The invention relates to oral dosage forms comprising dimebolin and donepezil and to processes for producing them.
Oral dosage form comprising dimebolin and donepezil

The invention relates to oral dosage forms comprising dimebolin and donepezil and to processes for producing them.

Dimebolin (synonyms Dimebon, latrepirdine) is a β-carboline derivative with antihistaminic and cognition-enhancing effects. Dimebolin appears suitable for the treatment of Huntington's disease, schizophrenia, amyotrophic lateral sclerosis, stroke, chronic and neuropathological pain or also for slowing down the ageing process. In addition, dimebolin appears promising for the treatment of neurodegenerative diseases, such as Alzheimer's disease, as described in EP 0 876 818 Bl.

The IUPAC name of dimebolin is 2,3,4,5-tetrahydro-2,8-dimethyl-5-(2-(6-methyl-3-pyridyl)ethyl)-1H-pyrido(4,3-b)indole. The chemical structure of dimebolin is shown in formula (1) below:

![Chemical structure of dimebolin](image)

(1)

Pharmaceutical compositions containing dimebolin are known from WO 2008/069963 A1 or WO 2007/087425 A1, for example.

Donepezil is a member of the group of reversible cholinesterase inhibitors. The inhibition of that enzyme causes an increase in the concentration of acetylcholine in the synaptic gap, as a result of which acetylcholine receptors are increasingly activated. Donepezil is used for the symptomatic treatment of mild to moderately severe dementia of the
Alzheimer's disease type, but is also used, beyond the scope of its approval, for vascular dementia.

The IUPAC name for donepezil is \((RS)-1\text{-benzyl}-4\text{-}[\,(5,6\text{-dimethoxyindane-1\text{-one-2\text{-yl}}})\text{methyl}j\text{piperidine. The chemical structure of donepezil is shown in formula (2) below:}

\[
\begin{align*}
\text{(2)}
\end{align*}
\]

Pharmaceutical compositions containing donepezil are known from WO 2006/045512 A1.

It is known from WO 2008/069963 A1 that dimebolin can act as an NMDA antagonist and can therefore be used in the treatment of neurodegenerative diseases such as Alzheimer's disease. In addition, WO 2008/069963 A1 also specifically discloses two oral dosage forms of dimebolin, though these are not particularly advantageous with regard to either their release behaviour or their processability.

Furthermore, WO 2008/051599 A2 discloses the administration of combinations of active agents. However, no pharmaceutical formulation is disclosed which permits the advantageous joint oral administration of two active agents against Alzheimer's disease.

The object of the present invention is therefore to provide dosage forms, preferably oral dosage forms, which contain two active agents together and can be used for the combination therapy of degenerative diseases and in particular Alzheimer's disease. In addition, it was an object of the invention to provide dosage forms in which possible interactions between the two active agents could be ruled out. It was a further object of the
present invention to provide production processes in which the active agents could be processed simply and without complex procedures.

It was unexpectedly possible to achieve the above-mentioned objects by means of an oral dosage form comprising dimebolin and donepezil in a specific weight ratio and by processes for producing them. The objects are achieved particularly advantageously if active agents with a specific particle size distribution, excipients with a specific plasticity and/or specific production processes are used.

The subject matter of the invention is therefore an oral dosage form comprising dimebolin and donepezil in a weight ratio of between 20:1 and 1:5.

A further subject matter of the present invention is a process for producing the oral dosage form of the invention, comprising:

a) mixing dimebolin, donepezil and optionally pharmaceutical excipients, and
d) converting the mixture into a suitable dosage form, preferably directly compressing the resulting mixture into tablets. The purpose of this process variant is in particular to produce the single-phase oral dosage form described below.

A further subject matter of the present invention is a process for producing the oral dosage form of the invention, comprising:
a2) mixing the active agent with pharmaceutical excipients,
b2) granulating the resulting mixture,
c2) mixing the resulting granules with the second active agent and optionally further pharmaceutical excipients,
d2) converting the mixture resulting from step c2) into a suitable dosage form, preferably compressing the resulting mixture into tablets. The purpose of this process variant is in particular to produce the two-phase oral dosage form described below.

In the two embodiments of the process of the invention, steps a1) and a2) and d1) and d2) respectively are preferably identical.

In the context of this invention, the term "dimebolin" comprises \(\text{2,3,4,5-tetrahydro-2,8-dimethyl-5-(2-(6-methyl-3-pyridyl)ethyl)-1H-pyrido(4,3-b)indole}\) according to formula
In addition, the term "dimebolin" comprises all the pharmaceutically acceptable salts, hydrates, polymorphous forms and/or solvates thereof. The term "dimebolin" preferably comprises dimebolin dihydrochloride. Dimebolin dihydrochloride exhibits a pronounced polymorphism and, according to WO 2009/111540 A1, has six different polymorphous forms, namely anhydrous dimebolin dihydrochloride, dimebolin dihydrochloride hemihydrate, dimebolin dihydrochloride monohydrate, dimebolin dihydrochloride dihydrate, dimebolin dihydrochloride trihydrate and amorphous dimebolin dihydrochloride. Dimebolin dihydrochloride dihydrate and dimebolin dihydrochloride trihydrate are preferably used.

In the context of this invention, the term "donepezil" comprises (i?S)-1-benzyl-4-[(5,6-dimethoxyindane-1-one-2-yl)methyl]piperidine or DL-1-benzyl-4-[(5,6-dimethoxyindane-1-one-2-yl)methyl]piperidine dione in accordance with formula (2) above. In addition, the term "donepezil" comprises all the pharmaceutically acceptable salts, hydrates, polymorphous forms and/or solvates thereof. It is preferable for donepezil hydrochloride, especially donepezil monohydrochloride to be used.

In the oral dosage form of the invention, the weight ratio between (A) dimebolin and (B) donepezil is usually between 20:1 and 1:5, preferably between 15:1 and 1:3, more preferably between 10:1 and 1:2, particularly preferably between 8:1 and 1:1 and especially between 7:1 and 2:1.

In the context of this invention, oral dosage forms are understood to mean capsules, tablets, pellets, granules or powders, for example. In a preferred embodiment, the oral dosage form of the invention is a tablet.

