The invention relates to oral multiple unit formulations consisting of delayed-release pellets which contain tramadol or physiologically tolerable salts thereof and at least one pharmaceutically acceptable, release-delaying substance, and to processes for their preparation.

Tramadol ((1RS;2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol) is an analgesic which is effective in severe and medium-severe pain.

The oral tramadol delayed-release pharmaceutical forms on the market are formulated on the basis of tablet preparations which have the known disadvantages of the single unit dosage form in comparison with the multiple unit dosage form. Single units are individual pharmaceutical forms which, for example, pass undisintegrated through the gastrointestinal tract (matrix tablets), become smaller and smaller due to breakdown (erosion tablets) or whose active compound is only released in the intestine (enteric-coated tablets).
Multiple units are pharmaceutical forms which break down into a large number of sub-units after taking and in which the sub-units are carriers of the properties of the pharmaceutical form. In the case of the single unit delayed-release medicaments, considerable variations in the gastric residence time can occur, which can lead to an irregular passage through the gastrointestinal tract and thus to differing blood level values. Local irritation is also to be feared less with multiple unit pharmaceutical forms than with single unit pharmaceutical forms. The same applies to the danger of "dose dumping", the too rapid release of the active compound from delayed-release medicaments (H. Blume, "Biopharmazeutische Aspekte von Multiple Unit Dosage Forms; ein Vergleich mit Single Units" [Biopharmaceutical aspects of multiple unit dosage forms; a comparison with single units], publication of

Capsugel, Basle (Switzerland), via a symposium in November 1988 in Hamburg).

The tramadol pharmaceutical forms preferably described in EP 147 780, EP 624 366, EP 654 263, EP 731 694 and DE 43 29 794 are also single unit pharmaceutical forms of this type which can have the abovementioned disadvantages.

Pharmaceutical formulations having delayed-release coatings are described, for example, in EP 147 780 in the form of tablets and granules which contain an active compound core and are coated with a film of polyvinyl alcohol.

In EP 624 366, oral tramadol preparations with delayed release are pointed out, which preferably can be administered in the form of tablets. The active compound is in this case embedded, in particular, in a delayed-release matrix of hydrophilic or hydrophobic polymers, long-chain fatty acids or fatty alcohols and one or more polyalkylene glycols.

Alternatively to this, film-coated spheroids are described. The active compound is embedded in a "spheronizing" material, such as microcrystalline cellulose, and coated with a controlled-release film.

In EP 731 694 (WO95/14460), opioid delayed-release formulations, for example pellets, are described which guarantee an analgesic effect for at least 24 hours after oral administration.

The pellets consist of an active compound-containing core which is covered with a polymer film suitable for delaying release. Besides the polymers, the film in particular contains an acid-soluble compound and a plasticizer.

The use of plasticizers, however, can be very disadvantageous.

Known disadvantages of the plasticizers are that these migrate out of the membrane, which can affect the release of active compound in the course of storage.

In EP 147 780, page 2 describes that a chemical interaction between plasticizer and the active compound can also occur, which leads to a reduction in the shelf-life of the product.

In Sucker, Fuchs, Speiser "Pharmazeutische Technologie" [Pharmaceutical technology] Thieme Verlag Stuttgart, 1978, it is also mentioned that besides its actual film-improving property, the plasticizer affects the water vapour permeability and the disintegration. The admittedly low but noticeable vapour pressure furthermore leads to an evaporation of the plasticizers associated with the alteration of the physical properties, such as the dissolution rate of the film.

To date there is still no tramadol pellet form on the market. Pellet formulations are distinguished by a large surface area because of the presence of many, often a few hundred, sub-units per therapeutic dose. In the case of readily soluble substances such as tramadol hydrochloride, this can lead to a need for delayed-release material, which clearly reduces the content of active compound in the pellet formulation in an undesirable manner.
This is particularly undesirable in the case of active compounds which are administered in a relatively high dose, because the pellet quantity necessary necessitates the use of a larger hard gelatine capsule. This is therapeutically undesirable, because it is unpleasant for the patient.

