(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 200062798 B2
(10) Patent No. 781058

(54) Title
Delayed-action form of administration containing tramadol saccharinate

(51)^6 International Patent Classification(s)
A61K 031/135 A61K 009/52
A61K 009/32

(21) Application No: 200062798

(22) Application Date: 2000.08.03

(87) WIPO No: WO01/15683

(30) Priority Data

(31) Number	(32) Date	(33) Country
19940944	1999.08.31	DE
19940740	1999.08.31	DE
10023699	2000.05.16	DE

(43) Publication Date : 2001.03.26
(43) Publication Journal Date : 2001.05.31
(44) Accepted Journal Date : 2005.05.05

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AU 200062798

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
8. März 2001 (08.03.2001)

PCT

(10) Internationale Veröffentlichungsnummer
WO 01/15683 A1

(51) Internationale Patentklassifikation⁷: **A61K 31/135**, 9/32, 9/52

(21) Internationales Aktenzeichen: PCT/EP00/07527

(22) Internationales Anmeldedatum: 3. August 2000 (03.08.2000)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:

199 40 944.7	31. August 1999 (31.08.1999)	DE
199 40 740.1	31. August 1999 (31.08.1999)	DE
100 23 699.5	16. Mai 2000 (16.05.2000)	DE

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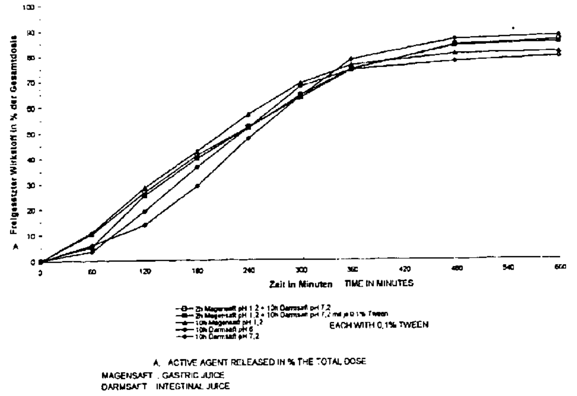
(81) Bestimmungsstaaten *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI,

[Fortsetzung auf der nächsten Seite]

(54) Title: DELAYED-ACTION FORM OF ADMINISTRATION CONTAINING TRAMADOL SACCHARINATE

(54) Bezeichnung: RETARDIERTE DARREICHUNGSFORM ENTHALTEND TRAMADOLSACCHARINAT



(57) Abstract: The invention relates to tramadol forms of administration whose action is delayed by means of a coating and which contain the active agent tramadol in the form of tramadol saccharinate and optionally, other adjuvants.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft durch einen Überzug retardierte Tramadol-Darreichungsformen, die den Wirkstoff Tramadol als Tramadolsaccharinat sowie ggf. weitere Hilfsstoffe enthalten.

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FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:

— *Mit internationalem Recherchenbericht*

— *Vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen.*

Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

Sustained-release form of administration containing tramadol saccharinate

The present invention relates to forms of administration of tramadol, retarded by a coating, which contain the active substance tramadol as tramadol saccharinate, optionally together with other auxiliary substances.

The very readily water-soluble tramadol hydrochloride - (1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride - is often used for the control of intense and moderately intense pain.

The administration of tramadol hydrochloride in the form of sustained-release preparations represents a therapeutic improvement for this active substance. Even for this active substance with its relatively short half-life in the organism, retardation makes it possible to provide a preparation with a long-lasting action and also, through more constant blood levels, to reduce side effects and improve the patients' observance of the dosage instructions.

The active substance tramadol hydrochloride can be retarded e.g. by the application of sustained-release film coatings to pharmaceutical forms containing tramadol hydrochloride. However, retardation of this active substance with the aid of film coatings is relatively expensive because film coatings from aqueous coating systems for very readily water-soluble active substances of this kind frequently constitute an inadequate diffusion barrier and the permeability of these film coatings for tramadol hydrochloride usually changes during storage (P.B. O'Donnell, J.W. McGinity, "Mechanical Properties of Polymeric Films, Prepared from Aqueous Polymeric Dispersions in Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms", Drugs and the Pharmaceutical Science, vol. 79, ed. J.W. McGinity, Marcel Decker, New York, Basle, Hong Kong 1997).

