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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR INTRANASAL ADMINISTRATION OF DIHYDROERGOTAMINE, APOMORPHINE AND MORPHINE

(57) Abstract

The invention relates to pharmaceutical compositions for the intranasal administration of dihydroergotamine, apomorphine and morphine comprising one of these pharmacologically active ingredients in combination with a cyclodextrin and/or a disaccharide and/or a polysaccharide and/or a sugar alcohol.

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PHARMACEUTICAL COMPOSITIONS FOR INTRANASAL ADMINISTRATION OF DIHYDROERGOTAMINE, APOMORPHINE AND MORPHINE

This invention is related to pharmaceutical compositions for nasal administration of dihydroergotamine, apomorphine and morphine, and methods of administering such compositions.

Dihydroergotamine mesylate (DHE) has been used in migraine therapy already for a long time. In patients with migraine attacks, DHE is suitable for basic interval treatment using tablets or solution, both for oral application, as well as for acute treatment by intravenous or intramuscular injection. DHE has been introduced in a nasal spray to avoid the parenteral and the oral route of administration. The nasal spray seems a good alternative, because it is less painful, less expensive and less inconvenient than injection therapy. Secondly, nausea and vomiting are common in migraine patients, making a nasal spray much more efficient than oral treatment.

A nasal spray containing DHE 4 mg/ml in an aqueous solution has been studied extensively by a number of investigators. Some of these investigators report, that besides DHE the nasal spray also contains glucose 5% and caffeine 1%. It was found that 1 mg of DHE, nasally administered, had the equivalence of 10 mg orally, and almost 40% of the bioavailability of the i.m. administration (PG Andersson and LT Jespersen, Cephalalgia 1986; 6: 51-54).

The maximal venoconstrictor effect of 1 mg nasal DHE amounted to about 40%, of 0.5 mg i.m. DHE to about 50% of the initial venous diameter (W.H. Aellig and J.Rosenthaler, Eur. J. Clin. Pharmacol. 1986; 30: 581-584).

Nasal DHE appeared to be equally effective than a combination of oral ergotamine and caffeine in relieving

migraine attacks (D Wirt et al, Cephalalgia 19 9; 9, suppl. 1 410-411) Another stu n 904 pati s confirmed the effica y of nasal D nd reported side effects in 18.4% of patients: nas irritation, nausea, vomiting, fatigue, vertigo, breathlessness, tachycardia and perspiration. Only 3.9% of the patients refused further treatment with nasal DHE (G. Jenzer and M.F. Bremgartner, Schweiz. Rundsch. Med. Prax. 1990: 79: 914-917). Lataste et al (Cephalalgia 1989; 9 suppl. 10: 342-343) and Di Serio et al (Cephalalgia 1989; 9 suppl. 10: 344-345), confirm the efficacy of nasal DHE in the acute management of migraine. In contrast, Tulunay et al (Cephalalgia 1987; 7: 131-133) found little difference in nasal DHE and placebo.

Most of these studies are very encouraging and therefore nasal DHE, in the pharmaceutical composition studied by the above mentioned authors, seems an interesting alternative for oral and parenteral DHE preparations. Nasal DHE in the composition of DHE mesylate 4 mg/ml in 5% glucose and 1% caffeine, is available on prescription in several countries (e.g. Switzerland, France, Belgium).

Nevertheless, there is an urgent need for another DHE nasal drug formulation, because the nasal preparation, presently on the market, is not stable. It is on the market as a separate glass ampoule (containing the DHE formulation) which has to be broken by the patient and sprayed in the nose using a separate spray device. After opening of the ampoule, the spray can be used no longer than 24 hours.

Accordingly, it is an object of the invention to provide a highly stable pharmaceutical composition, suitable for nasal administration, capable of introducing efficiently a therapeutical amount of DHE into the human body. It has surprisingly been found that a pharmaceutically acceptable DHE composition can be formulated, suitable for nasal administration, without the presence of a special

caffeine-glucose vehicle and without the necessity of presenting the formulation in a separate glass ampoule.

