alprazolam has been found to be included in the cavity of beta- and gamma-cyclodextrins to form molecular inclusion complexes. Inclusion complexes of alprazolam may therefore be prepared according to methods known in the art such as spray drying, freeze drying and kneading, as described above. The complexes according to the invention may also be incorporated into microspheres by methods appreciated in the art. The complexes according to the invention are stable and highly water soluble.

Penetration enhancers may be used to promote the passage of alprazolam across the mucosal membranes. Typical permeation enhancers include fatty acids and their salts such as sodium caprate, sodium caprylate and sodium oleate, sodium laurate, and bile salts such as sodium glycodeoxycholate, sodium glycocholate, sodium cholate and sodium laurodeoxycholate. Other penetration enhancers may include tensides, ionic surfactants such as sodium lauryl sulphate, or non-ionic surfactants such as polyethylene glycol 660 hydroxystearate or polyoxyethylene lauryl ethers, fusidates such as sodium taurodihydrofusidate. Other specific enhancers include azone and chitosan. Combinations of permeation enhancers such as polyoxyethylene 8 lauryl ether and sodium glycocholate or mixed micelles such as sodium caprate and sodium glycocholate may also be used. The penetration enhancers may also

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be used in combination with sulfoalkyl derivatives. Typical concentrations of permeation enhancers are between 0,1 % to 5 %, more preferably between 0,25 % to 3 % by weight of the composition.

Liquid compositions suitable for nasal or oral administration may contain a suitable quantity of viscosity modifying agents such as hypromellose or carbopol 934P and preservative agents such as benzalkonium chloride, chlorhexidine gluconate or thiomersal.

Oral compositions may contain suitable flavouring and sweetening agents such as cherry, mint, spearmint, vanilla, aspartame, sucrose, xylitol, saccharin and the like.

Typical sublingual or buccal tablets may include lubricants such as magnesium stearate, calcium stearate and sodium stearyl fumarate to facilitate tablet compression, diluents such as lactose, microcrystalline cellulose, maize starch and the like and mucoadhesive agents such as chitosan, carbopol 934P, and hydroxypropylcellulose and the like.

Typical disintegrants to enhance sublingual tablet disintegration may include sodium carboxymethylcellulose, sodium starch glycolate, polyplasdone XL, and dried starch.

Typical suppositories may be formulated according to methods known in the art described in the Pharmaceutical Codex 12th Edition, the Pharmaceutical Press, pp 170 - 176 or Remington's Pharmaceutical Sciences 18th Edition, Mack Publishing Company, pp 1609 - 1614.

The following examples illustrate the present invention.

EXAMPLE 1

An excess of alprazolam is added to aqueous solutions of varying concentrations of beta-cyclodextrin. The mixtures are shaken for 24 hours and filtered. The filtrate is analysed by Ultraviolet spectrophotometry for alprazolam concentration. The concentration of alprazolam is plotted as a function of beta-cyclodextrin concentration in Figure 1.

EXAMPLE 2

An excess of alprazolam is added to aqueous solutions of varying concentrations of methyl-beta-cyclodextrin and 2-hydroxypropyl-beta-cyclodextrin. The mixtures are shaken for 24 hours and filtered. The filtrate is analysed by Ultraviolet spectrophotometry for alprazolam concentration. The concentration of alprazolam is plotted as a function of cyclodextrin concentration in Figure 2.

EXAMPLE 3

Alprazolam (6,53 g) and 2-hydroxypropyl-beta-cyclodextrin (200,4 g) are mixed. Purified deionised water (70 ml) is added with vigorous kneading to form a uniform paste with optional heating. Kneading is continued for 5 hours and the paste is dried in vacuo at 80°C. The dried complex is crushed and passed through a 250 micron sieve.

EXAMPLE 4

Alprazolam (6,0g) and methyl-beta-cyclodextrin (198 g) are mixed. Purified deionised water (70 ml) is added with vigorous kneading to form a uniform paste with optional heating. Kneading is continued for 5 hours and the paste is dried in vacuo at 80°C. The dried complex is crushed and passed through a 250 micron sieve.

