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(54) **Title**: ORAL DOSAGE FORM FOR THE MODIFIED RELEASE OF DIMEBOLIN

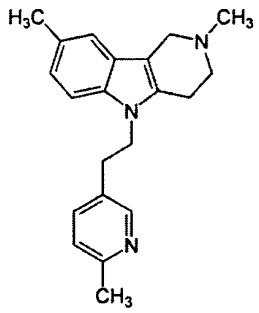
(57) **Abstract**: The invention relates to oral dosage forms for the modified release of dimebolin, and to processes for producing it.

Oral dosage form for the modified release of dimebolin

The invention relates to oral dosage forms for the modified release of dimebolin, and to processes for producing it.

Dimebolin (synonyms Dimebon, latrepirdine) is a β-carboline derivative with anti-histaminic and cognition–enhancing effects. Dimebolin appears suitable for the treatment von Huntington's disease, schizophrenia, amyotrophic lateral sclerosis, stroke, chronic and neuropathological pain, for a cognitive improvement or also to slow down the ageing process. In addition, dimebolin appears to be promising for the treatment of neurodegenerative diseases, such as Alzheimer's disease, as described in EP 0 876 818 B1.

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:



(1)

WO 2007/087425 relates to the use of dimebolin and related substances for the treatment of schizophrenia. The international application is not, however, concerned with formulations of dimebolin.

The international patent application published under the number WO 2009/111540 relates to processes for the preparation of pyridyl ethyl-substituted carbolines and discloses various polymorphs of dimebolin, such as form A (anhydrous dimebolin

dihydrochloride, form B (dimebolin dihydrochloride hemihydrate), form C (dimebolin dihydrochloride monohydrate), form D (dimebolin dihydrochloride dihydrate), form F (dimebolin dihydrochloride trihydrate) and also amorphous dimebolin dihydrochloride. Dimebolin thus exhibits a pronounced polymorphism.

Especially in the case of diseases or complaints that impair the patients' mental capacity, it is desirable to provide a dosage form which enables a treatment plan that is as simple as possible but is nevertheless effective. As far as the efficacy of the treatment is concerned, it is generally an advantage, irrespective of the indication, to ensure that the active agent is delivered as constantly as possible and that the level of active agent in the blood is as constant as possible. Especially with regard to the treatment of pain, it is desirable to keep the effect as unbroken as possible. Another point is that many of the diseases and complaints mentioned above require treatment with medication over a lengthy time. The provision of a dosage form which only needs to be taken once a day and yet ensures efficacy over 24 hours is therefore desirable.

Dimebolin monohydrochloride has different solubilities at pH 7.0 and pH 7.2, which justifies the assumption that its solubility behaviour is pH-dependent. So far, solubility data are not available for all the polymorphs and possible salts. The differences in physical properties which are typical of polymorphs give grounds for expecting that the various polymorphs will exhibit different solubilities. In addition, different salts and/or hydrates and/or solvates may exhibit different solubilities. A dosage form would therefore be advantageous which permitted release of the active agent which was not, or not substantially, dependent on the solubility of the specific form in which the active agent was present, but which was largely determined by the dosage form.

It is therefore an object of the invention to provide an oral dosage form in which the release of dimebolin is determined less by the solubility of the dimebolin form used than by the dosage form in which the dimebolin is contained.

This object is achieved by an oral dosage form for the modified release of dimebolin, comprising

(a) dimebolin or one of its pharmaceutically acceptable salts, and

(b) a combination modifying the release of dimebolin from the dosage form, comprising

(c) a water-soluble excipient, and

(d) a water-insoluble excipient.

The dosage form is usually a solid dosage form, i.e. a dosage form typically comprising exclusively solid components. The oral dosage form of the invention is preferably 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 in which both the active agent and the modifying combination (b) of the excipients (c) and (d) are present in one phase. That phase preferably has a substantially homogeneous structure. A homogeneous structure within a phase is understood here to mean the substantially uniform distribution of all the components within that phase. A single-phase structure of a tablet is therefore preferably understood herein to mean the substantially uniform distribution of all the components within that tablet phase, a possible tablet coating (coat, film coating, jacket) not being regarded as part of that tablet phase. If dimebolin and the excipients (c) and (d) are present in mixed form, the mixture is to be deemed single-phase, irrespective of whether one of the substances is present as granules or as powder or in some other form.

In a particularly preferred embodiment, the oral dosage form is a matrix tablet. The matrix serves to modify the release of the dimebolin and contains not only dimebolin but also the release-modifying combination (b) with the excipients (c) and (d). To put it another way, the excipients (c) and (d) in these embodiments act as a matrix former and/or a matrix modifier. The matrix thus forms the above-mentioned

one phase. If a matrix tablet of this kind is coated, it should preferably be with one or more layers which do not modify the release of dimebolin, or at most only to a negligible extent.

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 comprises a first phase and a discrete second phase, which is different therefrom. The arrangement of the first and second phases relative to one another can take different forms, as long as the first and second phases are spatially separated, although it is also possible for them to be adjacent to one another or slightly overlapping. In two-phase embodiments, at least one of the excipients (c) and (d) is contained in a phase that does not include any dimebolin; it is, however, highly preferable for both excipients (c) and (d) to be contained in the same phase.

In an embodiment of this kind, the oral dosage form may, for example, have a layered structure. In a preferred embodiment, it has a dimebolin-containing core as the first phase, and a coat surrounding the core to modify the release of dimebolin as the second phase. The coat typically contains the modifying combination (b). It is also possible for a plurality of coats to be provided, such as in a succession of layers, wherein, for example, one each of the excipients (c) and (d) can account for one each of the coats, it being preferable that the combination (b) is provided in the same coat. In this way, the water-soluble excipient (c) can modify the barrier properties of the non-water-soluble excipient (d), thus enabling fine adjustment of the release behaviour. To put it another way, the water-soluble and the non-water-soluble excipients act together in modifying the release of dimebolin from the oral dosage form. As an alternative to a coat containing the excipients (c) and (d), it is also possible to provide other, additional coats, wherein these preferably do not influence the release of dimebolin, or only to a negligible extent.