The invention is thus based on the object of providing tramadol multiple unit formulations in a design which is particularly acceptable and simple for the patient, which avoid the disadvantages of single units and thus guarantee a delayed, highly reproducible release.

The invention accordingly relates to multiple unit formulations comprising individual pellets which are delayed to an identical or different extent, which

consist of a starter material coated with tramadol or its physiologically tolerable salts, which is coated with one or more membrane layers of at least one pharmaceutically acceptable, release-delaying substance, the active substance being released from the pellets in the gastrointestinal tract in delayed form.

The mechanisms controlling the active compound release from pellets can essentially be described by the following functional principles:
A first possibility for the formulation of delayed-release pellets consists in the control of the release by an outer membrane.
Another way of achieving a suitable delayed release consists in constructing pellets free of an outer membrane, whose release takes place through a controlled-release matrix.
A third possibility finally consists in the combination of both measures mentioned, i.e. the combination of the matrix and membrane control, to achieve the desired properties.

Tramadol hydrochloride is distinguished by solubility properties which are utilized in the multiple unit formulations according to the invention for the formulation of typical membrane-controlled diffusion pellets.

The pellets contained in the multiple unit formulations consist of an active compound-containing core, which is coated with one or more membrane layers which are used to control the active compound release.
A rapidly disintegrating or rapidly soluble active compound layer (initial dose), which is suitable for control of the release immediately after administration, can be applied to the membrane using a suitable binding agent.

The active compound can be processed in unaltered form or alternatively in the form of mixtures which positively affect the processability of the active compound.
For example, mixtures with colloidal silica such as Aerosil200, sucrose or other suitable substances can be used.

The pellet core itself consists of an internal, inert starter material, to which the active compound is applied using a suitable solution.
As a starter material for pellet preparation, it is possible to employ, for example, sucrose crystals or alternatively sucrose-maize starch pellets (nonpareils, neutral pellets, sugar spheres USP 23/NF 18).

On account of its good solubility in water, lower alcohols such as ethanol, isopropanol and alcohol/water mixtures or acetone, the active compound can be applied to the starter material in solutions of these solvents. The process can be accelerated by simultaneously applying the active compound in powder form and active compound in dissolved form or using solvents alone.

Another preferred variant of this preparation sub-step is to apply the active compound to the starter material in powder form using a suitable binding agent solution. This application of the active compound is carried out in layers such that after larger or smaller application quantities the process is interrupted for a longer or shorter time.

Only sufficient binding agent solution, which can contain a binding agent or a combination of several binding agents, is employed such that the active compound is attached to the starter material. The active compound layer thus consists mainly of the active compound itself and only to 10% or less of one or more binding agents.

The binding agents and/or the release-delaying substances employed can be polyvinylpyrrolidones, such as PVP 25, hydrophilic cellulose ethers, such as hydropropylmethylcellulose [sic], ethylcelluloses of various degrees of ethylation and various chain lengths, shellacs, copolymers with anionic character based on methacrylic acid and methyl methacrylate or ethyl acrylate corresponding to the substances methacrylic acid copolymer type A, B and C described in USP 23/NF 18, such as Eudragit L®, Eudragit S® and Eudragit L 100-55® or ammonio methacrylate copolymer type A and B, such as Eudragit RL® and Eudragit RS®, cellulose acetate phthalate and hydroxypropylmethyl-cellulose acetate phthalate.

Suitable solvents for the binding agents and/or for the release-delaying substances are in particular water, lower alcohols such as ethanol, isopropanol, alcohol/water mixtures or acetone.

The release-delaying substances can be processed separately or in combination with one another. Preferably, substances from the ethylcelluloses group and/or from the shellacs group are employed. For example, combinations of ethylcellulose with shellac in the ratio 1:9 to 9:1 can be used. Likewise, combinations of ethylcellulose with Eudragit S® are suitable.