The manufacture of these retarded tramadol hydrochloride preparations therefore requires relatively expensive coating processes with multilayer films or time-consuming tempering processes, as described in US-PS 5,645,858, US-PS 5,580,578, US-PS 5,681,585 or US-PS 5,472,712, in K. Bauer, "Coated Pharmaceutical Dosage Forms", Medpharm Scientific Publishers, Stuttgart 1998, B. Sutter, Thesis, University of Düsseldorf, 1987, or in F.N. Christensen, Proceed. Intern. Symp. Contr. Rel. Bioact. Mater. 17, 124, 1990. If such coatings are applied from organic solvents, the associated environmental and solvent residue problems further increase the cost of retarding tramadol hydrochloride.

The object of the invention was therefore to provide a form of administration of the active substance tramadol, retarded with the aid of a coating, whose active substance release profile immediately after preparation is stable on storage without the need for laborious and expensive coating processes or time-consuming and hence cost-intensive tempering processes.

In a first aspect, the invention relates to forms of administration, provided with a sustained-release coating, which contain the active substance tramadol as tramadol saccharinate, optionally together with other auxiliary substances.

Surprisingly, the active substance release profile of the retarded forms of administration according to the invention immediately after preparation is stable on storage without the sustained-release coating having to undergo tempering after the conventional drying.

To prepare the tramadol saccharinate, tramadol - (1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol - and/or at least one appropriate, preferably water-soluble salt are reacted with saccharin and/or at least one, preferably water-soluble saccharin salt. The tramadol salt used is preferably tramadol hydrochloride and the saccharin salt used is preferably the sodium, potassium, calcium or ammonium salt and particularly preferably the sodium salt.

The tramadol saccharinate can also be formed in situ during the preparation of the forms of administration.

In terms of the present invention, in situ formation means that a readily water-soluble salt of tramadol is mixed with a water-soluble salt of saccharin, moistened and granulated several times, optionally extruded and/or formulated under some other energy input, preferably under pressure and/or with the application of heat.

For the in situ formation of tramadol saccharinate, the tramadol can be used as a water-soluble, pharmaceutically acceptable salt, preferably as tramadol hydrochloride, and the water-soluble, pharmaceutically acceptable salt of saccharin used is preferably the sodium, potassium, calcium or ammonium salt and particularly preferably the sodium salt.

The forms of administration according to the invention, provided with a sustained-release coating film, are preferentially suitable for oral administration.

In one preferred embodiment of the present invention, the forms of administration according to the invention are tablets, capsules or suspensions.

In another preferred embodiment of the present invention, the forms of administration according to the invention are multiparticulate, preferably in the form of microtablets, microcapsules, micropellets, granules, active substance crystals or pellets, optionally filled into capsules or compressed to tablets, or in a hydrophilic or lipophilic liquid, preferably as a homogeneous suspension, and particularly preferably in the form of juices or oral dispersions. If the forms of administration according to the invention are granules or pellets, they can preferably have a size in the range 0.1 to 3 mm and particularly preferably in the range 0.5 to 2 mm.

If the forms of administration according to the invention are microtablets, they can preferably have a diameter in the range 0.5 to 5 mm, particularly preferably in the range 1 to 3 mm and very particularly preferably in the range 1 to 2 mm.

If the forms of administration according to the invention are active substance crystals, microparticles, micropellets or microcapsules, they can preferably have a diameter in the range 10 µm to 1 mm, particularly preferably in the range 15 µm to 0.5 mm and very particularly preferably in the range 30 µm to 200 µm.

Depending on the embodiment, the forms of administration according to the invention can also contain, as additional constituents, the conventional auxiliary substances known to those skilled in the art.

If the forms of administration according to the invention are tablets or microtablets, they can preferably contain, as additional auxiliary substances, microcrystalline cellulose, cellulose ethers, lactose, starch and starch derivatives, sugar alcohols, calcium hydrogenphosphate and the conventional binders, flow regulators, lubricants and optionally disintegrants known to those skilled in the art.

If the forms of administration according to the invention are pellets, granules or micropellets, they can preferably contain, as additional auxiliary substances, microcrystalline cellulose, cellulose ethers, lactose, starch and starch derivatives, sugar alcohols, calcium hydrogenphosphate, fatty alcohols, glycerol esters or fatty acid esters.

If the forms of administration according to the invention are microcapsules or microparticles, they can contain the conventional auxiliary substances known to those skilled in the art, depending on the type of production process.

The various forms of administration according to the invention can be produced by different methods known to those skilled in the art.