If the first phase is a tablet core and the second phase a coat, one can also speak of coated tablets.

Depending on the nature of the excipients (c) and (d), hybrids or mixed forms of the above-mentioned embodiments are also conceivable. For example, matrix tablets may be equipped with a coat additionally modifying the release, wherein the modifying combination (b) of the excipients (c) and (d) is used in a joint function and arrangement in a single phase, i.e. together as a matrix or coat.

It is already clear from the above description of the preferred structure of the oral dosage forms that the present oral dosage forms are ones that have a single dose unit (known as "single units"). In contrast to multiple-unit dosage forms, no functional sub-units are formed, such as by functional coats of active agent sub-units with the release-modifying combination (b). This means that the oral dosage form is a single dose unit and that the modification of the release is provided for the entire active agent, not for single, individual active agent particles or sub-units. It is specifically the case that the oral dosage form does not disintegrate into discrete sub-units, each of which releases the active agent in a modified way.

In the context of this invention, the term "dimebolin" comprises 2,3,4,5-tetrahydro-2,8-dimethyl-5-(2-(6-methyl-3-pyridyl)ethyl)-1H-pyrido(4,3-b)indole according to formula (1) above. In addition, the term "dimebolin" comprises all the pharmaceutically acceptable salts, hydrates, polymorphous forms and/or solvates thereof, even if they are not explicitly mentioned. Dimebolin dihydrochloride is preferably used. Dimebolin dihydrochloride exhibits a pronounced polymorphism, as explained above with reference to WO 2009/111540 A1, especially form A (anhydrous dimebolin dihydrochloride), form B (dimebolin dihydrochloride hemihydrate), form C (dimebolin dihydrochloride monohydrate), form D (dimebolin dihydrochloride dihydrate), form F (dimebolin dihydrochloride trihydrate and amorphous dimebolin dihydrochloride. Dimebolin dihydrochloride dihydrate and dimebolin dihydrochloride trihydrate or a combination thereof are preferably used. When reference is made herein to an amount of dimebolin, the statement of the amount relates to the 2,3,4,5-tetrahydro-2,8-dimethyl-5-(2-(6-methyl-3-pyridyl) ethyl)-1H-pyrido(4,3-b)indole *per se*, irrespective of the form in which the dimebolin is present.

In each case, one or more excipients (c) and (d) can be used. In the following, reference will be made to one excipient in each case, for the sake of simplicity. The excipient may be a single excipient, but it may also comprise a mixture of excipients, provided that they possess the respective water-solubility or water-insolubility concerned.

The modifying combination (b) of the excipients (c) and (d) must be capable of modifying the release of dimebolin from the oral dosage form. For this purpose, the excipients (c) and (d) in combination possess the release-modifying properties. Embodiments are, however, also conceivable in which each of the excipients (c) and (d) alone can achieve a modification of the release.

The water-soluble excipient (= component (c)) is generally a pharmaceutical excipient specified in the European Pharmacopoeia which exhibits a water-solubility of less than 33 mg/l, measured at 25° C. The water-soluble substance preferably exhibits a solubility of more than 50 mg/ml, even more preferably more than 100 mg/ml. Water-solubility is determined in the context of this invention using the column elution method in accordance with EU Directive DIR 67-548 EEC, Annex V, Chap. A6.

In a preferred embodiment, the water-soluble excipient (c) is a polymer, particularly preferably a hydrophilic polymer. Hydrophilic polymers are understood to mean polymers which possess hydrophilic groups. Examples of suitable hydrophilic groups are hydroxy, alkoxy, acrylate, methacrylate, sulphonate, carboxylate and quaternary ammonium groups. Hydroxy groups are preferable.

The water-soluble excipient (c) may, for example, comprise one or more of the following polymers: cellulose derivatives, such as hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC) and in particular its sodium salts (Na-CMC), guar flour, alginic acid and/or alginates, pectin, gum traganth, synthetic polymers such as polymethacrylates, polyvinyl pyrrolidone (povidone), polyvinyl acetates (PVAC), vinyl pyrrolidone/vinyl acetate copolymers (such as Kollidon®, e.g.

Kollidon® VA64, BASF), polyvinyl alcohol (PVA), water-soluble polymers of acrylic acid and their salts, e.g. polyacrylic acid, polyacrylamide, polyalkylene glycols, such as polypropylene glycol or preferably polyethylene glycol, co-block polymers of polyethylene glycol, especially co-block polymers of polyethylene glycol and polypropylene glycol (Pluronic®, BASF). Dextrins can also be used.

In general, the water-soluble polymer (c) used in the context of this invention is preferably a polymer which has a glass transition temperature (Tg) higher than 15° C, more preferably 40° C to 150° C, especially 50° C to 100° C.

The term "glass transition temperature" (Tg) is used to describe the temperature at which amorphous or partially crystalline polymers change from the solid state to the liquid state. In the process, a distinct change in physical parameters, e.g. hardness and elasticity, occurs. Beneath the Tg, a polymer is usually glassy and hard, whereas above the Tg, it changes into a rubber-like to viscous state. The glass transition temperature is determined in the context of this invention by means of dynamic differential scanning calorimetry (DSC). For this purpose a Mettler Toledo DSC 1 apparatus, for example, can be used. The work is performed at a heating rate of 1-20° C/min, preferably 5-15° C/min, and at a cooling rate of 5-25° C/min, preferably 10-20° C/min. The melting temperature is determined in accordance with Ph. Eur., 6th edition, chapter 2.2.15 (Open Capillary Method).

In addition, the polymer which can be used as a water-soluble polymer (c) preferably has a weight-average or number-average molecular weight of 1,000 to 100,000 g/mol, more preferably 4,000 to 70,000 g/mol, especially 5,000 to 50,000 g/mol. When the water-soluble polymer (c) is dissolved in (distilled) water in an amount of 2 % by weight, the resulting solution preferably has a viscosity of 0.1 to 8 mPa×s, more preferably 0.3 to 6 mPa×s, especially 0.5 to 4 mPa×s, measured at 25° C in accordance with Ph. Eur. 6. edition, chapter 2.2.10.