A particularly preferred embodiment of the subject according to the invention consists in employing mixtures of ethylcellulose and shellacs both as binding agents and release-delaying substances. By the use of the same polymers for the application of the active compound to the starting material and for the delayed release, tramadol pellets of particularly simple composition are obtained, which are easy to prepare, contain only a few different auxiliaries and are thus of great advantage to the patient.

Further constituents which the multiple unit formulations according to the invention can contain are pharmaceutically customary auxiliaries such as release agents and flow-regulating agents, for example highly disperse silica, talc and magnesium stearate.

The pellets can optionally be delayed to a different extent, caused by different layer thicknesses of the membrane or alternatively by the use of different delayed-release agents. A further possibility for the control of the release of the active compound is thus afforded.

In contrast to the single unit formulations, these multiple unit formulations comprising pellets which are delayed to an identical or different extent pass continuously through the pylorus, even in its closed state, and are dispersed through the entire gastrointestinal region. This leads to a very uniform passage through the gastrointestinal tract.

The pellets are prepared by customary methods (Pharmaceutical Pelletization Technology, edited by Isaac Ghebre-Sellassie, Marcel Dekker Verlag, New York and Basle, 1989).

A preferred process for the preparation is carried out in the following way:

The starter cores are initially introduced into the coating pan or another suitable apparatus, and the active compound or an active compound mixture is added to these continuously or batchwise and attached to the starter material using a solution of binding agents. Using an identical or another solution of binding agents and/or release-regulating substances, after the loading of the starter material with active compound a membrane is applied until the release corresponds to the standards required. The active compound-containing pellets releasing the active compound in delayed form

can be coated with additional active compound, which is not released in delayed form but as initial dose, by various processes known to the person skilled in the art, for example sugar-coating or spraying-on of solutions.
Apart from in a coating pan, the coating can also be carried out in a fluidized bed.

By means of drying processes during and/or after the individual working steps, acceptable threshold values for the solvents used are established.

In WO 95/14460, a complicated process for the preparation of pellets having a coating of ethylcellulose and a plasticizer is shown.
In the so-called "curing" process, instead of the customary afterdrying, the pellets are exposed to a temperature and moisture stress which is technically difficult to realize, which is carried out, for example, at 60 degrees Celcius [sic] and 80% relative atmospheric humidity. Due to the extreme conditions, this process is not suitable for every active compound. On account of the moisture sensitivity of tramadol, tramadol pellets would disintegrate under these conditions.

The tramadol pellets according to the invention have a particle diameter of 0.4 - 3.0 mm, preferably the diameter is in the range 0.6 - 1.6 mm.

For oral administration, the pellets, which are optionally delayed to a different extent, can preferably be dispensed in gelatine capsules or be compressed with suitable auxiliaries to give tablets.
Dispensing in capsules has the great advantage that, for patients with problems in swallowing capsules or tablets, taking can be considerably facilitated. By means of opening the capsules, the delayed-release pellets can be removed and swallowed with liquid or

chyme. Otherwise, the delayed-release pellets according to the invention can also be administered via a stomach or duodenal tube.

The content of the active compound to be released in delayed form in the multiple unit formulations is between 30 and 85% by weight. Multiple unit formulations with a content of active compound which is to be released in delayed form of between 50 and 75% by weight are preferred.

The content of pharmaceutically acceptable, release-delaying substances 2 to 40% by weight.

Depending on the design of the formulations according to the invention, it is possible to administer the daily dose necessary for the desired therapeutic effects by single (24-hour preparation) or twice-repeated administration (12-hour preparation). Restriction to specific dosages and to a specific dose range is not specified. The active compound quantity and the active compound release can be suited to all therapeutic conditions. In bioavailability studies, it was confirmed that after the administration of the formulation according to the invention in the form of capsules which contain, for example, 50 to 200 mg of tramadol hydrochloride, all biopharmaceutical parameters correspond to the necessary requirements according to the progress of science for a tramadol delayed-release preparation.