According to the invention, the nasal pharmaceutical composition contains DHE and/or a salt of DHE (mesylate or tartrate) and a cyclodextrin and/or other saccharides and/or sugar alcohols. Such compositions appear to result in a surprisingly high bioavailability and a superior stability of DHE.

The term "cyclodextrins" refers to cyclic oligosaccharides, like α-, ß- and γ-cyclodextrin and their derivatives, preferably ß-cyclodextrin and its derivatives, preferably methylated ß-cyclodextrin, with a degree of CH_3-substitution between 0.5 and 3.0, more preferably between 1.7 and 2.1. The term "saccharides" refers to disaccharides, like lactose, maltose, saccharose and also refers to polysaccharides, like dextrans, with an average molecular weight between 10.000 and 100.000, preferably 40.000 and 70.000. The term "sugar alcohols" refers to mannitol and sorbitol.

The nasal composition, according to the invention, can be administered as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. The administration of the nasal composition may also take place using a nasal tampon or nasal sponge, containing the invention composition.

In particular, powder formulations show a surprisingly high bioavailability and superior stability of the DHE. In addition, powder formulations have the advantage that no preservatives are necessary. Preservatives are known to decrease the ciliary movement, which may be harmful in chronic nasal medication (Hermens W.A.J.J. and Merkus F.W.H.M., Pharm. Res. 1987; 4: 445-449).

Nasal powder compositions can be made by mixing the active agent and the excipient, both possessing the desired particle size. Other methods to make a suitable powder formulation can be selected. Firstly, a solution of the active agent and the cyclodextrin and/or the other saccharide and/or sugar alcohol is made, followed by precipitation, filtration and pulverization. It is also possible to remove the solvent by freeze drying, followed by pulverization of the powder in the desired particle size by using conventional techniques, known from the pharmaceutical literature. The final step is size classification for instance by sieving, to get particles that are less than 100 microns in diameter, preferably between 50 and 100 microns in diameter. Powders can be administered using a nasal insufflator. Powders may also be administered in such a manner that they are placed in a capsule. The capsule is set in an inhalation or insufflation device. A needle is penetrated through the capsule to make pores at the top and the bottom of the capsule and air is sent to blow out the powder particles. Powder formulation can also be administered in a jet-spray of an inert gas or suspended in liquid organic fluids.

Also the active agent can be brought into a viscous basis, using vehicles, conventionally used, for example natural gums, methylcellulose and derivatives, acrylic polymers (carbopol) and vinyl polymers (polyvinylpyrrolidone). In the invention compositions many other excipients, known from the pharmaceutical literature, can be added, such as preservatives, surfactants, co-solvents, adhesives, anti-oxidants, buffers, viscosity enhancing agents, and agents to adjust the pH or the osmolarity.

The required amount for a nasal administration of a liquid or semi-solid nasal administration form is generally between 0.05 ml and 0.2 ml, preferably about 0.1 ml per nostril. The amount of a powder nasal formulation is

generally between 1 and 15 mg, preferably about 5 to 10 mg per nostril. Doses of DHE in the nasal pharmaceutical composition of the invention, suitable in the treatment of migraine attacks, are preferably in the range from 0.25 to 0.5 mg per nostril.

The following examples illustrate the invention in more detail, but are not construed as limiting the invention:

EXAMPLE 1 (liquid)

Dihydroergotamine mesylate	250 mg
Methyl-ß-cyclodextrin D.S. 1.8	2.5 g
Benzalkonium Chloride	0.01 %
Sodium EDTA	0.05-0.1 %
Sorbitol	5 %
Purified water to	100 ml

100 µl = 250 µg DHE mesylate

EXAMPLE 2 (gel)

Dihydroergotamine mesylate	0.5 g
Methyl-ß-cyclodextrin D.S. 1.8	5 g
Benzalkonium Chloride	0.01 %
Sodium EDTA	0.05-0.1 %
Sorbitol	5 %
Hydroxypropylmethylcellulose	1-2 %
Purified water to	100 ml