In addition, the term "water-soluble excipient" (c) comprises solid, non-polymeric compounds. Solid, non-polymeric compounds of this kind may, for example, especially be organic compounds having polar side groups and the above-mentioned

solubility. Examples of these are sugar alcohols or disaccharides. Examples of suitable sugar alcohols are mannitol, sorbitol, xylitol, lactose, isomalt, glucose, fructose and mixtures thereof. The term "sugar alcohols" herein may also include monosaccharides. In addition, fatty acid derivatives such as sodium lauryl sulphate may also be used.

Further solid, non-polymeric compounds which are suitable as "water-soluble excipients" are inorganic compounds or salts, such as alkali or alkaline earth metal salts (or their mixed salts), with the necessary above-mentioned water-solubility. Sodium chloride and potassium chloride are examples of suitable inorganic water-soluble excipients (c).

The non-water-soluble excipient (= component (d)) is generally a pharmaceutical excipient specified in the European Pharmacopoeia which exhibits a water-solubility of less than 33 mg/1, measured at 25° C. The non-water-soluble substance preferably exhibits a solubility of 10 mg/1 or less, more preferably 5 mg/ml or less, especially 0.01 to 2 mg/ml (determined using the column elution method in accordance with EU Directive DIR 67-548 EEC, Annex V, Chap. A6).

Component (d) may be a non-water-soluble polymer or a non-water-soluble pharmaceutical excipient, with polymer-like properties for example. In preferred embodiments, the non-water-soluble excipient (d) is substantially intended to counter the release of the active agent, while the function of the active agent (c) in embodiments of this kind is to enable the fine adjustment of the release behaviour. Excipient (d) may, for example, account for the main part of the matrix, while excipient (c) can serve to adjust the porosity or the structure or the properties of the matrix in general.

It has been found that the release profile can be favourably influenced especially by the choice of an excipient (d) with an appropriate molecular weight and degree of cross-linking, suitable viscosity (based on a solution of component (d) in water), suitable swelling behaviour and/or suitable glass transition or melting temperature.

Examples of suitable non-water-soluble polymers (d) are cellulose, e.g. cellulose powder, microcrystalline cellulose (e.g. obtainable under the trade name Avicel®), cellulose derivatives such as ethyl cellulose (EC), ethyl hydroxyethyl cellulose, methyl cellulose (MC); starch, corn starch; synthetic polymers such as polyvinyl acetate, polacrilin potassium, sodium-polystyrene sulphonate, non-water-soluble polymers based on acrylic acid and/or methacrylic acid and their derivatives, such as cross-linked polyacrylic acid or polymers based on acrylate and/or methacrylate, such as Eudragit® NE 30 D (polymer of ethyl acrylate and methyl methacrylate), and cholestyramine resinate. Mixtures of the above-mentioned substances and polymers can also be used.

Polacrilin potassium is a carboxylic cation exchange resin with little cross-linking, which is made from methacrylic acid and divinyl benzene and is one of the preferred non-water-soluble excipients (d).

For non-water-soluble excipients (d), it is, however, also possible to use wax, fat, fatty acid, monoglycerides, diglycerides and/or triglycerides. These substances are particularly advantageous as matrix formers in matrix tablets.

"Fats" are understood to mean esters of glycerol (glycerin) with three fatty acids. The fatty acids in the ester or a fat may be the same or different. The fatty acids may be saturated or unsaturated, and may be odd or even in number. The physical properties of a fat are determined by the chain lengths and in particular by the frequency of double bonds, i.e. the degree of saturation in the fatty acids. Fats can be solid or liquid at room temperature and normal pressure (25° C, 1,013 hPa). In the context of the present invention, solid fats can be used:

Waxes are typically understood phenomenologically as substances which, at 20° C (and 1,013 hPa), are kneadable, solid to friable and hard, have a coarse to fine crystalline structure, are translucent to opaque, but not glassy, melt without decomposing at temperatures above 40° C (and 1,013 hPa) and are of low viscosity at temperatures little higher than their melting point. They exhibit a highly temperature-dependent consistency and solubility and can be polished with slight pressure.

In addition, waxes herein are preferably selected from the group consisting of or comprising esters of fatty acids, preferably higher fatty acids (C>12), with alcohols with the exception of glycerin, preferably long-chain, aliphatic alcohols, especially the so-called wax alcohols (C>22), or mixtures of such esters. Waxes can be solid or liquid at room temperature and normal pressure (25° C, 1,013 hPa). In the context of the present invention, solid waxes can be used:

Fatty acids are saturated or unsaturated carboxylic acids. Fatty acids can be used herein which are solid at room temperature and normal pressure (25° C, 1,013 hPa). Fatty acids are as a rule and herein preferably unbranched, i.e. straight-chain. Examples of fatty acids which can be used in accordance with the invention are: tridecanoic acid, myristic acid, pentadecanoic acid, palmitic acid, margaric acid, stearic acid, nonadecanoic acid, arachidic acid, behenic acid, lignoceric acid, cerotic acid, melissic acid, palmitoleic acid, oleic acid, erucic acid, linoleic acid, linolenic acid, elaeostearic acid, arachidonic acid and clupanodonic acid. A preferred fatty acid is stearic acid.

Triglycerides are esters of the trihydric alcohol glycerol (glycerin, propane-1,2,3-triol) with three carboxylic acid radicals. The carboxylic acid radicals may be the same or different. Diglycerides are esters of glycerin with two carboxylic acid radicals. Depending on the position of the carboxylic acid radicals, a distinction is made between 1.2- and 1.3-diglycerides. Here too, the carboxylic acid radicals may be the same or different. Monoglycerides are esters of glycerin with only one carboxylic acid radical (monoesters).