In a first preferred embodiment, the oral dosage form of the invention, especially the tablet of the invention, has a single-phase structure.

In the context of this invention, a single-phase structure is understood to mean a structure which has a uniform structure within a particular phase. A uniform structure within a particular phase is understood here to mean the substantially uniform spatial distribution of all the components within that phase. A single-phase structure of a tablet is therefore understood to mean the substantially uniform spatial distribution of all the
components within that tablet phase, a possible tablet coating not being regarded as part of that tablet phase.

In a second preferred embodiment, the oral dosage form of the invention, especially the tablet of the invention, has a two-phase structure. In this embodiment, the dosage form has a first phase and a second phase. As described above, in this alternative embodiment the tablet of the invention therefore has a first phase, in which the components of that phase are preferably distributed spatially uniformly within that phase, and a second phase, in which the components of that phase are preferably distributed spatially uniformly within that phase. In this context, the arrangement of the first and second phases to one another can take any form desired. The first phase may, for example, form a first tablet core and the second phase the second tablet coating and vice versa. With an arrangement of this kind, one speaks of coated tablets. It is also possible for the two phases to be arranged in such a way that the first phase is arranged as a layer on the second phase and vice versa. With an arrangement of this kind, one speaks of bilayer tablets.

In a particularly preferred variant of the second embodiment, the tablet of the invention comprises a first phase (preferably an intragranular phase), which is uniformly distributed in the form of granules in the second phase (preferably an extragranular phase) in the form of a powder mixture. In this context, each of the phases preferably contains an active agent, in particular the first phase dimebolin and the second phase donepezil. Alternatively the second phase may also be granulated. In this case, a first granulated phase and a second granulated phase are subsequently blended and compressed.

Dimebolin is generally used in the oral dosage form of the invention in an amount of 2 to 40 % by weight, preferably 3 to 30 % by weight, more preferably 4 to 25 % by weight, especially 5 to 20 % by weight, based on the total weight the oral dosage form.

Donepezil is generally used in the oral dosage form of the invention in an amount of 0.5 to 35 % by weight, preferably 1 to 25 % by weight, more preferably 3 to 20 % by weight, especially 5 to 15 % by weight, based on the total weight the oral dosage form.
In a preferred embodiment, the dimebolin per se or a pharmaceutically acceptable salt thereof used in the dosage form has a water content of 0.1 to 15 % by weight in each case, more preferably 1.0 to 14 % by weight, e.g. 4.0 to 13 % by weight, and particularly preferably 6.0 to 12.5 % by weight.

In a preferred embodiment, the donepezil per se or a pharmaceutically acceptable salt thereof used in the dosage form has a water content of 0.01 to 10 % by weight in each case, more preferably 0.25 to 8.0 % by weight, e.g. 0.57 to 7.5 % by weight, and particularly preferably 1.0 to 5 % by weight.

In the context of this application, the water content is preferably determined according to the Karl Fischer method, using a coulometer at 160° C. A Metrohm 831 KF coulometer with a titration cell without a diaphragm is preferably used. Usually, a 150 mg sample of dimebolin or donepezil is analysed.

The oral dosage forms of the invention may contain not only dimebolin and donepezil, but also further pharmaceutical excipients. These are usually the excipients with which the person skilled in the art is familiar, especially those which are described in the European Pharmacopoeia. Examples of excipients used are disintegrants, anti-stick agents, additives to improve the powder flowability, wetting agents and/or lubricants. Where appropriate, further excipients can also be used. These excipients will be explained in more detail below.

In a preferred embodiment, the oral dosage form of the invention contains a (C) filler in addition to the active agents. Similarly, mixtures of the fillers described below are possible.

For the purposes of this invention, fillers are understood to mean substances which are described as pharmaceutical fillers in the state of the art. These fillers are typically substances which are needed in order to form the body of the oral dosage form in the case of dosage forms with small amounts of active agent, so as to obtain a sufficient amount of dosage form mixture for a suitable dosage form size.

Lactose, lactose derivatives, starch, chitin, cellulose and derivatives thereof, e.g. microcrystalline cellulose (e.g. Avicel®), sucrose, dextrates, dextrin, dextrose, maltodextrin,
hydrogenated vegetable oil, kaolin, alkali or alkaline earth salts such as calcium phosphates, e.g. dicalcium hydrogen phosphate (e.g. in the form of the dihydrate or preferably the anhydrate), calcium carbonate, magnesium carbonate, magnesium oxide, calcium sulphate, sodium chloride, potassium chloride and mixtures thereof can be used as fillers for the purposes of the invention. Similarly, SiO₂ modified microcrystalline cellulose (e.g. Prosolv®, Rettenmaier & Sonne, Germany) can be used.

Other fillers that can be used are sugar alcohols and/or sugars (especially monosaccharides and disaccharides) such as mannitol, sorbitol, xylitol, isomalt, glucose, fructose, maltose and mixtures thereof.

In principle, it is also possible to use mixtures of the above-mentioned fillers. The fillers are preferably selected from mannitol, microcrystalline cellulose, silicified microcrystalline cellulose, lactose, dicalcium hydrogen orthophosphate (preferably as the anhydrate) and starch. Particularly preferred fillers are lactose, microcrystalline cellulose and mixtures thereof.

In the case of lactose, alpha-lactose monohydrate is preferably used. In particular alpha-lactose monohydrate with a tapped density of 450 to 550 g/l and a bulk density of 550 to 680 g/l. The average particle size (D50) of a-lactose monohydrate is preferably between 60 and 200 μm.

In the preferred embodiment of a single-phase structure of the tablet of the invention, fillers are usually employed in amounts of between 15 and 95 % by weight, preferably between 25 and 85 % by weight, more preferably between 35 and 75 % by weight, particularly preferably between 45 and 75 % by weight, based on the total weight of the tablet.