Active compound release

A suitable in vitro model for the analytical assessment of the active compound release should reconstruct the physiological pH course of the gastrointestinal tract and have test liquids which range from acidic via weakly acidic to weakly alkaline pH. The main criterion for in vitro quality assessment of the active compound release of delayed-release preparations of the multiple unit type with active compounds with the solubility

behaviour of tramadol hydrochloride is the detection of an adequate delay in the acidic pH range and, besides the desired degree of delay, in particular a complete release of active compound in the weakly acidic to weakly alkaline range.

An apparatus suitable for this type of investigation is described in the American pharmacopoeia (USP 23) as "apparatus 3" on pages 1793 and 3012, a more detailed description of the apparatus is found in the Journal of Pharmaceutical Sciences, Volume 80 (1991), pages 991-994.

The invention is intended to be illustrated in greater detail by examples, which should not be restrictions of the subject of the invention.

Example 1

Preparation of the active compound-containing cores

Using about 1150 g of a 20% strength solution of ethylcellulose/shellac (2:8) in an about 96% [v/v] ethanol/water mixture, 4020 g of tramadol hydrochloride/Aerosil®200 mixture were applied in a coating pan to 1000 g of neutral pellets of suitable size (e.g. with a diameter between 0.5 and 0.6 mm). The cores obtained were then dried and sieved (0.8 - 1.4 mm).

Application of the membrane

Membranes were applied to 5.25 kg of the active compound-containing cores thus prepared by adding 390 g of a 20% strength solution of ethylcellulose/shellac (2:8) to an about 96% [v/v] ethanol/water mixture. As a release agent, 780 g of talc were sprinkled in.

Recipe

	Parts by weight (%)
Tramadol hydrochloride	65.5
Neutral pellets	16.4
Ethylcellulose	1.0
Shellac	4.0
Aerosil 200	0.3
Talc	12.8
Ethanol/water mixture about 96% [v/v]	q.s.

The in vitro release of tramadol hydrochloride from the delayed-release pellets according to Example 1 was determined in apparatus 3 according to USP 23/NF 18. The temperature of the release medium was 37°C, the stroke count of the sample tubes 20 strokes/minute and the quantity of test solution per investigation interval 175 ml.

The investigation was begun with test solution pH 1.5, after the first hour the tubes with the samples in each case changed to 175 ml of test solution pH 4.5, after the 2nd hour to a test solution pH 6.9, after the 4th hour to a new test solution pH 6.9, after the 6th hour to test solution pH 7.2 and after the 8th hour to a test solution pH 7.5. The quantity of active compound released in the solution medium at the above-mentioned times was determined spectrophotometrically. The following release values were determined:

Time in hours	Proportion released in % by weight
1	34
2	51
4	65
6	75
8	84
12	98

The in vitro release curve of the delayed-release pellets according to Example 1 is shown in Figure 1.

Example 2

Delayed-release pellets of the following recipe were prepared analogously to Example 1:

	Parts by weight (%)
Tramadol hydrochloride	50.0
Neutral pellets	12.2
Ethylcellulose	8.4
Eudragit S®	0.9
Aerosil 200®	0.2
Talc	28.3
Acetone	q.s.

The in vitro release investigation was carried out analogously to Example 1.
The following release values were determined:

Time in hours	Proportion released in % by weight
1	30
2	51
4	70
6	81
8	88
12	94

The in vitro release curve of the delayed-release pellets according to Example 2 is shown in Figure 2.

Example 3

Delayed-release pellets of the following recipe were prepared analogously to Example 1:

	Parts by weight (%)
Tramadol hydrochloride	40.3
Neutral pellets	10.1
Ethylcellulose	6.7
Aerosil 200®	0.2
Talc	42.7
Ethanol/water mixture about 96% [v/v]	q.s.