Examples of monoglycerides which can be used in accordance with the invention are, for instance: glycerin (mono)behenate (2,3-dihydroxypropyl docosanate), glycerin monostearate, glycerin monocaprate, glycerin monococoate, glycerin monoerucate, glycerin monohydroxystearate, glycerin monoisostearate, glycerin monolanolate, glycerin monolaurate, glycerin monolinoleate, glycerin monomyristate, glycerin monooleate, glycerin monopalmitate, glycerin monoricinoleate, glycerin (mono)myristate, glycerin montanate and mixtures thereof, such as glyce-

rin palmitate stearate, the monoester of glycerin with a mixture of palmitic and stearic acid. Glycerin palmitate stearate is one of the preferred excipients (d).

Examples of diglycerides that can be used in accordance with the invention are diesters with the same carboxylic acid radicals as those mentioned for the monoglycerides, such as glycerin dilaurate, glycerin dimyristate, glycerin dioleate, glycerin dipalmitate, glycerin distearate, glycerin diisostearate, and mixtures thereof and diesters with different carboxylic acid radicals (mixed diesters) such as glycerin palmitostearate (Precirol®) and mixtures thereof.

Triglycerides that can be used in accordance with the invention comprise, for example, glycerin tricaprylic acid ester, glycerin trilaurate, glycerin trioleate, glycerin triricinoleate, glycerin tristearate and mixtures thereof.

The excipients (d) mentioned as non-water-soluble, in particular the polymers, preferably possess one or more of the functional properties mentioned below (MW, cross-linking, viscosity in solution, swelling ratio, melting or glass transition temperature).

A suitable non-water-soluble polymer (d) may, for example, have a weight-average molecular weight of 50,000 to 2,500,000 g/mol, preferably 250,000 to 2,000,000 g/mol, more preferably 350,000 to 1,500,000 g/mol. The non-water-soluble polymer (d) can be linear or preferably cross-linked. In the latter case, the non-water-soluble polymer (d) preferably exhibits a degree of cross-linking of 0.1 to 10 %, especially 0.5 to 5 %. (Degree of cross-linking = number of carbon atoms linked to more than one chain / total number of carbon atoms in the polymer chain).

When the non-water-soluble polymer (d) is (at least partially) dissolved in (distilled) water in an amount of 2 % by weight, the resulting solution preferably has a viscosity of more than 2 mPa×s, more preferably 4 mPa×s, particularly preferably more than 8 mPa×s, especially more than 10 mPa×s and, for example, up to 500 mPa×s, measured at 25° C in accordance with Ph. Eur. 6th edition, chapter 2.2.10.

The non-water-soluble excipient (d) is preferably selected from: ethyl cellulose, ethyl hydroxyethyl cellulose, polyvinyl acetate, starch, corn starch, microcrystalline cellulose, cellulose powder, stearic acid, wax, fat, glycerol palmitate stearate, polacrilin potassium, sodium polystyrene sulphonate, polyacrylic acid derivatives, such as polymers based on acrylate and/or methacrylates, and cholestyramine resinate.

Plastic, non-water-soluble excipients (d) are particularly preferable, because it has been found that these can be used particularly advantageously for modifying, especially retarding, the release.

In the art, it is customary to classify plasticity or brittleness in terms of the "yield pressure". 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., Nyström, 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. Méthode rapide de détermination du comportement à la compression pour des études de préformulation. Pharm. Acta Helv., 57, 136-143 (1982)). The yield pressure describes the pressure that has to be reached for the substance to begin to flow plastically. The yield pressure 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 here is preferably carried out at 25° C and a deformation rate of 0.1 mm/s. In the context of the present invention, non-water-soluble excipients (d) are preferable, especially when they have a yield pressure of no more than 150 MPa, preferably 100 to 80 MPa.

In exemplary embodiments, the non-water-soluble excipient (d) has a high specific surface area, e.g. at least 1.5 m^2/g, preferably about 2.0 to 10 m^2/g, determined by gas adsorption in accordance with Ph. Eur., 6th edition 2.9.26.

The component (d) may be a swellable polymer or some other swellable substance, such as one with polymer-like properties. In embodiments of this kind, the non-water-soluble polymer (d) preferably has a swelling ratio of 1.5 to 4.5, preferably

2.0 to 4.0. The swelling ratio expresses the volume in millilitres which 1 g substance, including any mucilage that might be adhering to it, reaches after swelling in an aqueous solution after 4 hours. The swelling ratio is determined in accordance with Ph. Eur. 4th edition, Chapter 2.8.4.

In addition, the component (d) is preferably a substance, such as a polymer and/or a swellable substance with a glass transition temperature or a melting temperature of less than 200° C, more preferably 20° C to 180° C, especially 30° C to 170° C.

Excipients (c) and/or (d) are preferably not pH-dependent regarding their solubility or insolubility.

Preferred embodiments comprise one of the following combinations (b) of a water-soluble excipient (c) and a non-water-soluble excipient (d) modifying the release of dimebolin from the dosage form:

- a mixture of polyvinyl acetate and polyvinyl pyrrolidone (Kollidon® SR) (d) and lactose (Ludipress®) (c), preferably in the form of a matrix tablet;
- a copolymer of acrylic and methacrylic acid esters with quaternary ammonium groups, e.g. Eudragit RS PO (d) and lactose monohydrate (c); preferably in the form of a matrix tablet;
- a copolymer of acrylic and methacrylic acid esters with quaternary ammonium groups in salt form, e.g. Eudragit RL PO (d) and lactose monohydrate (c); preferably in the form of a matrix tablet;
- ethyl cellulose, e.g. with an ethoxy content of 47.5 to 49.0 % (e.g. ethyl cellulose N10 or ethyl cellulose N14) (d) and lactose monohydrate (c); preferably in the form of a matrix tablet;
- ethyl cellulose (e.g. Aquacoat ECD) (d) and polyethylene glycol (c), preferably as a coat, preferably on a tablet;
- a copolymer of ethyl acrylate and methyl methacrylate (e.g. with a neutral character) (e.g. Eudragit NE 30 D) (d) and polyethylene glycol (c), preferably as coat, preferably on a tablet;

- a copolymer of acrylic and methacrylic acid esters with quaternary ammonium groups, e.g. Eudragit 30 D or Eudragit RL 30 D, (d) and polyethylene glycol (c), preferably as a coat, preferably on a tablet;
- a mixture of polyvinyl acetate and polyvinyl pyrrolidone (Kollidon® SR) (d) and polyethylene glycol (c), preferably as a coat, preferably on a tablet;

A further preference is also for combinations which correspond to the above combinations and in which polyethylene glycol or lactose, or lactose monohydrate, replace one another or are replaced by another sugar alcohol.