In the preferred embodiment, in which the tablet of the invention comprises a first and a second phase, fillers are usually employed in the first phase in amounts of between 0 and 40 % by weight, preferably between 5 and 35 % by weight, particularly preferably between 10 and 20 % by weight, based on the total weight the tablet, and in the second phase in amounts of between 0 and 70 % by weight, preferably between 10 and 60 % by weight, particularly preferably between 25 and 55 % by weight, based on the total weight of the tablet.
In a further preferred embodiment, the filler has a yield pressure value of less than 80 MPa. In the following, the meaning of the "yield pressure value" for the purposes of this invention will be explained.

Excipients (especially fillers) can generally be classified with regard to the change in the shape of the particles under a compressive force (compaction): plastic excipients are characterised by plastic deformation, whereas when compressive force is exerted on brittle excipients, the particles tend to break into smaller particles. Brittle behaviour on the part of the filler can be quantified by the increase in the surface area in a moulding.

In the art, it is customary to classify the brittleness in terms of the "yield pressure value". According to a simple classification, the values for the "yield pressure" here are low for plastic substances but high in the case of friable substances on the other hand [Duberg, M., Nystrom, C., 1982, Studies on direct compression of tablets VI. Evaluation of methods for the estimation of particle fragmentation during compaction. Acta Pharm. Suec. 19, 421-436; Humbert-Droz P., Mordier D., Doelker E. Methode rapide de determination du comportement à la compression pour des etudes de preformulation. Pharm. Acta Helv., 57, 136-143 (1982)]. The "yield pressure value" describes the pressure that has to be reached for the excipient (i.e. preferably the filler) to begin to flow plastically.

The "yield pressure value" is preferably calculated using the reciprocal of the gradient of the Heckel plot, as described in York, P., Drug Dev. Ind. Pharm. 18, 677 (1992). The measurement in this case is preferably made at 25°C and a deformation rate of 0.1 mm/s.

In the context of the present invention, an excipient (especially a filler) is deemed a non-brittle excipient if it has a "yield pressure value" of no more than 150 MPa, preferably 5 to 80 MPa. An excipient is usually described as a brittle excipient if it has a "yield pressure value" of more than 80 MPa, preferably more than 150 MPa. Brittle excipients may have a yield pressure value of up to 500 MPa.

Examples of preferred non-brittle fillers are mannitol or lactose. Examples of preferred brittle fillers are microcrystalline cellulose (MCC), especially with a specific surface
area of 0.7 - 3.0 m²/g, the specific surface area being determined by means of the gas adsorption method according to Ph. Eur., 6th edition 2.9.26., method 1, dicalcium hydrogen phosphate, tricalcium phosphate and/or calcium carbonate.

In a preferred alternative embodiment, the filler comprises at least one filler with a yield pressure value of less than 80 MPa and one filler with a yield pressure value of more than 80 MPa.

The oral dosage form of the invention also optionally contains (D) disintegrants.

"Disintegrants" for the purposes of the invention are understood to mean substances which accelerate the disintegration of an oral dosage form, especially a tablet, after it is placed in water. Suitable disintegrants are organic disintegrants such as starch, pregelatinised starch, carrageenan, croscarmellose and/or crospovidone. Alkaline disintegrants are likewise used. The term "alkaline disintegrants" means disintegrants which, when dissolved in water, produce a pH level of more than 7.0. Starch, especially pregelatinised corn starch, is preferred as the disintegrant.

In the preferred embodiment of a single-phase structure of the dosage form of the invention, especially the tablet of the invention, disintegrants are usually employed in amounts of 2 to 25 % by weight, preferably 5 to 15 % by weight, particularly preferably 7 to 12 % by weight, based on the total weight of the tablet.

In the preferred embodiment, in which the dosage form of the invention, especially the tablet of the invention comprises a first and a second phase, disintegrants are usually employed in the first phase in amounts of between 0 and 10 % by weight, preferably between 1 and 7 % by weight, particularly preferably between 1.5 and 5 % by weight, based on the total weight the tablet, and in the second phase in amounts of between 1 and 20 % by weight, preferably between 2 and 15 % by weight, particularly preferably between 3 and 10 % by weight, based on the total weight of the tablet.

In addition, the oral dosage form of the invention optionally contains (E) lubricants.
Lubricants are generally used in order to reduce sliding friction. In particular, the intention is to reduce the sliding friction found during tablet pressing between the punches moving up and down in the die and the die wall, on the one hand, and between the edge of the tablet and the die wall, on the other hand. Suitable lubricants are, for example, stearic acid, adipic acid, sodium stearyl fumarate, (Pruv®), magnesium stearate and/or calcium stearate. Magnesium stearate is preferred.

In the preferred embodiment of a single-phase structure of the invention, lubricants are usually employed in amounts of 0 to 5 % by weight, preferably 0.1 to 4 % by weight, particularly preferably 0.5 to 3 % by weight, based on the total weight of the tablet.

In the embodiment in which the dosage form of the invention, especially the tablet of the invention, comprises a first and a second phase, lubricants are preferably used only in the second phase in amounts of 0 to 5 % by weight, preferably 0.1 to 4 % by weight, particularly preferably 0.5 to 3 % by weight, based on the total weight the tablet.

In addition, the oral dosage form of the invention optionally contains (F) binders.

In the context of this invention, binders are understood to mean substances with the aid of which solids, preferably powders, can be adhered together. In this context, the binder preferably wets all the solid particles uniformly. The nature of the binder can be used to give the filler new processing and material properties. In this context, the binders are preferably dissolved in solvent and added in liquid form to the fillers to be bound.

The dosage form of the invention may, for example, comprise the following polymers as binders: polysaccharides, such as hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC, especially sodium and calcium salts), ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose (HPC); guar flour, alginic acid and/or alginates; synthetic polymers such as polyvinyl pyrrolidone (povidone), polyvinyl acetate (PVAC), polyvinyl alcohol (PVA), polymers of acrylic acid and their salts, polyacrylamide, polymethacrylates, vinyl pyrrolidone/vinyl acetate copolymers (such as Kollidon® VA64, BASF), polyalkylene glycols, such as polypropylene glycol or preferably polyethylene glycol, co-block polymers of poly-
ethylene glycol, especially co-block polymers of polyethylene glycol and polypropylene glycol (Pluronic®, BASF), and mixtures of the polymers mentioned.