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EXAMPLE 5

Dissolution behaviour of the inclusion complexes prepared in Examples 3 and 4 and their corresponding physical mixtures were evaluated in phosphate buffer pH 6,8 using USP Apparatus I (basket, 100rpm, 500ml, 37°C). Compressed disks (200mg) containing an amount of inclusion complex or physical mixture equivalent to 1 mg alprazolam were prepared using a single punch and die. The dissolution rate of alprazolam from the systems is shown in Figures 3 and 4.

The complexes of Examples 3 and 5 result in a significantly faster dissolution rate within the first 20 minutes compared with the physical mixture.

EXAMPLE 6

The unit composition of a sublingual tablet containing the equivalent of 1,0 mg alprazolam is as follows:

Alprazolam / 2-hydroxypropyl-beta-cyclodextrin complex	
(from Example 3)	32,7 mg
Lactose NF	19 mg
Sodium stearyl fumarate	0,6 mg

The complex is blended with lactose and the lubricant. The mixture is formed into sublingual tablets by compression at 10 – 30 N.

EXAMPLE 7

The powdered inclusion complexes prepared according to Examples 3 and 4 were stored in an oven at 60°C. Chromatographic analysis showed the complexes to be chemically stable after one months storage at 60°C.

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EXAMPLE 8

Methylated beta-cyclodextrin D.S.1.8 (200 g) is dissolved in 90 ml purified deionised water. Alprazolam (2.5 g) is added to the solution with stirring until a clear solution is obtained. Benzalkonium chloride (0.01%) is added as a preservative. The volume is adjusted to 1000 ml by addition of purified deionised water. The tonicity of the final solution is adjusted by addition of sodium chloride. The solution is filtered through a 0.45 μm filter. Each 0.1 milliliter of solution contains 0.25 mg alprazolam. The solution is well tolerated after intranasal administration by drops or spray.