In preferred single-phase embodiments, preferably matrix tablets, the amount of water-soluble excipient (c) lies in a range from 5 to 85 % by weight, e.g. 10 to 80 % by weight or 20 to 70 % by weight. The amount of non-water-soluble excipient (d) in such embodiments ranges, for example, from 5 to 80 % by weight, such as 8 to 60 % by weight or 10 to 40 % by weight., based on the total weight of the oral dosage form.

In two-phase embodiments, a first phase, containing dimebolin, may, for example, account for 10 to 90 % by weight, such as up to 87.5 % by weight or up to 85 % by weight of the oral dosage form, while a dimebolin-free second phase, preferably a coat, may correspondingly account for 90 to 10 % by weight, such as at least 12.5 % by weight, at least 15 % by weight or at least 20 % by weight. This second phase preferably contains the modifying combination b). There are preferably no further phases present, so that in this respect, the two phases add up to 100 % by weight of the oral dosage form. Embodiments of this kind preferably encompass tablet cores (first phase) provided with a coat (second phase), wherein dimebolin is contained in the tablet core and the coat contains the modifying combination b). In two-phase embodiments, especially in the preferred embodiments, the amount of water-soluble excipient (c) in the respective phase, such as the coat, lies in a range from 5 to 75 % by weight, e.g. 7.5 to 50 % by weight or 10 to 25 % by weight, such as up to 20 % by weight, based on the total weight of the phase, especially the coat. The amount of non-water-soluble excipient (d) in the respective phase in such embodiments ranges, for example, up to 95 % by weight, e.g. 25 to 90 % by

weight, such as 40 to 80 % by weight or 50 to 70 % by weight., based on the total weight of the phase, especially the coat.

In preferred embodiments of the present invention, water-soluble excipient (c) and non-water-soluble excipient (d) are used in an amount in which the weight ratio of component (c) to component (d) is 10 : 1 to 1 : 10, more preferably 5 : 1 to 1 : 5. In single-phase embodiments, such as matrix tablets, water-soluble excipient (c) and non-water-soluble excipient (d) may, for example, be used in an amount in which there is an excess of water-soluble excipient, e.g. the weight ratio of component (c) to component (d) can be 10 : 1 to 2 : 1, e.g. at least 3 : 1, such as at least 4 : 1. In two-phase embodiments, such as when the modifying combination is present in one phase, preferably a coat, water-soluble excipient (c) and non-water-soluble excipient (d) may, for example, be used in an amount in which there is an excess of non-water-soluble excipient, e.g. the weight ratio of component (c) to component (d) may be 1 : 10 to 1 : 2, such as at least 1 : 3 or at least 1 : 4.

It is advantageous for components (c) and (d) to be used in particulate form and for the volume-average particle size (D_{50}) of components (c) and (d) to be less than 500 µm, preferably 5 to 200 µm.

Dimebolin is generally used in the oral dosage form of the invention in an amount of 10 to 60 % by weight, preferably 12.5 to 50 % by weight, more preferably 13 to 40 % by weight, especially 15 to 30 % by weight, based on the total weight of the oral dosage form.

The oral dosage form may additionally contain, as an optional component, an excipient (e) whose solubility is pH-dependent. Excipients of this kind exhibit a solubility which is dependent on the pH of the solvent medium. Examples of such excipients (e) whose solubility is pH-dependent are, for example, polymers based on polymethacrylic acid, e.g. polymethacrylates such as Eudragit® L 100-55; cellulose derivatives whose solubility is pH-dependent, such as hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate phthalate (HPMCAP), cellulose acetate succinate; pH-dependent acrylic acid derivatives,

such as carbomers (also known as Carbopol®), e.g. Carbomer 941; polyvinyl derivatives, such as polyvinyl alcohol phthalates, polyvinyl acetate phthalates, polyvinyl butyl phthalate; and natural gums.

The additional excipients (e) are particularly advantageous in a matrix tablet in which the release can be adjusted so that it is independent of the solubility of the dimebolin.

The amount of additional excipient (e) whose solubility is pH-dependent depends on the choice of modifying combination (b). It does, however, generally lie in the range from 1 to 45 % by weight, preferably between 1.5 and 35 % by weight, e.g. 2 to 25 % by weight of the total oral dosage form. If an excipient whose solubility is pH-dependent is used in a two-phase embodiment, such as in a coat, e.g. a tablet, the amount may, for example, lie in the range from 2 to 40 % by weight, preferably in the range from 5 to 25 % by weight, such as in the range from 7.5 to 15 % by weight , based on the total weight of the phase in which the excipient whose solubility is pH-dependent is contained.

The oral dosage form of the invention is intended and suitable for modifying the release of dimebolin. The modification may consist in retarding the release, delaying the release or a combination of the two.

The release in the present case is not based on the use of an osmotic release system.

The release profile of the oral dosage form of the invention according to the USP method (paddle, 900 ml test medium in phosphate buffer at pH 6.8 and 37° C, 75 r.p.m.) after 10 minutes usually has a content released of no more than 90 %, more preferably no more than 75 %, even more preferably no more than 50 % and particularly preferably no more than 30 %.

The release according to the USP method (paddle, 900 ml test medium in phosphate buffer at pH 6.8 and 37° C, 75 r.p.m.) after one hour is preferably no more

than 95 %, more preferably no more than 90 %, even more preferably no more than 75 % and particularly preferably no more than 50 % of the total amount of dimebolin contained.