Binders particularly preferably used are polyvinyl pyrrolidone, preferably with a weight-average molecular weight of 10,000 to 60,000 g/mol, especially 12,000 to 40,000 g/mol, a copolymer of vinyl pyrrolidone and vinyl acetate, especially with a weight-average molecular weight of 40,000 to 70,000 g/mol and/or polyethylene glycol, especially with a weight-average molecular weight of 2,000 to 10,000 g/mol, and HPMC, especially with a weight-average molecular weight of 20,000 to 90,000 g/mol and/or preferably a content of methyl groups of 10 to 35 % and a content of hydroxy groups of 1 to 35 %. Their weight-average molecular weight is usually determined by means of gel permeation chromatography.

Preferred solvents for the binders mentioned are water and ethanol. A solution is preferably employed which contains 1 to 10 % by weight, more preferably 2 to 5 % by weight binder.

In the preferred embodiment in which the dosage form of the invention, especially the tablet of the invention, comprises a first and a second phase, binders are preferably only used in the first phase in amounts of 0.1 to 5 % by weight, preferably 0.5 to 3 % by weight, particularly preferably 0.8 to 2 % by weight, based on the total weight of the tablet.

Furthermore, the oral dosage form of the invention may additionally contain a (G) flow-regulating agent.

In the context of this invention, flow-regulating agents are understood to mean substances whose task is to reduce both the interparticulate friction (cohesion) between the individual particles in a tableting mixture and their adherence to the wall surfaces of the press mould (adhesion). One example of an additive to improve the powder flowability is disperse silica (e.g. Aerosil®). Preferably, silica is used with a specific surface area of 50 to 400 m²/g, more preferably 100 to 250 m²/g, determined by gas adsorption in accordance with Ph. Eur., 6th edition 2.9.26., method 1.
In the preferred embodiment of a single-phase structure of the tablet of the invention, flow-regulating agents are usually employed in amounts of 0 to 10 % by weight, preferably 0.1 to 5 % by weight, particularly preferably 1 to 3 % by weight, based on the total weight of the tablet.

In the preferred embodiment in which the tablet of the invention comprises a first phase with a single-phase structure and a second phase with a single-phase structure, flow-regulating agents may be employed both in one of the two phases and in both phases, usually in amounts of 0 to 10 % by weight, preferably 0.1 to 5 % by weight, particularly preferably 1 to 3 % by weight, based on the total weight of the tablet.

It lies in the nature of pharmaceutical excipients that they sometimes perform more than one function in a pharmaceutical formulation. In the context of this invention, in order to provide an unambiguous delimitation, the fiction will therefore preferably apply that each substance can only perform one function. This means that a substance which is used as a particular excipient is not simultaneously also used as a further pharmaceutical excipient. For example, MCC - if used as a filler - does not also count as a disintegrant (even though microcrystalline cellulose also exhibits a disintegrating effect). To put it another way, two excipients with different functions, e.g. fillers and disintegrants, should be different from one another in material terms, i.e. they should be formed from different substances.

The oral dosage form of the invention is preferably used in the treatment of neurodegenerative diseases, especially Alzheimer's disease.

For the purposes of the invention, neurodegenerative diseases are understood to mean a group of diseases of the nervous system which usually progress slowly, are hereditary or occur sporadically. Alzheimer's disease is understood to mean the pathological loss of mental (cognitive) faculties, accompanied by a decline in intellectual functions such as thought and memory.

The oral dosage form of the invention is preferably used in the treatment of Alzheimer's disease patients in whom a monotherapy with dimebolin is inadequate. A monotherapy
is understood to mean the treatment of Alzheimer's disease with a drug that only contains one active agent, preferably dimebolin.

In the context of this invention an inadequate monotherapy is understood to mean a treatment of Alzheimer's disease patients with an active agent, preferably dimebolin, which does not sufficiently slow the progression of the disease and thus does not sufficiently prevent the entry into an advanced stage of the disease.

The oral dosage forms of the invention are preferably suitable for administration once daily, preferably in the evenings.

The present invention further relates to a process for producing the oral dosage form of the invention.

In a first embodiment, the process of the invention for producing the oral dosage form of the invention comprises

a) mixing dimebolin, donepezil and optionally pharmaceutical excipients, and
d) converting the mixture into a suitable dosage form, preferably compressing the resulting mixture into tablets. This process is in particular suitable for producing the single-phase dosage form of the invention, in particular for producing the single-phase tablets of the invention.

"Mixing" is to be understood for the purposes of the invention as meaning a process of combining substances with the aim of achieving a substantially homogeneous distribution of different substances by the action of mechanical forces. Mixing for the purposes of the invention is performed in conventional mixing devices, such as roll mixers, shaking mixers, free-fall mixers, shear mixers, ploughshare mixers, planetary mixing kneaders, Z or sigma kneaders or fluid or intensive mixers. A free-fall mixer (Turbula®) is preferably used. Dry mixing is preferably performed. "Dry mixing" is intended here to mean mixing as described above without the addition of liquids, such as water, organic solvents etc.

The mixing time is usually 1 minute to 2 hours, preferably 5 minutes to 1.5 hours, more preferably 10 minutes to 1 hour.
In the process of the invention, it is preferable that dimebolin and donepezil are used in particulate form, with the particle size distribution of dimebolin and donepezil being matched to one another.

In the context of the invention, the dimebolin used has a $D_{50}$ value of the particle size distribution of 1 to 150 µm, preferably 5 to 120 µm, more preferably 8 to 80 µm, particularly preferably 10 to 70 µm and especially 15 to 120 µm.

In a preferred embodiment, the dimebolin used normally has a $D_{10}$ value of the particle size distribution of between 0.5 and 50 µm, preferably between 2.0 and 20 µm.

In a further preferred embodiment, the dimebolin used normally has a $D_{90}$ value of the particle size distribution of less than 250 µm, preferably less than 200 µm, more preferably 10 to 160 µm, even more preferably 15 to 120 µm and especially 20 to 105 µm.