EXAMPLE 9

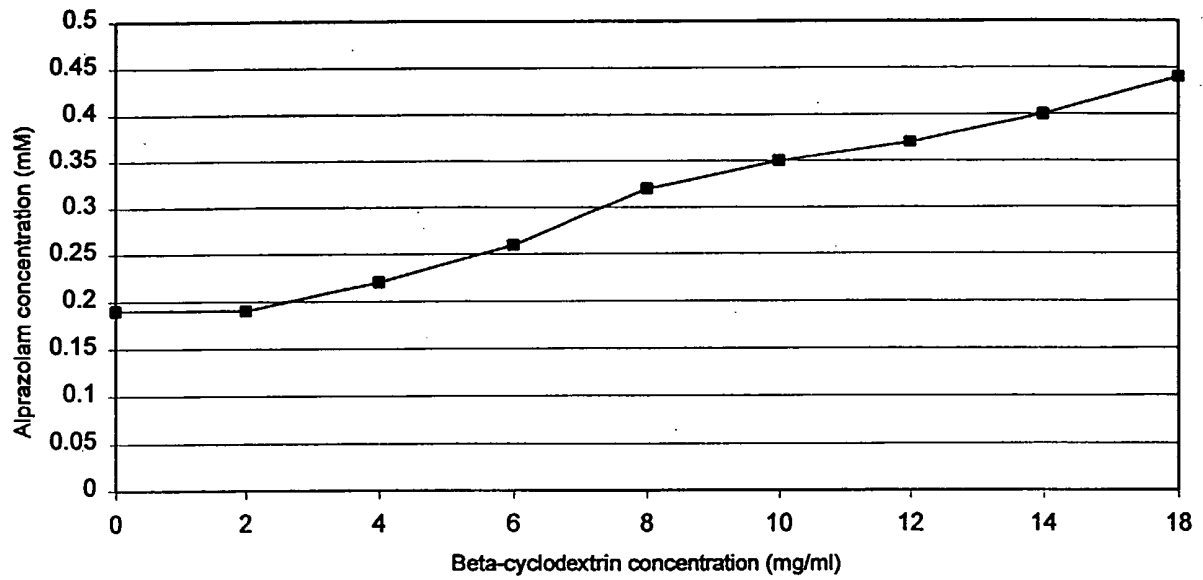
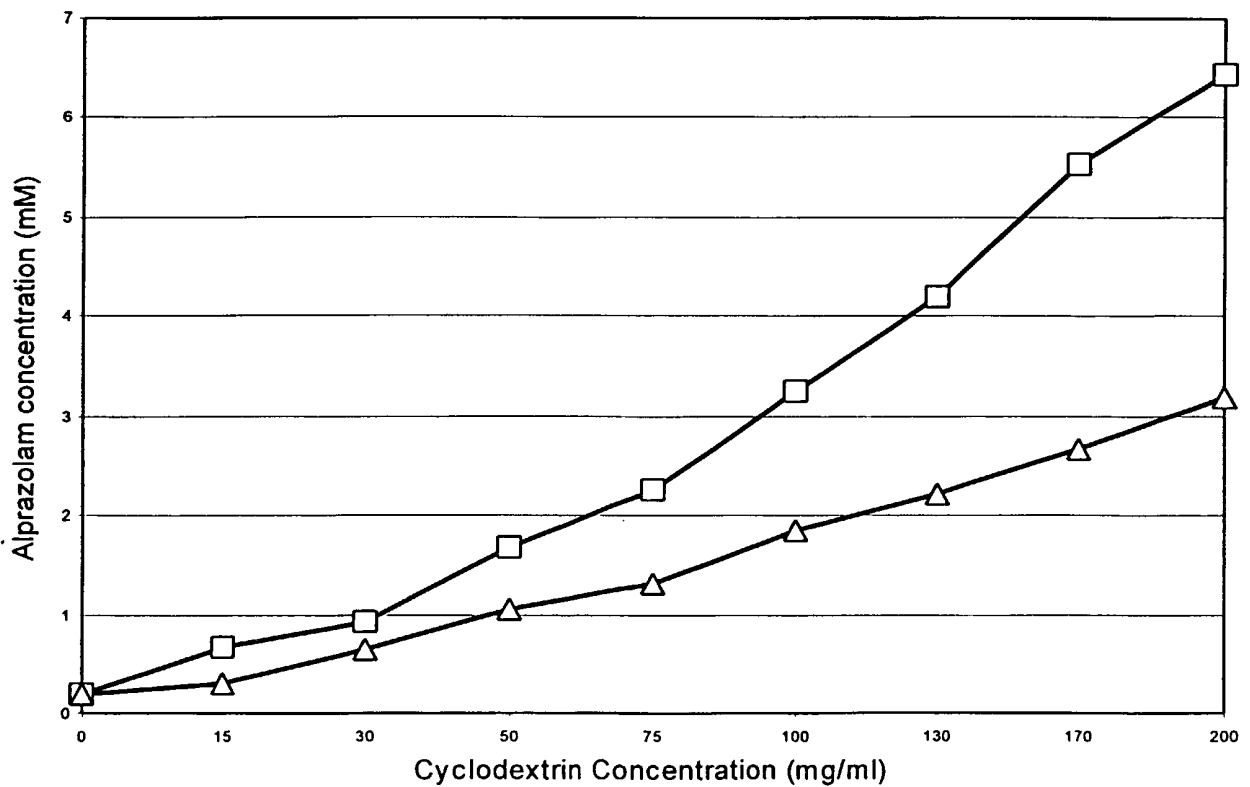
The solution obtained from Example 8 is packaged in a suitable metered dose aerosol dispenser adapted for intranasal application. The concentration of the solution provides convenient dispensing of 0.25 mg alprazolam per 0.1 ml.