In exemplary embodiments, the release profile of the oral dosage form of the invention according to the USP method (paddle, 900 ml test medium in phosphate buffer at pH 6.8 and 37° C, 75 r.p.m.) after 6 hours has a content released of no more than 98 %, more preferably no more than 90 %, even more preferably no more than 80 % and particularly preferably no more than 70 % auf.

The oral dosage form of the invention is particularly suitable for peroral administration, and preferably for administration once daily.

The oral dosage forms of the invention preferably do not contain any further active agent. They are therefore suitable and intended in particular for a monotherapy.

The oral dosage form is preferably intended for the treatment of Huntington's disease, schizophrenia, amyotrophic lateral sclerosis, stroke, chronic and neuropathological pain, neurodegenerative diseases, in particular Alzheimer's disease, for a cognitive improvement and/or in order to slow down the ageing process.

In addition to the above-mentioned ingredients, the oral dosage form may also comprise further pharmaceutically acceptable excipients, such as disintegrants, fillers, flow-regulating agents, binders, foam inhibitors, and/or lubricants or anti-stick agents.

"Disintegrants" is the term used herein to describe a substance which accelerates the disintegration of a dosage form, especially a tablet, after it is placed in water. Suitable disintegrants are, for example, organic disintegrants such as carrageenan, croscarmellose and/or crospovidone (such as Kollidon® CL). Alkaline disintegrants can likewise be used. The term "alkaline disintegrants" means disintegrants which, when dissolved in water, produce a pH level of more than 7.0. Suitable alkaline disintegrants are salts of alkali and alkaline earth metals. Preferred exam-

ples here are sodium, potassium, magnesium and calcium. As anions, carbonate, hydrogen carbonate, phosphate, hydrogen phosphate and dihydrogen phosphate are preferred. Examples are sodium hydrogen carbonate, sodium hydrogen phosphate, calcium hydrogen carbonate and the like. Croscarmellose or crospovidone are preferable. Disintegrants may, for example, be contained in amounts of 0 % by weight to 25 % by weight, such as 1 % by weight to 10 % by weight, based on the total weight of the oral dosage form. In the context of the present invention, the disintegrant, if present, should be different from the water-soluble excipients (c) and (d).

Flow-regulating agents are particularly preferable if the oral dosage form is present in the form of a tablet. Their 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 or colloidal silica (e.g. Aerosil®). Preferably, silica is used with a specific surface area of 50 to 400 m^2/g, determined by gas adsorption in accordance with Ph. Eur., 6th edition 2.9.26. Flow-regulating agents may, for example, be contained in an amount of 0 to 10 % by weight, such as 0.2 to 5 % by weight, based on the total weight of the oral dosage form. In the context of the present invention, the flow-regulating agent, if present, should be different from the water-soluble excipients (c) and (d).

In a further embodiment, the oral dosage form, especially when present in tablet form, may, for example, additionally contain 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, sodium stearyl fumarate, (Pruv®), magnesium stearate, calcium stearate or mixtures thereof. In the context of the present invention, the lubricant too, if present, should be different from the water-soluble excipients (c) and (d). Lubricant may, for example, be contained in an amount of 0 to 10 % by weight, preferably 0.1 to 5 % by weight or, for example, up to 1 % by weight, based on the total weight of the oral

dosage form.

The oral dosage form may also contain an anti-stick agent, for example in an amount between 0 and 10 % by weight, e.g. 2 to 9 % by weight based on the total weight of the oral dosage form. Anti-stick agent may, for example, advantageously be contained in a coat, e.g. in an amount of 10 to 30 % by weight of the total weight of the coat, such as 15 to 25 % by weight of the total weight of the coat. Talcum may, for example, be used as an anti-stick agent.

The oral dosage form may additionally contain a foam inhibitor, for example in an amount of up to 0.5 % by weight, preferably in an amount of up to 0.1 % by weight and particularly preferably in an amount of up to 0.05 % by weight of the total weight of the oral dosage form.

The oral dosage form may optionally also contain a binder, such as polyvinyl pyrrolidone (PVP) for example. The binder may, for example, be contained in an amount of 0 % by weight or 0.3 to 15 % by weight, e.g. up to 10 % by weight or up to 5 % by weight, based on the total weight of the oral dosage form, or alternatively based on one phase, such as a tablet core.

If the oral dosage form is present as a two-phase formulation, such as a coated tablet, especially one in which the water-soluble and the non-water-soluble excipients are contained in a different phase from dimebolin, e.g. in the coat (the "jacket"), the dimebolin-containing phase, the tablet core for example, may preferably contain one or more fillers. "Fillers" generally means substances which serve to form the body of the tablet in the case of tablets with small amounts of active agent (e.g. less than 70 % by weight). This means that fillers "dilute" the active agents in order to produce an adequate tablet-compression mixture. The normal purpose of fillers, therefore, is to obtain a suitable tablet size. In single-phase embodiments, it is preferable for no filler to be used in addition to the excipients (c) and (d).

Examples of preferred fillers are lactose, lactose derivatives, starch, starch derivatives, treated starch, talcum, calcium phosphate, sucrose, calcium carbonate, magnesium carbonate, magnesium oxide, maltodextrin, calcium sulphate, dextrates,

dextrin, dextrose, hydrogenated vegetable oil, kaolin, sodium chloride, and/or potassium chloride.

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 performs only one function. I.e. a substance which is used as a particular excipient, such as a water-soluble excipient in the modifying combination, is not simultaneously also used as a further pharmaceutical excipient, such as a filler. Lactose, for example – if used as a water-soluble excipient of the combination, such as in a matrix tablet – is not also counted as a filler in addition. To put it another way, two excipients with different functions, e.g. fillers and lubricants, or a water-soluble excipient of the release modifying combination and a filler, should be different from one another in material terms, i.e. they should be formed from different substances. On the other hand, when a combination modifying the release of dimebolin from the dosage form is used in a coat, in a non-modified releasing core for example, any lactose contained is regarded as filler.