The in vitro release investigation was carried out analogously to Example 1.
The following release values were determined:

Time in hours	Proportion released in % by weight
1	34
2	59
4	81
6	89
8	92
12	93

The in vitro release curve of the delayed-release pellets according to Example 3 is shown in Figure 3.

Example 4

Delayed-release pellets of the following recipe were prepared analogously to Example 1:

	Parts by weight (%)
Tramadol hydrochloride	59.7
Neutral pellets	14.9
Ethylcellulose	0.7
Shellac	4.7
Aerosil 200®	0.3
Talc	19.7
Ethanol/water mixture about 96% [v/v]	q.s.

The in vitro release investigation was carried out analogously to Example 1.
The following release values were determined:

Time in hours	Proportion released in % by weight
1	35
2	52
4	72
6	84
8	95
12	100

The in vitro release curve of the delayed-release pellets according to Example 4 is shown in Figure 4.

Figure 5

Delayed-release pellets of the following recipe were prepared analogously to Example 1:

	Parts by weight (%)
Tramadol hydrochloride	48.8
Neutral pellets	12.2
Ethylcellulose	0.6
Shellac	2.3
Eudragit RS®	2.2
Aerosil 200®	0.2
Talc	33.7
Ethanol/water mixture about 96% [v/v]	q.s.

The in vitro release investigation was carried out analogously to Example 1.
The following release values were determined:

Time in hours	Proportion released in % by weight
1	31
2	58
4	76
6	83
8	86
12	89

The in vitro release curve of the delayed-release pellets according to Example 5 is shown in Figure 5.

Example 6

Delayed-release pellets of the following recipe were prepared analogously to Example 1:

	Parts by weight (%)
Tramadol hydrochloride	64.4
Neutral pellets	16.1
Ethylcellulose	3.5
Shellac	2.3
Aerosil 200®	0.3
Talc	13.4
Ethanol/water mixture about 96% [v/v]	q.s.

The in vitro release investigation was carried out analogously to Example 1.
The following release values were determined:

Time in hours	Proportion released in % by weight
1	39
2	57
4	70
6	78
8	84
12	93

The in vitro release curve of the delayed-release pellets according to Example 6 is shown in Figure 6.

Example 7

Delayed-release pellets of the following recipe were prepared analogously to Example 1:

	Parts by weight (%)
Tramadol hydrochloride	58.9
Neutral pellets	14.8
Ethylcellulose	0.6
Shellac	4.9
Aerosil 200®	0.3
Talc	20.5
Ethanol/water mixture about 96% [v/v]	q.s.

The in vitro release investigation was carried out analogously to Example 1.

The following release values were determined:

Time in hours	Proportion released in % by weight
1	3
2	11
6	47
10	69
14	82
22	98

The in vitro release curve of the delayed-release pellets according to Example 7 is shown in Figure 7.

Patent Claims

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1. Pharmaceutical multiple unit formulations comprising individual pellets which are delayed to an identical or different extent consisting of a starter material coated with tramadol or its physiologically tolerable salts, which is coated with one or more membrane layers of at least one pharmaceutically acceptable, release-delaying substance.

2. Pharmaceutical formulations according to Claim 1, characterized in that the active compound content which is to be released in delayed form is between 30 and 85% by weight and the content of pharmaceutically acceptable, release-delaying substances is between 2 and 40% by weight.

3. Pharmaceutical formulations according to Claim 1, characterized in that the active compound content which is to be released in delayed form is between 50 and 75% by weight and the content of pharmaceutically acceptable, release-delaying substances is between 2 and 40% by weight.

4. Pharmaceutical formulations according to Claim 1, characterized in that the starter materials employed for the delayed-release pellets are sucrose crystals or nonpareils (neutral pellets, sugar spheres).

5. Pharmaceutical formulations according to Claim 1, characterized in that tramadol or its physiologically tolerable salts is/are applied to the starter material as a solution or in powder form with an active compound solution or a suitable solvent or a suitable binding agent solution.