100 µl gel = 500 µg DHE

EXAMPLE 3A (powder)

Dihydroergotamine mesylate	0.5 mg
Methyl-ß-cyclodextrin	5 mg
Mannitol	4.5 mg

10 mg powder = 500 µg DHE mesylate

EXAMPLE 3B (powder)

Dihydroergotamine mesylate	0.5 mg
Dextran (average M.W. 70.000)	9.5 mg

10 mg powder = 500 µg DHE mesylate

EXAMPLE 3C (powder)

Dihydroergotamine mesylate	0.5 mg
ß-cyclodextrin	5 mg
Lactose	4.5 mg

10 mg powder = 500µg DHE mesylate

Apomorphine is a very potent dopamine agonist. It is used as an adjunctive medication in the treatment of Parkinson disease, complicated by motor fluctuations. Recently, encouraging results have been reported on the intranasal application of apomorphine in patients with Parkinson disease to relieve "off-period" symptoms in patients with response fluctuations (T. van Laar et al, Arch. Neurol. 1992; 49: 482-484). The intranasal applied apomorphine, used by these authors, consisted of an aqueous solution of apomorphine HCl 10 mg/ml. This formulation is also used for parenteral application and is published in different Pharmacopoeia's.

The exact nasal composition formulation used in the study by T. van Laar et al (1992) was:

Apomorphine HCl 0.5 H2O	1 g
Sodium metabisulphite	0.100 g
Sodium EDTA	0.010 g
NaCl	0.600 g
Benzalkonium Chloride	0.01 %
$NaH_2PO_4.2H_2O$	0.150 g
$Na_2HPO_4.2H_2O$	0.050 g

NaOH 1 M to adjust pH at 5.8
purified water to 100 ml
(from Pharm. Weekblad 1991; 126: 1113-1114)

By a metered dose nebulizer a dose of 1 mg apomorphine HCl (0.1 ml of the solution) was delivered with each nasal application by puff to the patients. A great disadvantage of this aqueous solution is the instability of the apomorphine.

An object of the invention is a nasal formulation of apomorphine with an improved bioavailability and stability of apomorphine.

According to the invention, the nasal pharmaceutical composition contains apomorphine and/or apomorphine salts and a cyclodextrin and/or other saccharides and/or sugar alcohols. Such compositions appear to result in a surprisingly high bioavailability and superior stability of apomorphine.

The term "cyclodextrins" refers to cyclic oligosaccharides, like α-, ß- and γ-cyclodextrin and their derivatives, preferably ß-cyclodextrin and its derivatives, preferably methylated ß-cyclodextrin, with a degree of CH_3-substitution between 0.5 and 3.0, more preferably between 1.7 and 2.1. The term "saccharides" refers to disaccharides, like lactose, maltose, saccharose and also refers to polysaccharides, like dextrans, with an average molecular weight between 10.000 and 100.000, preferably 40.000 and 70.000. The term "sugar alcohols" refers to mannitol and sorbitol.

The nasal composition, according to the invention, can be administered as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. The administration of the nasal composition may also take place using a nasal tampon or nasal sponge, containing the invention composition.

In particular, powder formulations show a surprisingly high bioavailability and superior stability of the apomorphine.

In addition, powder formulations have the advantage that no preservatives are necessary. Preservatives are known to decrease the ciliary movement, which may be harmful in chronic nasal medication (Hermens W.A.J.J. and Merkus F.W.H.M., Pharm. Res. 1987; 4: 445-449).

Nasal powder compositions can be made by mixing the active agent and the excipient, both possessing the desired particle size. Other methods to make a suitable powder formulation can be selected. Firstly, a solution of the active agent and the cyclodextrin and/or the other saccharide and/or sugar alcohol is made, followed by precipitation, filtration and pulverization. It is also possible to remove the solvent by freeze drying, followed by pulverization of the powder in the desired particle size by using conventional techniques, known from the pharmaceutical literature. The final step is size classification for instance by sieving, to get particles that are less than 100 microns in diameter, preferably between 50 and 100 microns in diameter. Powders can be administered using a nasal insufflator. Powders may also be administered in such a manner that they are placed in a capsule. The capsule is set in an inhalation or insufflation device. A needle is penetrated through the capsule to make pores at the top and the bottom of the capsule and air is sent to blow out the powder particles. Powder formulation can also be administered in a jet-spray of an inert gas or suspended in liquid organic fluids.