Another subject matter of the present invention is a process for producing an oral dosage form for the modified release of dimebolin in the form of a tablet, as described above, comprising

(I) mixing (a) dimebolin and (b) the combination modifying the release of dimebolin from the dosage form, comprising (c) a water-soluble excipient and (d) a non-water-soluble excipient, and optionally one or more additional pharmaceutically acceptable excipients, and subsequently compressing it into a tablet,

or

(II) (i) producing a tablet core containing (a) dimebolin and optionally one or more pharmaceutically acceptable excipients, and
(ii) coating the tablet core with the combination modifying the release of dimebolin from the dosage form, comprising (c) a water-soluble ex-

cipient and (d) a non-water-soluble excipient and optionally one or more additional pharmaceutically acceptable excipients.

Process (I) can be carried out as direct tableting, which means that the resulting mixture is compressed (compacted) directly into a tablet, without additional steps being performed.

"Mixing" is understood in the context of the present 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 is preferably used.

The time for the step of mixing (i) may, for example, be 0.5 minutes to 1 hour, such as about 2 minutes to 50 minutes, or 5 minutes to 45 minutes.

The mixing step can be accompanied by a step of jointly comminuting the particle sizes of (a) dimebolin and the excipients, for example by grinding them jointly.

Alternatively, process (I) may comprise one or more intermediate steps, such as compacting into a slug of material and/or granulation. If further intermediate steps are performed, it may be advantageous to process dimebolin and/or one or more of the excipients sequentially together.

The granulation may be dry granulation, wet granulation or melt-granulation, though wet and dry granulation are preferable. The two latter types of granulation have the advantage of being gentler for active agents and excipients. Furthermore, dry granulation in particular is an economical process.

"Granulating" 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 for-

mation of finer granules by breaking up coarser aggregates (disintegration, or break-down granulation).

Dry granulation is generally carried out using pressure or temperature. Wet granulation is generally carried out using dispersants and optionally surface stabilisers. 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 also be used.

The granulation time, especially in the case of wet granulation is usually 1 minute to 1 hour, preferably 2 minutes to 30 minutes. Dry granulation is usually carried out as a continuous process.

In one embodiment of the process of the invention, in which dry granulation is contemplated, the mixture is compacted into a slug of material. The compacting conditions here are preferably selected such that the compacted material has a density of 1.03 to 1.8 g/cm^3, especially 1.05 to 1.7 g/cm^3. The compacting is preferably carried out in a roll granulator. The rolling force per roll width in this case is preferably 2 to 50 kN/cm, more preferably 4 to 30 kN/cm, especially 10 to 25 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 preferably granulated. The granulating can generally be performed with processes known in the state of the art.

Wet granulation can also be performed with conventional methods. Wet granulation is generally carried out using a suitable dispersant or solvent, such as water. It may, for example, be performed in a fluidised-bed granulator or a mixer, such as a compulsory mixer. If wet granulation is performed, an additional drying step is usually employed. "Drying" for the purposes of this invention is understood to mean the separation of liquids adhering to solids. 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 one and the same apparatus.

With a suitable choice of excipients (c) and (d) and optionally further excipients, the optional granulation may also be performed as melt granulation.

The same applies analogously to the production of the tablet core in process (II), apart from the fact that in this case, the modifying combination (b) is not contained in the tablet core and accordingly the excipients (c) and (d) are not used in the production of the tablet core, but are instead used in the coat of the tablet core.

Any process known in the art can be used to apply a coat containing the modifying combination with excipients (c) and (d), e.g. spray-coating, cast-coating, tablet pressing with a jacket and the like.

The matrix tablet produced in accordance with process (I) may additionally be film-coated. It is then, however, preferable for the film coat to have no or at most only a negligible influence on the release of dimebolin. A film coat of this kind may, for example, be used to improve the appearance or taste or to make the tablet easier to swallow.

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

Example 1: Matrix tablet with excipient whose solubility is pH-dependent

The following ingredients were used to produce a matrix tablet by means of direct tableting as described below:

Ingredient	Property/Function	Amount [mg]	Percentage content
Dimebolin	Active agent	60	16.5
HPMC	Water-soluble excipient	140	38.6
Lactose	Water-soluble excipient	100	27.5
Carbomer 941	Excipient whose solubility is pH-dependent	10	2.8
Corn starch	Non-water-soluble, swelling excipient	50	13.8
Aerosil® (colloidal silica)	Flow-regulating agent	2	0.6
Magnesium stearate	Lubricant	1	0.3
	Σ	363	

Dimebolin and all the excipients with the exception of magnesium stearate were sieved through a screen with a mesh width of 1.25 mm into a free-fall mixer and mixed for 15 minutes. The resulting mixture was screened again using a screen with a mesh width of 1 mm and mixed for 10 minutes. After that, magnesium stearate was sieved in through a screen with a mesh width 0.5 mm and mixed once again for 5 minutes. The resulting mixture was then pressed into a (matrix) tablet.

Example 2: Production of a tablet core

A tablet core was first produced from the following ingredients as described below:

Ingredient	Property/Function	Amount [mg]	Percentage content
Dimebolin	Active agent	60	30.6
Avicel® PH 102 microcrystalline cellulose	Filler	80	40.8
Lactose (monohydrate)	Filler	50	25.5
Povidone 25	Binder	4	2.0
Aerosil® 200 (colloidal silica)	Flow-regulating agent	1.5	0.8
Magnesium stearate	Lubricant	0.75	0.4
	Σ	196.25	

Dimebolin and Avicel® were premixed together in a compulsory mixer for 5 minutes. Povidone 25 was dissolved in water. The premix of dimebolin and Avicel® was granulated with the povidone solution produced in this way and then dried. The dried granules were sieved through a screen with a mesh width of 1.25 mm. After that, lactose (monohydrate) and Aerosil® were added, and the mixture was mixed in a free-fall mixer for 15 minutes. After that, magnesium stearate was sieved in through a screen with a mesh width of 0.5 mm and mixed again for 5 minutes. The resulting mixture was pressed into a tablet, achieving a hardness of more than 80 N.

Example 3: Coating the tablet core

The tablet core from Example 2 was equipped with a coat to modify the release of dimebolin, using the following substances as illustrated below.