In a further preferred embodiment, the ratio between the $D_{90}$ value and the $D_{30}$ value ($=D_{90}/D_{30}$) of dimebolin has a value of between 1.1 and 5.0, preferably between 1.2 and 3.0, particularly preferably between 1.3 and 2.5. In a further preferred embodiment, the ratio between the $D_{50}$ value and the $D_{10}$ value ($=D_{50}/D_{10}$) of dimebolin has a value of between 1.1 and 5.0, preferably between 1.2 and 3.0, particularly preferably between 1.3 and 2.5.

In the context of the invention, the donepezil used has a $D_{50}$ value of the particle size distribution of 1 to 150 µm, preferably 5 to 120 µm, more preferably 8 to 80 µm, particularly preferably 10 to 70 µm and especially 15 to 55 µm.

In a preferred embodiment, the donepezil used normally has a $D_{10}$ value of the particle size distribution of between 0.5 and 50 µm, preferably between 2.0 and 20 µm.

In a further preferred embodiment, the donepezil used normally has a $D_{90}$ value of the particle size distribution of less than 250 µm, preferably less than 200 µm, more preferably 10 to 160 µm, even more preferably 15 to 120 µm and especially 20 to 105 µm.
In a further preferred embodiment, the ratio between the \( D_{90} \) value and the \( D_{50} \) value (= \( D_{90}/D_{50} \)) of donepezil has a value of between 1.1 and 5.0, preferably between 1.2 and 3.0, particularly preferably between 1.3 and 2.5. In a further preferred embodiment, the ratio between the \( D_{50} \) value and the "Dio" value (=\( D_{50}/D_{10} \)) of donepezil has a value of between 1.1 and 5.0, preferably between 1.2 and 3.0, particularly preferably between 1.3 and 2.5.

The ratio of \( D_{50} \) (dimebolin) : \( D_{50} \) (donepezil) is usually 5 : 1 to 1 : 5, preferably 3 : 1 to 1 : 3, more preferably 2 : 1 to 1 : 2, and especially 1.5 : 1 to 1 : 1.5. The ratio of Dio (dimebolin) : Dio (donepezil) is usually 5 : 1 to 1 : 5, preferably 3 : 1 to 1 : 3, more preferably 2 : 1 to 1 : 2, and especially 1.5 : 1 to 1 : 1.5. The ratio of \( D_{90} \) (dimebolin) : \( D_{90} \) (donepezil) is usually 5 : 1 to 1 : 5, preferably 3 : 1 to 1 : 3, more preferably 2 : 1 to 1 : 2, and especially 1.5 : 1 to 1 : 1.5.

The "particle size" of a particle to be determined is understood in accordance with the invention to mean the diameter of an equivalent particle which is assumed to be spherical and to have the same light-scattering pattern as the particle to be determined. In accordance with the invention, the particle size is determined by means of laser diffractionometry. Specifically, a Malvern Instruments Mastersizer 2000 was used to determine the particle size. It is preferable to perform a wet measurement with particles dispersed in a dispersant, 2,000 r.p.m., ultrasound 60 seconds with shading of 4 to 15 %. The evaluation is carried out for particles with a \( D_{50} \) value of less than 5.0 \( \mu \)m using the Mie method and for particles with a \( D_{50} \) value of at least 5.0 \( \mu \)m using the Fraunhofer method.

The terms "particles of the intermediate" and "intermediate particles" are used synonymously herein.

"Particle size distribution of the intermediate" is to be understood in the context of this invention as meaning the statistical distribution of the volume portions based on all the particle sizes of the particles of the intermediate. "Volume portion" means the volume-based proportion in per cent of all particles of a defined particle size.
The $D_{90}$ value of the particle size distribution of the intermediate describes the particle size at which 90% by volume of the particles have a smaller particle size than the particle size corresponding to the $D_{90}$ value.

Similarly, the $D_{50}$ value of the particle size distribution is defined as the particle size at which 50% by volume of the particles have a smaller particle size than the particle size corresponding to the $D_{50}$ value. Likewise, 50% by volume of the particles then have a larger particle size than the $D_{50}$ value.

Analogously, the $D_{10}$ value of the particle size distribution of the intermediate is defined as the particle size at which 10% by volume of the particles have a smaller particle size than the particle size corresponding to the $D_{10}$ value.

The process of compressing, especially by direct compression, can be carried out, as explained above, without further pre-treatment by compressing the mixture obtained from a).

Conventional tableting machines used in the production of tablets can be used for compression purposes. A rotary press or eccentric press is preferably used. In the case of rotary presses, a compressive force of 2 to 40 kN, preferably 2.5 to 35 kN, is usually applied. In the case of eccentric presses, a compressive force of 1 to 20 kN, preferably 2.5 to 10 kN, is usually applied. By way of example, the Korsch® EK0 is used.

In a second embodiment, the process of the invention for producing the oral dosage form of the invention comprises producing the first phase by means of granulation. In this embodiment, the process preferably comprises the following steps:

a2) mixing the active agent with pharmaceutical excipients,
b2) granulating the resulting mixture,
c2) mixing the resulting granules with the second active agent and optionally further pharmaceutical excipients,
d2) converting the mixture resulting from step c2) into a suitable dosage form, preferably compressing the resulting mixture into tablets.
"Granulation" is generally understood to mean the formation of relatively coarse or granular aggregate material as a powder by assembling and/or aggregating finer powder particles (agglomerate formation, or build-up granulation) and/or the formation of finer granules by breaking up coarser aggregates (disintegration, or break-down granulation). Granulation can conventionally mean wet or dry granulation. Granulation is generally carried out in conventional granulating devices, such as extruder, perforated-disk, perforated-roll, or fluidised-bed granulators. Compulsory mixers or spray dryers can likewise be used.

Dry granulation is generally carried out using pressure or temperature. Wet granulation is generally carried out using binders and/or solvents as described above.

The first phase is preferably produced by means of wet granulation. The granulation time, especially in the case of wet granulation is usually 1 minute to 1 hour, preferably 2 minutes to 30 minutes. In a preferred embodiment, the wet granulation is carried out in a fluidised bed granulator, such as a Glatt® GPCG 3 (Glatt GmbH, Germany).