Also the active agent can be brought into a viscous basis, using vehicles, conventionally used, for example natural gums, methylcellulose and derivatives, acrylic polymers (carbopol) and vinyl polymers (polyvinylpyrrolidone). In the invention compositions many other excipients, known from the pharmaceutical literature, can be added, such as preservatives, surfactants, co-solvents, adhesives,

anti-oxidants, buffers, viscosity enhancing agents, and agents to adjust the pH or the osmolarity.

The required amount for a nasal administration of a liquid or semi-solid nasal administration form is generally between 0.05 ml and 0.2 ml, preferably about 0.1 ml per nostril. The amount of a powder nasal formulation is generally between 1 and 15 mg, preferably about 5 to 10 mg per nostril. Doses of apomorphine in the pharmaceutical composition of the present invention, suitable in the treatment of Parkinson disease, are generally in the range of 0.1 to 2mg, preferably between 0.5 mg and 1 mg per nostril.

The following examples illustrate the present invention in more detail, but are not construed as limiting the invention:

EXAMPLE 1A (powder)

Apomorphine base	1 mg
Methyl-ß-cyclodextrin D.S. 2.1	5 mg
Mannitol	4 mg

10 mg powder = 1 mg Apomorphine

EXAMPLE 1B (powder)

Apomorphine HCl	2 mg
Mannitol	18 mg

20 mg powder = 2 mg Apomorphine HCl

EXAMPLE 1C (powder)

Apomorphine HCl	1 mg
Dextran (average M.W. 70.000)	9 mg

10 mg powder = 1 mg Apomorphine HCl

EXAMPLE 2 (gel)

Apomorphine HCl	500 mg
Methylated-ß-cyclodextrin D.S. 1.8	2.5 g
Hydroxypropylmethylcellulose	1-2 g
Benzalkonium Chloride	0.01 %
Sodium EDTA	0.1 %
Sodium metabisulphite	0.15 %
Sorbitol	4 %
pH adjusted to	4.5 - 5.5
purified water to	100 ml

0.2 ml gel = 1 mg Apomorphine HCl

EXAMPLE 3 (liquid)

Apomorphine HCl	1 g
Methylated-ß-cyclodextrin D.S. 1.1	4 g
Sodium metabisulphite	0.15 %
Sodium EDTA	0.1 %
Benzalkonium Chloride	0.01 %
NaCl	0.8 %
pH adjusted to	4.5 - 5.5
purified water to	100 ml

100 µl = 1 mg Apomorphine HCl

Morphine is one of the strongest analgesics. Morphine therapy is restricted to two groups of patients. Firstly, to hospitalized patients, after surgery and secondly, to cancer and burn patients. The latter treatment is chronic. Morphine is administered generally by injection and in chronic treatment by sustained release oral preparations. After single oral administration morphine has a poor effect, mainly due to a large first pass effect. Secondly, the oral route is not possible when the patient shows severe nausea, vomiting, bowel obstruction or confusion. There is a need for a non-parenteral administration, other then oral, because injection therapy needs interference of (para)medical personnel and is painful.

Buccal administration of morphine have been proposed (MDD Bell et al, Lancet 1985; 1: 71-73), but this route did not find a large acceptance in practice. Recently rectal administration of morphine has been studied (T.J. Wilkinson et al, Cancer Chemother. Pharmacol 1992; 31: 251-254 and N Babul et al Clin. Pharmacol. Ther. 1993; 54: 286-292). From both publications it can be concluded that rectal application in some cases may be an alternative when the parenteral route is impractical or undesirable and the oral route is not available due to the patients condition. Nasal administration of a strong analgesic could be a good alternative to parenteral therapy, because it may give a very rapid absorption and no first pass effect.