If the form of administration according to the invention is tablets, they can be produced for example by the compression of granules produced by means of moist, dry or hot-melt granulation, or by direct tableting of the tramadol saccharinate, optionally with additional auxiliary substances. The tablets can also be produced by the compression of coated pellets, active substance crystals, microparticles or microcapsules.

The pellet form of administration according to the invention can be produced by extrusion and spheronization, by cumulative pelleting or by direct pelleting in a high-speed mixer or in a rotary fluidized bed. It is particularly preferred to produce the pellets by the extrusion of moist masses and subsequent spheronization.
Microcapsules are produced by conventional microencapsulation processes, e.g. by spray drying, spray congelation or coacervation.

In one preferred embodiment of the forms of administration according to the invention, the sustained-release coating film is preferably based on a water-insoluble, optionally modified, natural and/or synthetic polymer, on a natural, semisynthetic or synthetic wax, on a fat or fatty alcohol, or on a mixture of at least two of the above-mentioned components.

The water-insoluble polymers used to produce a sustained-release coating are preferably poly(meth)acrylates, particularly preferably poly(C_{1-4})alkyl (meth)acrylates, poly(C_{1-4})dialkylamino(C_{1-4})alkyl (meth)acrylates and/or copolymers thereof, and very particularly preferably copolymers of ethyl acrylate and methyl methacrylate with a monomer molar ratio of 2:1 (Eudragit NE30D®), copolymers of ethyl acrylate, methyl methacrylate and trimethylammonium ethyl methacrylate-chloride with a monomer molar ratio of 1:2:0.1 (Eudragit RS®), copolymers of ethyl acrylate, methyl methacrylate and trimethylammonium ethyl methacrylate-chloride with a monomer molar ratio of 1:2:0.2 (Eudragit RL®), or a mixture of at least two of the above-mentioned copolymers. These coating materials are commercially available as 30 wt.% aqueous latex dispersions, i.e. as Eudragit RS30D®, Eudragit NE30D® or Eudragit RL30D®, and are preferably also used as such for coating purposes.

Other preferred water-insoluble polymers which can be used to produce the sustained-release coating of the forms of administration according to the invention are polyvinyl acetates, optionally in combination with additional auxiliary substances. They are commercially available as an aqueous dispersion containing 27 wt.% of polyvinyl acetate, 2.5 wt.% of povidone and 0.3 wt.% of sodium laurylsulfate (Kollicoat SR 30 D®).

In another preferred embodiment, the sustained-release coatings of the forms of administration according to the invention are based on water-insoluble cellulose derivatives, preferably alkyl celluloses, e.g. ethyl cellulose, or cellulose esters, e.g. cellulose acetate. The ethyl cellulose or cellulose acetate coatings are preferably applied from aqueous pseudolatex dispersion. Aqueous ethyl cellulose pseudolatex dispersions are commercially available as 30 wt.% dispersions (Aquacoat®) or as 25 wt.% dispersions (Surelease®).

As natural, semisynthetic or synthetic waxes, fats or fatty alcohols, the sustained-release coating of the forms of administration according to the invention can preferably be based on carnauba wax, beeswax, glycerol monostearate, glycerol monobehenate (Compritol ATO888®), glycerol ditripalmitostearate (Precirol ATO5®), microcrystalline wax, cetyl alcohol, cetylstearyl alcohol or a mixture of at least two of these components.

If the sustained-release coating is based on a water-insoluble, optionally modified, natural and/or synthetic polymer, the coating dispersion or solution can contain, in addition to the appropriate polymer, a conventional, physiologically acceptable plasticizer known to those skilled in the art, in order to lower the required minimum film temperature.

Examples of suitable plasticizers are lipophilic diesters of a C_6-C_{40} aliphatic or aromatic dicarboxylic acid and a C_1-C_8 aliphatic alcohol, e.g. dibutyl phthalate, diethyl phthalate, dibutyl sebacate or diethyl sebacate, hydrophilic or lipophilic citric acid esters, e.g. triethyl citrate, tributyl citrate, acetyltributyl citrate or acetyltriethyl citrate, polyethylene glycols, propylene glycol, glycerol esters, e.g. triacetin, Myvacet® (acetylated mono- and diglycerides, $C_{23}H_{44}O_5$ to $C_{25}H_{47}O_7$), medium-chain

triglycerides (Miglyol®), oleic acid or mixtures of at least two of said plasticizers.
Aqueous dispersions of Eudragit RS® and optionally Eudragit RL® preferably contain triethyl citrate.