After granulation, the granules are preferably dried. The drying step can be performed after or at the same time as the granulation step. "Drying" for the purposes of this invention is understood to mean the separation of liquids adhering to solids. The adhering liquids are preferably water in the form of contact moisture, capillary water, adsorption water, hydration water and water of constitution. Drying generally takes place in conventional drying equipment, such as cabinet or tray dryers, vacuum dryers, fluidised bed dryers, spray dryers or freeze dryers. The drying and granulation process is preferably performed in a cabinet dryer at 30 to 80° C, preferably at 35 to 70° C, particularly preferably at 40 to 60° C. The drying conditions are preferably selected such that drying continues until there is a drying loss of less than 4 %, preferably less than 3 %, particularly preferably less than 2 %.

In an alternative embodiment, the granulating in step (b2) may be performed by means of dry granulation, especially by means of compacting. The compacting is preferably carried out in a roll granulator. The rolling force is preferably 5 to 70 kN/cm, preferably 10 to 60 kN/cm, more preferably 15 to 50 kN/cm. The gap width of the roll granulator
is, for example, 0.8 to 5 mm, preferably 1 to 4 mm, more preferably 1.5 to 3 mm, especially 1.8 to 2.8 mm.

After that, the compacted material is usually granulated. The granulating can be performed with processes known in the state of the art. In a preferred embodiment, the granulating is performed in a screen mill. In this case, the mesh width of the screen insert is usually 0.1 to 5 mm, preferably 0.5 to 3 mm, more preferably 0.75 to 2 mm, especially 0.8 to 1.8 mm. A Comill® U5 apparatus (Quadro Engineering, USA), for example, is used for granulating, preferably followed by screening. In an alternative embodiment, the compacting can be performed in a compactor, wherein the compacted material is granulated through an integrated screen.

In a preferred embodiment (in the case of both wet and dry granulation), the granulation conditions are selected such that the resulting particles (granules) have a volume-average particle size (\(D_{50}\) value) of 50 to 800 µm, more preferably 110 to 650 µm, even more preferably 160 to 450 µm, especially 190 to 350 µm.

In addition, the granulation conditions are preferably selected such that the resulting granules have a bulk density of 0.2 to 0.85 g/ml, more preferably 0.3 to 0.8 g/ml, especially 0.4 to 0.7 g/ml. The Hausner factor is usually in the range from 1.02 to 1.3, more preferably from 1.04 to 1.20 and especially from 1.1 to 1.25. The "Hausner factor" in this context means the ratio of tapped density to bulk density. The tapped and bulk densities are preferably determined in accordance with Ph. Eur 6.0. 2.9.15.

After granulation (and in the case of wet granulation optionally after drying), the resulting granules are preferably mixed with the second phase (step c2). The mixing process is as defined above. After that, the resulting mixture is converted into a suitable dosage form, preferably compressed (step d2). The process of compression (d2) is performed as already described above under (d1).

In an alternative embodiment, the second phase is also granulated. In that case, the first granulated phase is first produced in steps (a2) to (c2), and then the second granulated phase is produced in analogous steps. The two granulated phases are mixed and then compressed jointly in step (d2).
In the process of the invention, the tableting conditions are preferably selected such that the resulting tablets have a diameter of 2 to 17 mm, preferably 7 to 15 mm, particularly preferably 9 to 13 mm.

In accordance with the invention, the tablets resulting from both the alternative embodiments described above preferably have a hardness of 50 to 200 N, preferably 60 to 180 N, particularly preferably 80 to 120 N. The hardness is determined in accordance with Ph. Eur. 6.0, section 2.9.8.

In addition, the resulting tablets preferably have a friability of less than 3 %, particularly preferably less than 2 %, especially less than 1 %. The friability is determined in accordance with Ph. Eur. 6.0, section 2.9.7.

Finally, the tablets of the invention usually have a "content uniformity" of 95 to 105 % of the average content, preferably 98 to 102 %, especially 99 to 101 %. (This means that all the tablets have a content of active agent of between 95 and 105 %, preferably between 98 and 102 %, especially between 99 and 101 % of the average content. The "content uniformity" is determined in accordance with Ph. Eur. 6.0, section 2.9.6.

In addition, in accordance with the invention, the resulting tablets preferably have a mass of 100 to 700 mg, preferably 200 to 600 mg, particularly preferably 300 to 500 mg, based on the total weight the non-film-coated tablet.

The preferred tablets of the invention may also be coated with a film layer. For this purpose, the methods of film-coating tablets which are standard in the state of the art may be employed. For film-coating, macromolecular substances are preferably used, such as modified celluloses, polymethacrylates, polyvinyl pyrrolidone, polyvinyl acetate phthalate, zein and/or shellack.

HPMC is preferably used, especially HPMC with a weight-average molecular weight of 10,000 to 150,000 g/mol and/or an average degree of substitution of -OCH$_3$ groups of 1.2 to 2.0.

The thickness of the coating is preferably 5 to 100 µπ, more preferably 10 to 80 µπ.
It should, however, be noted that all the statements regarding the weight of the active agents and excipients in this application always refer to the non-film-coated tablet.

The oral dosage forms of the invention can preferably serve as dosage forms with immediate release (or "H?" for short).

The release profile of the oral dosage forms of the invention according to the USP method after 10 minutes usually indicates a content of active agent released of at least 30 %, preferably at least 60 %, particularly preferably at least 90 %. The active agent release is determined here by means of the USP method at 75 r.p.m. in 0.1 N HC1 at 37° C with a paddle apparatus.

The oral dosage form of the invention, preferably the single-phase dosage form of the invention, especially the single-phase tablet of the invention, preferably comprises:

A) dimebolin in an amount of 2 to 30 % by weight, preferably 7 to 22 % by weight, particularly preferably 10 to 18 % by weight,

B) donepezil in an amount of 0.5 to 20 % by weight, preferably 1 to 7 % by weight, particularly preferably 1.5 to 5 % by weight,

C) filler in an amount of 20 to 90 % by weight, preferably 50 to 85 % by weight, particularly preferably 60 to 80 % by weight,

D) optionally disintegrant in an amount of 0 to 25 % by weight, preferably 2 to 15 % by weight, particularly preferably 7 to 12 % by weight, and

E) optionally lubricant in an amount of 0 to 5 % by weight preferably 0.1 to 4 % by weight, particularly preferably 0.5 to 3 % by weight, and

F) optionally binder in an amount of 0 to 5 % by weight, preferably 0.5 to 3 % by weight, particularly preferably 0.8 to 2 % by weight,

based on the total weight of the dosage form. In this context, in the case of a tablet, the individual statements of percentages refer to the content in the tablet without any film layer.