To overcome the drawbacks of the oral and parenteral routes of administration of morphine, the use of a nasal spray has been proposed (S.L. Verweij and R. van Gijn: Can morphine be administered nasally? Ziekenhuisfarmacie (Dutch) 1988; 4: 73-77). The composition of the nasal spray in this study was:

Morphine HCl.$3H_2O$	1.50 g
Sodium metabisulphite	0.03 g
Sodium EDTA	0.003 g
Benzylalcohol	0.3 ml
Propylene glycol	6 ml
Phosphate Buffer (0.01 mol/L; pH 6.00)	30 ml
Per puff of 100 μl the dose of morphine is	5 mg.

In 7 volunteers Verweij and van Gijn studied the pharmacokinetics of morphine after 4 puffs of about 100 μl (2 times 1 puff of 100, μl in each nostril). The exact dose which was delivered to the volunteers was 16 mg of morphine (range 15-18 mg) and the bioavailability of morphine from this nasal spray was 26-35%. The bioavailabilty of morphine after oral application is estimated to be about 40% (J. Säwe, Clin. Pharmacokinetics

1986; 11: 87-106). This means, that the bioavailability of morphine after giving the nasal spray as described by Verweij and van Gijn is relatively low. After nasal absorption there is no first pass effect and therefore the nasal bioavailability should be higher than the oral.

The nasal absorption of morphine has been studied also by F Chast et al (J. Pharm. Clin. 1992; 11: 257-261). They delivered nasally and orally 20 mg morphine acetate in an aqueous solution to 6 patients and compared the nasal absorption with the oral absorption of the same solution. They found, as expected, higher blood levels of morphine after the nasal application. Unfortunately, the nasal solutions, as described by the preceding studies of Verweij and van Gijn and of Chast and coworkers, are not stable and the bioavailability of morphine can be improved.

An object of the invention is to provide a highly stable pharmaceutical composition, suitable for nasal administration, and showing an superior bioavailability of morphine.

According to the invention, the nasal pharmaceutical composition contains morphine and/or morphine salts (hydrochloride, sulphate, acetate) and a cyclodextrin and/or other saccharides and/or sugar alcohols. Such compositions appear to result in a surprisingly high bioavailability and superior stability of morphine.

The term "cyclodextrins" refers to cyclic oligosaccharides, like α-, ß- and γ-cyclodextrin and their derivatives, preferably ß-cyclodextrin and its derivatives, preferably methylated ß-cyclodextrin, with a degree of CH_3-substitution between 0.5 and 3.0, more preferably between 1.7 and 2.1. The term "saccharides" refers to disaccharides, like lactose, maltose, saccharose and also refers to polysaccharides, like dextrans, with an average molecular

weight between 10.000 and 100.000, preferably 40.000 and 70.000. The term "sugar alcohols" refers to mannitol and sorbitol.

The nasal composition, according to the invention, can be administered as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. The administration of the nasal composition may also take place using a nasal tampon or nasal sponge, containing the invention composition.

In particular, powder formulations show a surprisingly high bioavailability and superior stability of the morphine. In addition, powder formulations have the advantage that no preservatives are necessary. Preservatives are known to decrease the ciliary movement, which may be harmful in chronic nasal medication (Hermens W.A.J.J. and Merkus F.W.H.M., Pharm. Res. 1987; 4: 445-449).

Nasal powder compositions can be made by mixing the active agent and the excipient, both possessing the desired particle size. Other methods to make a suitable powder formulation can be selected. Firstly, a solution of the active agent and the cyclodextrin and/or the other saccharide and/or sugar alcohol is made, followed by precipitation, filtration and pulverization. It is also possible to remove the solvent by freeze drying, followed by pulverization of the powder in the desired particle size by using conventional techniques, known from the pharmaceutical literature. The final step is size classification for instance by sieving, to get particles that are less than 100 microns in diameter, preferably between 50 and 100 microns in diameter. Powders can be administered using a nasal insufflator. Powders may also be administered in such a manner that they are placed in a capsule. The capsule is set in an inhalation or insufflation device. A needle is penetrated through the capsule to make pores at the top and the bottom of the

capsule and air is sent to blow out the powder particles. Powder formulation can also be administered in a jet-spray of an inert gas or suspended in liquid organic fluids.