Ingredient	Property/Function	Amount [mg[	Percentage proportion of coat
Eudragit® NE 30 D	Non-water-soluble excipient	32	64.0
PEG 6,000	Water-soluble excipient	8	16.0
Talcum	Anti-stick agent	10	20.0
Foam inhibitor	Foam inhibitor	0.01	0.0

The tablet core was preheated to approx. 33° C in a perforated boiler. After that, a dispersion of the above-mentioned ingredients was applied to the tablet core under a spray pressure of 1.5 bar and at a product temperature of approx. 31° C. The coated tablet was then after-dried in a tray dryer cabinet at 40° C for 2 hours.

Example 4: Coating the tablet core

A tablet core produced in accordance with Example 2 was equipped with a coat to modify the release of dimebolin, using the following substances as illustrated in Example 3, though the coat in this Example comprised an excipient whose solubility was pH-dependent, unlike Example 3.

Ingredient	Property/Function	Amount [mg[	Percentage proportion of coat
Eudragit® NE 30 D	Non-water-soluble excipient	32	58.2
Eudragit® L100-55	Soluble depending on pH	5	9.1
NaOH	Solvent	q.s.	
PEG 6,000	Water-soluble excipient	8	14.5
Talcum	Anti-stick agent	10	18.2
Foam inhibitor	Foam inhibitor	0.01	0.0

Claims:

1. An oral dosage form for the modified release of dimebolin, comprising
   (a) dimebolin or one of its pharmaceutically acceptable salts, and
   (b) a combination modifying the release of dimebolin from the dosage form, comprising
      (c) a water-soluble excipient, and
      (d) a non-water-insoluble excipient.

2. The oral dosage form as claimed in claim 1 in the form of a tablet, preferably in the form of a matrix tablet.

3. The oral dosage form as claimed in claim 2, wherein the water-soluble excipient (c) is contained in the tablet, especially the matrix tablet, in an amount of 5 to 85 % by weight and/or the non-water-soluble excipient (d) is contained in the tablet, especially the matrix tablet, in an amount of 5 to 80 % by weight, based on the total weight of the oral dosage form in each case.

4. The oral dosage form as claimed in claim 1 in the form of a tablet, wherein the tablet comprises a core containing dimebolin and a coat surrounding the core, which contains the modifying combination (b).

5. The oral dosage form as claimed in claim 4, wherein the water-soluble excipient (c) is contained in the coat in an amount of 5 to 75 % by weight and/or the non-water-soluble excipient (d) is contained in the coat in an amount of up to 95 % by weight, based on the total weight of the coat in each case.

6. The oral dosage form as claimed in any of the preceding claims, which possesses a single dose unit.

7. The oral dosage form as claimed in any of the preceding claims, wherein the water-soluble excipient (c) is selected from the group comprising:

cellulose derivatives, such as hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose, hydroxypropyl cellulose (HPC), carboxymethyl cellulose, sodium salt of carboxymethyl cellulose, guar flour, alginic acid, alginates, pectin, gum traganth; polymethacrylates, polyvinyl pyrrolidone (povidone), polyvinyl acetates (PVAC), vinyl pyrrolidone/vinyl acetate copolymer, polyvinyl alcohol (PVA), water-soluble polymers of acrylic acid and their salts, polyacrylamide, polyalkylene glycols, polypropylene glycol and polyethylene glycol.

8. The oral dosage form as claimed in any of the preceding claims, wherein the non-water-soluble excipient (d) is selected from the group comprising:
ethyl cellulose, ethyl hydroxyethyl cellulose, polyvinyl acetate, starch, microcrystalline cellulose, cellulose powder, stearic acid, wax, fat, glycerol palmitate stearate, non-water-soluble polymers based on acrylic acid and/or methacrylic acid and their derivatives, polacrilin potassium, sodium-polystyrene sulphonate and cholestyramine resinate.

9. The oral dosage form as claimed in any of the preceding claims, further comprising an excipient whose solubility is pH-dependent.

10. The oral dosage form as claimed in claim 8, wherein the excipient whose solubility is pH-dependent is selected from the group comprising:
polymers based on polymethacrylic acid, cellulose derivatives whose solubility is pH-dependent, hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate phthalate (HPMCAP), cellulose acetate succinate, acrylic acid derivatives whose solubility is pH-dependent, carbomers, polyvinyl derivatives, polyvinyl alcohol phthalate, polyvinyl acetate phthalate, polyvinyl butyl phthalate and natural gums.

11. The oral dosage form as claimed in any of the preceding claims, which has a release profile according to which, using the USP paddle method at 75 revolutions per minute, after 10 minutes in 900 ml phosphate buffer at pH 6.8 and

37° C, no more than 90 %, more preferably no more than 75 %, 50 % or 30 % dimebolin is released.

12. The oral dosage form as claimed in any of the preceding claims, wherein the amount of dimebolin lies in the range from 10 to 60 % by weight of the total weight of the oral dosage form.

13. The oral dosage form as claimed in any of the preceding claims, for administration once daily.

14. The oral dosage form as claimed in any of the preceding claims, for the treatment of Huntington's disease, schizophrenia, amyotrophic lateral sclerosis, stroke, chronic and neuropathological pain, neurodegenerative diseases, in particular Alzheimer's disease, for a cognitive improvement and/or in order to slow down the ageing process.

15. A process for producing an oral dosage form for the modified release of dimebolin in the form of a tablet as claimed in claim 2, comprising:

(I) mixing (a) dimebolin or one of its pharmaceutically acceptable salts and (b) the combination modifying the release of dimebolin from the dosage form, comprising (c) a water-soluble excipient and (d) a non-water-soluble excipient, and optionally one or more additional pharmaceutically acceptable excipients, and subsequently compressing it into a tablet,

or

(II) producing a tablet core containing (a) dimebolin or one of its pharmaceutically acceptable salts and one or more pharmaceutically acceptable excipients, and

coating the tablet core with the combination modifying the release of dimebolin from the dosage form, comprising (c) a water-soluble excipient and (d) a non-water-soluble excipient and optionally one or more additional pharmaceutically acceptable excipients.