In an alternative embodiment, the oral dosage form of the invention comprises a first phase, containing
A) dimebolin in an amount of 2 to 30 % by weight, preferably 7 to 22 % by weight, particularly preferably 10 to 18 % by weight,

C) filler in an amount of 0 to 30 % by weight, preferably 5 to 25 % by weight, particularly preferably 10 to 20 % by weight,

D) optionally disintegrant in an amount of 0 to 10 % by weight, preferably 1 to 7 % by weight, particularly preferably 1.5 to 5 % by weight,

F) binder in an amount of 0 to 5 % by weight, preferably 0.5 to 3, particularly preferably 0.8 to 2 % by weight,

and a second phase, containing

B) donepezil in an amount of 0.5 to 25 % by weight, preferably 1 to 15 % by weight, particularly preferably 1.5 to 5 % by weight,

C) filler in an amount of 20 to 70 % by weight, preferably 30 to 65 % by weight, particularly preferably 35 to 60 % by weight,

D) optionally disintegrant in an amount of 0 to 20 % by weight, preferably 2 to 15 % by weight, particularly preferably 3 to 10 % by weight, and

E) optionally lubricant in an amount of 0 to 5 % by weight, preferably 0.1 to 4 % by weight, particularly preferably 0.5 to 3 % by weight,

based on the total weight of the dosage form, especially the tablet. In this context, in the case of a tablet, the individual statements of percentages refer to the content in the tablet without any film layer.

The invention will now be explained in more detail with reference to the following examples.

EXAMPLES

Production of the oral dosage forms of the invention

Different oral dosage forms of the invention, comprising dimebolin and donepezil (Examples 1 to 4), were produced. The amount of dimebolin specified refers here to the amount of active agent in the form of the (anhydrous) free base. The amount of donepezil specified, on the other hand, refers to the amount of donepezil monohydrochloride.
Example 1: Tablet with single-phase structure

1. Dimebolin 60 mg
2. MCC 60 mg
3. Pregelatinised starch 15 mg
4. Donepezil HCl 10 mg
5. Pregelatinised starch 28 mg
6. MCC 64 mg
7. Lactose monohydrate 176 mg
8. Magnesium stearate 5 mg

Dimebolin (in the form of a dihydrochloride), microcrystalline cellulose (MCC) and pregelatinised starch were passed through a screen (# 0.8 mm) and mixed in a Turbula® T10B for 15 min.

Donepezil (in the form of the monohydrochloride), pregelatinised starch, MCC and lactose monohydrate were screened into a separate mixing vessel and mixed in the Turbula® la® for 15 min. After mixing, the mixture was passed through a 0.8 mm screen.

The dimebolin premix was then added to the donepezil premix. The mixture was mixed in the Turbula® for 15 min, and then magnesium stearate was added through a screen (0.8 mm) and mixed in the Turbula® for 5 min.

The finished mixture was pressed into tablets of 11 mm diameter each, hardness 80-120 N using a Korsch® EK0.
**Example 2: Tablet with single-phase structure**

1. Dimebolin 60 mg
2. Calcium hydrogen phosphate 60 mg
3. Kollidon® VA 64 10 mg
4. Donepezil HCl 10 mg
5. Kollidon® VA 64 10 mg
6. Calcium hydrogen phosphate 80 mg
7. Aerosil® 200 15 mg
8. Polyvinyl pyrrolidone (PVP) 20 mg
9. Calcium hydrogen phosphate 100 mg
10. Magnesium stearate 5 mg

Dimebolin (in the form of a dihydrochloride), calcium hydrogen phosphate and Kollidon® VA 64 were passed through a screen (mesh width 0.8 mm) and mixed in the Turbula® for 15 min. Donepezil (in the form of the monohydrochloride), Kollidon® VA 64 and calcium hydrogen phosphate were screened into a separate mixing vessel and mixed in the Turbula® for 15 min. After mixing, the mixture was passed through a 0.8 mm screen. The dimebolin premix was then added to the donepezil premix. The mixture was mixed in the Turbula® for 15 min. After that, polyvinyl pyrrolidone (PVP), calcium hydrogen phosphate and Aerosil® 200 were added through a screen (mesh width 0.8 mm) and mixed in the Turbula® for 10 min. Magnesium stearate was added through a screen (mesh width 0.8 mm) and mixed in the Turbula® for 3 min. The finished mixture was pressed into tablets of 11 mm diameter each, hardness 80-120 N.
Example 3: Tablet with a first and second phase, wet granulation

First phase: granules containing dimebolin:

1. Dimebolin 60 mg
2. MCC 60 mg
3. Starch 15 mg
4. Polyvinyl pyrrolidone 5 mg
5. Demineralised water q.s.

Second phase containing donepezil HC1:

6. Donepezil HC1 10 mg
7. Starch 28 mg
8. MCC 64 mg
9. Lactose monohydrate 176 mg
10. Magnesium stearate 5 mg

Dimebolin (in the form of a dihydrochloride), MCC and pregelatinised starch were passed through a screen (mesh width 0.8 mm) and mixed in a Diosna® for 2 min. The mixture was granulated with an 8 % aqueous solution of polyvinyl pyrrolidone (Mw 25,000) and then dried in a drying cabinet at 40°C - 60°C until there was a drying loss of less than 2%.

Donepezil (in the form of the monohydrochloride), pregelatinised starch, MCC and lactose monohydrate from the second phase were screened into a separate mixing vessel and mixed in the Turbula® for 15 min. After mixing, the mixture was passed through a screen (mesh width 0.8 mm).