Also the active agent can be brought into a viscous basis, using vehicles, conventionally used, for example natural gums, methylcellulose and derivatives, acrylic polymers (carbopol) and vinyl polymers (polyvinylpyrrolidone). In the invention compositions many other excipients, known from the pharmaceutical literature, can be added, such as preservatives, surfactants, co-solvents, adhesives, anti-oxidants, buffers, viscosity enhancing agents, and agents to adjust the pH or the osmolarity.

The required amount for a nasal administration of a liquid or semi-solid nasal administration form is generally between 0.05 ml and 0.2 ml, preferably about 0.1 ml per nostril. The amount of a powder nasal formulation is generally between 1 and 15 mg, preferably about 5 to 10 mg per nostril.

Doses of morphine in the pharmaceutical composition of the present invention, suitable in the treatment of pain, are in the range from 1 to 20 mg.

The following examples illustrate the present invention in more detail, but are not construed as limiting the invention:

EXAMPLE 1A (powder)

Morphine sulphate $5H_2O$	13.3 mg
Methyl-ß-cyclodextrin D.S. 2.1	11.7 mg
Mannitol	5 mg

30 mg powder = 10 mg morphine

EXAMPLE 1B (powder)

Morphine sulphate $5H_2O$	13.3 mg
ß-cyclodextrin	6.7 mg

20 mg powder = 10 mg morphine

EXAMPLE 1C (powder)

Morphine HCl $3H_2O$	13.1 mg
Dextran (average MW 70.000)	16.9 mg

30 mg powder = 10 mg morphine

EXAMPLE 2(gel)

Morphine (as salt)	1.5 g
Methyl-B-cyclodextrin D.S. 1.8	5 g
(Hydroxypropyl)methylcellulose	1-2 %
Benzalkonium Chloride	0.01 %
Sodium EDTA	0.1 %
Sodium metabisulphite	0.15 %
Sorbitol	4 %
Purified water to	50 ml

0.2 ml gel = 6 mg morphine

EXAMPLE 3 (liquid)

Morphine (as salt)	4 g
Methyl-ß-cyclodextrin D.S. 2.1	4 g
Methylcellulose	0.25 %
Sodium metabisulphite	0.15 %
Sodium EDTA	0.1 %
Benzalkonium Chloride	0.01 %
Mannitol	4 %
Purified water to	100 ml

100 µl = 4 mg morphine

CLAIMS

1. A pharmaceutical composition for nasal administration comprising dihydroergotamine and/or a dihydroergotamine-salt and a cyclodextrin and/or an other saccharide and/or a sugar alcohol.

2. A pharmaceutical composition according to claim 1, wherein the dihydroergotamine salt is dihydroergotamine mesylate and/or tartrate.

3. A pharmaceutical composition according to claim 1 or 2, wherein the cyclodextrin is α- or ß- or γ-cyclodextrin and/or a derivative of α- or ß- or γ-cyclodextrin.

4. A pharmaceutical composition according to any of claims 1 - 3, wherein the cyclodextrin is ß-cyclodextrin and/or a derivative.

5. A pharmaceutical composition according to claim 4, wherein the derivative of ß-cyclodextrin is a methylated ß-cyclodextrin with a degree of substitution between 0.5 and 3.0.

6. A pharmaceutical composition according to any of claims 1 - 5, wherein the saccharides a disaccharide, preferably lactose and/or a polysaccharide, preferably dextran, having an average molecular weight between 10.000 and 100.000, preferably between 40.000 and 70.000 .