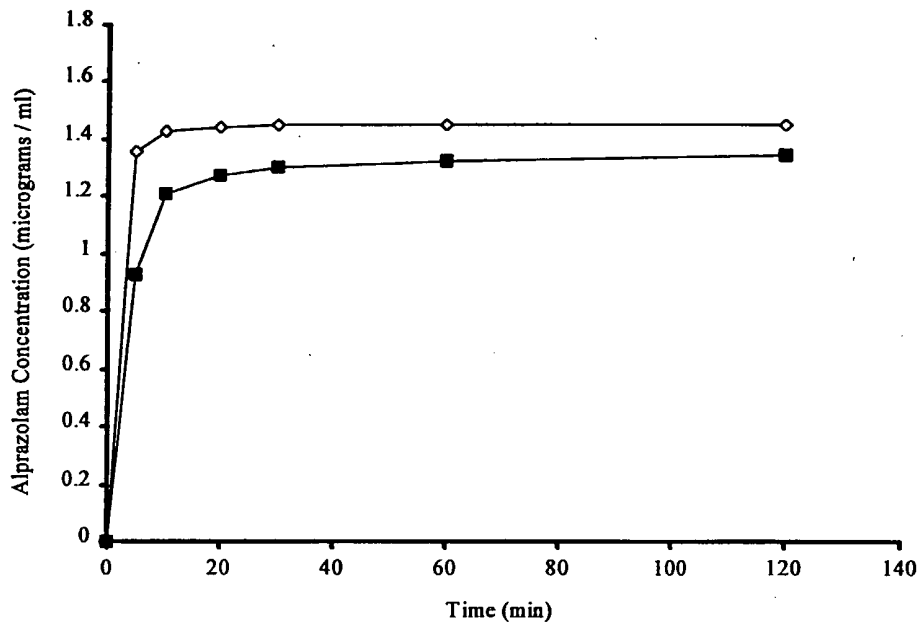
CLAIMS

1. An inclusion complex of (a) alprazolam and (b) a water soluble 2-hydroxypropyl-beta-cyclodextrin with a degree of substitution between 3.9 and 5.1 hydroxypropyl groups per cyclodextrin molecule.
2. An inclusion complex according to claim 1, wherein the inclusion complex has a stoichiometry of (a) to (b) of from 1:1 mol/mol to 1:10 mol/mol inclusive.
3. An inclusion complex according to claim 2, wherein the inclusion complex has a stoichiometry of (a) to (b) of from 1:1 mol/mol to 1:7 mol/mol inclusive.
4. A pharmaceutical composition for transmucosal delivery comprising an inclusion complex according to claim 1, and a pharmaceutically acceptable carrier therefor.
5. A pharmaceutical composition according to claim 4, wherein the inclusion complex has a stoichiometry of (a) to (b) of from 1:1 mol/mol to 1:10 mol/mol inclusive.
6. A pharmaceutical composition according to claim 5, wherein the inclusion complex has a stoichiometry of (a) to (b) of from 1:1 mol/mol to 1:7 mol/mol inclusive.
7. A pharmaceutical composition according to any one of claims 4 to 6, wherein the pharmaceutical composition comprises a solution of the inclusion complex of alprazolam and the cyclodextrin in a pharmaceutically acceptable liquid carrier.
8. A pharmaceutical composition according to claim 7, formulated for administration as drops, a spray or an aerosol.

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9. A pharmaceutical composition according to any one of claims 4 to 6, wherein the inclusion complex of alprazolam and the beta-cyclodextrin is a solid mixed with or incorporated into a pharmaceutically acceptable solid carrier.
10. A pharmaceutical composition according to claim 9, formulated as sublingual tablets, buccal tablets, buccal patches, nasal inhalation powders, suppositories, and powder aerosols.
11. The use of the inclusion complex of claim 1, in the manufacture of a medicament for use in the treatment of generalised anxiety disorder or for the management of panic disorders.
12. A method of preparing the inclusion complex of claim 1, comprising forming an aqueous solution of (a) alprazolam and (b) a water soluble cyclodextrin in purified deionized water, wherein the cyclodextrin is a 2-hydroxypropyl-beta-cyclodextrin with a degree of substitution between 3.9 and 5.1 hydroxypropyl groups per cyclodextrin molecule.
13. A method according to claim 12, wherein the alprazolam and cyclodextrin have a stoichiometry of from 1:1 mol/mol to 1:10 mol/mol inclusive.
14. A method according to claim 13, wherein the alprazolam and cyclodextrin have a stoichiometry of from 1:1 mol/mol to 1:7 mol/mol inclusive.
15. The use of the inclusion complex of claim 1, for the treatment of generalised anxiety disorder or for the management of panic disorders.

$\frac{1}{2}$ Fig 1Fig 2

$\frac{2}{2}$ Fig 3Fig 4