The sufficiently dried granules from the first phase were passed through a screen (mesh width 0.8 mm) and added to the premix from the second phase. The mixture was mixed in the Turbula® for 15 min. After that, magnesium stearate was added through a screen (mesh width 0.8 mm) and mixed in the Turbula® for 5 min. The finished mixture was pressed into tablets of 11 mm diameter each, hardness 80-120 N.
Example 4: Tablet with a first and second phase, dry-compacting

First phase: granules containing dimebolin:

1. Dimebolin 60 mg
2. MCC 60 mg
3. Pregelatinised starch 15 mg
4. Cross-linked polyvinyl pyrrolidone 5 mg

Second phase containing donepezil HCl:

5. Donepezil HCl 10 mg
6. Pregelatinised starch 28 mg
7. MCC 64 mg
8. Lactose monohydrate 160 mg
9. Cross-linked polyvinyl pyrrolidone 10 mg
10. Magnesium stearate 5 mg

Dimebolin (in the form of a dihydrochloride), MCC, pregelatinised starch and cross-linked polyvinyl pyrrolidone were passed through a screen (mesh width 0.8 mm) and mixed in the Turbula® for 10 min. The mixture was compacted using a Gerteis Macro-Pactor and passed through a screen (mesh width 0.8 mm). Donepezil (in the form of the monohydrochloride), pregelatinised starch, MCC, 50 % lactose-monohydrate and cross-linked polyvinyl pyrrolidone for the outer phase were screened into a separate mixing vessel and mixed in the Turbula® for 10 min. The mixture was compacted and passed through a screen (mesh width 0.8 mm). The screened premixes were combined and mixed in the Turbula® for 15 min. After that, magnesium stearate was added through a screen (mesh width 0.8mm) and mixed in the Turbula® for 5 min. The finished mixture was pressed into tablets of 11 mm diameter each, hardness 80-120 N.
Claims

1. An oral dosage form comprising dimebolin and donepezil in a weight ratio of between 20:1 and 1:5.

2. The oral dosage form as claimed in claim 1 for use in the treatment of neurodegenerative diseases, especially Alzheimer's disease, wherein the administration is preferably once daily, especially in the evening.

3. The oral dosage form as claimed in either of claims 1 or 2 for use in the treatment of Alzheimer's disease patients in whom a monotherapy with dimebolin is inadequate.

4. The oral dosage form as claimed in any of claims 1 to 3, containing a filler with a yield pressure value of less than 80 MPa.

5. The oral dosage form as claimed in any of claims 1 to 4, containing at least one filler with a yield pressure value of less than 80 MPa and at least one filler with a yield pressure value of more than 80 MPa.

6. The oral dosage form as claimed in any of claims 1 to 5, which comprises:
   A) dimebolin in an amount of 2 to 30% by weight,
   B) donepezil in an amount of 0.5 to 20% by weight,
   C) filler in an amount of 25 to 90% by weight,
   D) optionally disintegrant in an amount of 2 to 20% by weight, and
   E) optionally lubricant in an amount of 0 to 5% by weight,
   F) optionally binders in an amount of 0.1 to 5% by weight,
   based on the total weight of the oral dosage form.

7. The oral dosage form as claimed in any of claims 1 to 6, wherein the oral dosage form has a single-phase structure.
8. The oral dosage form as claimed in any of claims 1 to 6, wherein the oral dosage form comprises a first phase and a second phase, wherein dimebolin is preferably contained in the first phase and donepezil in the second phase.

9. The oral dosage form as claimed in any of claims 1 to 8 in the form of a tablet with a hardness of 50 to 200 N, a friability of less than 3% and a content uniformity of 95 to 105%.

10. The oral dosage form as claimed in either of claims 8 or 9, wherein the first phase contains

   A) dimebolin in an amount of 2 to 25% by weight,
   C) filler in an amount of 0 to 40% by weight,
   D) optionally disintegrant in an amount of 0.5 to 10% by weight,
   F) binders in an amount of 0.1 to 15% by weight,

and the second phase contains

   B) donepezil in an amount of 0.5 to 20% by weight,
   C) filler in an amount of 25 to 90% by weight,
   D) optionally disintegrant in an amount of 1 to 20% by weight, and
   E) optionally lubricant in an amount of 0.1 to 5% by weight,

based on the total weight of the oral dosage form.

11. A process for producing an oral dosage form as claimed in any of claims 1 to 10, comprising

   a) mixing dimebolin, donepezil and optionally pharmaceutical excipients, and
   d) converting the mixture into a suitable dosage form, preferably compressing the resulting mixture into tablets.

12. The process for producing an oral dosage form as claimed in any of claims 8 to 10, comprising

   a) mixing the active agent with pharmaceutical excipients,
   b) granulating the resulting mixture,
   c) mixing the resulting granules with the second active agent and optionally further pharmaceutical excipients,
d2) converting the mixture resulting from step c2) into a suitable dosage form, preferably compressing the resulting mixture into tablets.

13. The process as claimed in claim 12, wherein the granulating (b2) is performed as wet granulation.

14. The process as claimed in either of claims 12 or 13, wherein dimebolin is added in step a2) as the first active agent and donepezil in step c2) as the second active agent.

15. The process as claimed in any of claims 11 to 14, wherein dimebolin with an average particle size (D50) of 5 to 125 \( \mu \text{m} \) and donepezil with an average particle size (D50) of 10 to 150 \( \mu \text{m} \) are used.
### INTERNATIONAL SEARCH REPORT

**International application No:**

PCT/EP2011/003925

---

**A. CLASSIFICATION OF SUBJECT MATTER**


---

**ADD.**

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

---

**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

---

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

---

Further documents are listed in the continuation of Box C.

**X** 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" later 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)
- "O" 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

**X** "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**X** "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

**X" document member of the same patent family

---

Date of the actual completion of the international search

25 November 2011

---

Date of mailing of the international search report

05/12/2011

---

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

Kling, Isabelle
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2667553 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 101631547 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2086538 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2010507672 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20090087009 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2010152108 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2008051599 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2010007730 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2010057104 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2009095265 A1</td>
</tr>
</tbody>
</table>