7. A pharmaceutical composition according to any of claims 1-6, wherein the sugar alcohol is mannitol and/or sorbitol.

8. A pharmaceutical composition according to any of claims 1-7 in powder form, suitable for nasal administration, wherein the particles of the powder have a diameter between 50-100 microns.

9. A process of preparing a nasal pharmaceutical composition according to any of claims 1 - 8, which process comprises combining dihydroergotamine and/or its salts with a cyclodextrin and/or a disaccharide and/or a polysaccharide and/or a sugar alcohol.

10. A method of treating migraine attacks by administering a pharmaceutical composition, according to any of claims 1 - 8, to the nasal mucosa.

11. A pharmaceutical composition for nasal administration comprising apomorphine and/or an apomorphine salt and a cyclodextrin and/or an other saccharide and/or a sugar alcohol.

12. A pharmaceutical composition according to claim 11, wherein the apomorphine salt is apomorphine hydrochloride.

13. A pharmaceutical composition according to claim 11 or 12, wherein the cyclodextrin is α- or ß- or γ-cyclodextrin and/or a derivative of α- or ß- or γ-cyclodextrin.

14. A pharmaceutical composition according to any of claims 11 - 13, wherein the cyclodextrin is ß-cyclodextrin and/or a derivative.

15. A pharmaceutical composition according to claim 14, wherein the derivative of ß-cyclodextrin is a methylated ß-cyclodextrin with a degree of substitution between 0.5 and 3.0.

16. A pharmaceutical composition according to any of claims 11 - 15, wherein the saccharide is a disaccharide, preferably lactose and/or a polysaccharide, preferably dextran, having an average molecular weight between 10.000 and 100.000, preferably between 40.000 and 70.000.

17. A pharmaceutical composition according to any of claims 11 - 16, wherein the sugar alcohol is mannitol and/or sorbitol.

18. A pharmaceutical composition according to any of claims 11 - 17 in powder form, suitable for nasal administration, wherein the particles of the powder have a diameter between 50-100 microns.

19. A process of preparing a nasal pharmaceutical composition according to any of claims 11 - 18, which process comprises combining apomorphine and/or its salts with a cyclodextrin and/or a disaccharide and/or a polysaccharide and/or a sugar alcohol.

20. A method of treating Parkinson disease by administering a pharmaceutical composition according to any of claims 11 - 18, to the nasal mucosa.

21. A pharmaceutical composition for nasal administration comprising morphine and/or morphine salts and a cyclodextrin and/or an other saccharide and/or a sugar alcohol.

22. A pharmaceutical composition according to claim 21, wherein the morphine salt is morphine hydrochloride and/or acetate and/or sulphate.

23. A pharmaceutical composition according to claim 21 or 22, wherein the cyclodextrin is α- or ß- or γ-cyclodextrin and/or a derivative of α- or ß- or γ-cyclodextrin.

24. A pharmaceutical composition according to any of claims 21 - 23, wherein the cyclodex-trin is ß-cyclodextrin and/or a derivative.

25. A pharmaceutical composition according to claim 24, wherein the derivative of ß-cyclodextrin is a methylated ß-cyclodextrin with a degree of substitution between 0.5 and 3.0.

26. A pharmaceutical composition according to any of claims 21 - 25, wherein the saccharide is a disaccharide, preferably lactose and/or a polysaccharide, preferably dextran, having an average molecular weight between 10.000 and 100.000, preferably between 40.000 and 70.000.

27. A pharmaceutical composition according to any of claims 21 - 26, wherein the sugar alcohol is mannitol and/or sorbitol.

28. A pharmaceutical composition according to any of claims 21 - 27 in powder form, suitable for nasal administration, wherein the particles of the powder have a diameter between 50-100 microns.

29. A process of preparing a nasal pharmaceutical composition, according to any of claims 21 - 28, which process comprises combining morphine and/or its salts with a cyclodextrin and/or a disaccharide and/or a polysaccharide and/or a sugar alcohol.

30. A method of relieving pain by administering a pharmaceutical composition according to any of claims 21 - 28, to the nasal mucosa.