6. Pharmaceutical formulation according to Claim 5, characterized in that the solvents employed are water,

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lower alcohols such as ethanol, isopropanol, alcohol/water mixtures or acetone.

7. Pharmaceutical formulations according to Claim 5, characterized in that the binders employed are polyvinylpyrrolidones, such as PVP 25, hydrophilic cellulose ethers, such as hydropropylmethylcellulose [sic], ethylcelluloses of various degrees of ethylation and various chain lengths, shellacs, copolymers with anionic character based on methacrylic acid and methyl methacrylate or ethyl acrylate corresponding to the substances methacrylic acid copolymer type A, B and C described in USP 23/NF 18, such as Eudragit L®, Eudragit S® and Eudragit L 100-55® or ammonio meth-acrylate copolymer type A and B, such as Eudragit RL® and Eudragit RS®, cellulose acetate phthalate and hydroxypropylmethylcellulose acetate phthalate alone or in combination.

8. Pharmaceutical formulations according to one of the preceding claims, characterized in that tramadol or its physiologically tolerable salts is/are preferably applied to the starter material in powder form using a binding agent solution consisting of ethylcellulose and shellac in an ethanol/water mixture.

9. Pharmaceutical formulations according to Claim 1, characterized in that one of the following substances is contained as a pharmaceutically acceptable, release-delaying substance: ethylcelluloses having various chain lengths and degrees of ethylation, shellacs, copolymers with anionic character based on methacrylic acid, methyl methacrylate and ethyl acrylate such as methacrylic acid copolymer type A, B and C (Eudragit L®, EudragitS ® [sic] and Eudragit L 100-55®), ammonio methacrylate copolymer type A and B (Eudragit RL® and Eudragit RS®), cellulose acetate phthalate and hydroxypropylmethylcellulose acetate phthalate.

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10. Pharmaceutical formulations ~~according~~ to Claim 9, characterized in that the pharmaceutically acceptable, release-delaying substances can also be contained as a combination.

11. Pharmaceutical formulations according to Claims 9 and 10, characterized in that a substance from the ethylcelluloses group and/or from the shellacs group is preferably employed as pharmaceutically acceptable, release-delaying substances.

12. Pharmaceutical formulations according to Claim 11, characterized in that the ratio between a substance of the ethylcelluloses group and of the shellacs group is preferably 1:9 to 9:1.

13. Pharmaceutical formulations according to Claim 1, characterized in that release agents and glidants such as silica, talc or magnesium stearate can be contained as further auxiliaries.

14. Pharmaceutical formulations according to Claim 1, characterized in that a rapidly disintegrating or rapidly soluble active compound layer can be applied to the outer release-delaying layer of the delayed-release pellets as an initial dose.

15. Pharmaceutical formulations according to Claim 1, characterized in that the particle diameter of the delayed-release pellets is 0.4 - 3.0 mm, preferably 0.6 - 1.6 mm.

16. Pharmaceutical formulations according to Claim 1 in the form of capsules or tablets.

17. Pharmaceutical formulations according to Claim 16, characterized in that the delayed-release pellets can be removed from the capsules and, if desired, administered separately.

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18. Pharmaceutical formulations according to Claim 1, characterized in that the active compound is released in the gastrointestinal tract in delayed form.

19. Pharmaceutical formulations according to Claim 1 for single (24-hour preparation) or twice-repeated dosage (12-hour preparation).

20. Process for the preparation of multiple unit formulations according to Claim 1, characterized in that the active compound or an active compound mixture is applied to a starter material with the aid of an alcoholic, alcoholic/aqueous, aqueous or acetone solution or binding agent solution, then treated with a solution consisting of the release-delaying substances, if desired using release agents, to construct a suitable membrane, it being possible additionally to apply an initial dose of the active compound to the delayed-release pellets prepared in this way and the pellets obtained then being dispensed in capsules or compressed to give tablets.

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