The sustained-release coating of the form of administration according to the invention preferably contains the plasticizer(s) in amounts of 5 to 50 wt.%, particularly preferably 10 to 40 wt.% and very particularly preferably 10 to 30 wt.%, based on the amount of polymer(s) used. In individual cases, for example for cellulose acetate, it is also possible to use larger amounts of plasticizers, preferably of up to 110 wt.%.

The sustained-release coating can also contain other conventional auxiliary substances known to those skilled in the art, e.g. lubricants, preferably talcum or glycerol monostearate, coloured pigments, preferably iron oxides or titanium dioxide, or surfactants, e.g. Tween 80®.

The tramadol release profile obtained immediately after production of the form of administration according to the invention can be adjusted by the conventional methods known to those skilled in the art, e.g. by means of the thickness of the coating or by the use of additional auxiliary substances as constituents of the coating. Examples of suitable auxiliary substances are hydrophilic or pH-dependent pore-forming agents such as sodium carboxymethyl cellulose, cellulose acetate-phthalate, hydroxypropyl methyl cellulose acetate-succinate, lactose, polyethylene glycol or mannitol, or water-soluble polymers such as polyvinylpyrrolidone or water-soluble celluloses, preferably hydroxypropyl methyl cellulose or hydroxypropyl cellulose.

To further enhance the retardation, the sustained-release coating can also contain insoluble or lipophilic auxiliary substances such as alkylated silicon dioxide, which is marketed e.g. as Aerosil R972®, or magnesium stearate.

The forms of administration according to the invention for the release of tramadol saccharinate can additionally have an enteric coating which dissolves as a function of pH. Because of this coating, the forms of administration according to the invention can pass through the stomach undissolved and the tramadol saccharinate is only released in the intestinal tract. The enteric coating preferably dissolves at a pH of between 5 and 7.5.
The enteric coating is preferably based on methacrylic acid/methyl methacrylate copolymers with a monomer molar ratio of 1:1 (Eudragit L®), methacrylic acid/methyl methacrylate copolymers with a monomer molar ratio of 1:2 (Eudragit S®), methacrylic acid/ethyl acrylate copolymers with a monomer molar ratio of 1:1 (Eudragit L30D-55®), methacrylic acid/methyl acrylate/methyl methacrylate copolymers

with a monomer molar ratio of 7:3:1 (Eudragit FS®), shellac, hydroxypropyl methyl cellulose acetate-succinates, cellulose acetate-phthalates or a mixture of at least two of these components, which can optionally also be used in combination with the above-mentioned water-insoluble poly(meth)acrylates, preferably in combination with Eudragit NE30D® and/or Eudragit RL® and/or Eudragit RS®.

The coatings of the form of administration according to the invention can be applied by the conventional processes known to those skilled in the art which are suitable for the particular coating, e.g. by the spraying of solutions, dispersions or suspensions, by the hot-melt process or by the powder application process. The solutions, dispersions or suspensions can be used in the form of aqueous or organic solutions or dispersions, preferably aqueous dispersions. Organic solvents which can be used are alcohols, for example ethanol or isopropanol, ketones, e.g. acetone, esters, for example ethyl acetate, and chlorinated hydrocarbons, e.g. dichloromethane, preference being given to alcohols and ketones. It is also possible to use mixtures of at least two of the above-mentioned solvents.
These processes are known from the state of the art, e.g. H. Sucker, Georg Thieme Verlag, 1991, pages 347 et seq. They are introduced here by way of reference and thus form part of the disclosure.

If the forms of administration according to the invention are multiparticulate, the sustained-release coating is preferably applied in such a way that, after preparation, the multiparticulate forms containing the tramadol saccharinate are coated with the appropriate polymers and optionally other auxiliary substances from aqueous and/or organic media, preferably from aqueous media, by the fluidized bed process, and the coating is preferably dried simultaneously at conventional temperatures in the fluidized bed without subsequently being tempered. In the case of poly(meth)acrylate coatings, the coating is preferably dried at an air inlet temperature in the range 30 to 50°C and particularly preferably in the range 35 to 45°C.

In the case of coatings based on cellulose, e.g. ethyl cellulose or cellulose acetate, drying preferably takes place at a temperature in the range 50 to 80°C and particularly preferably in the range 55 to 65°C.

Wax coatings can be applied by hot-melt coating in a fluidized bed and, after coating, cooled to complete the solidification at temperatures below the appropriate melting range. Wax coatings can also be applied by spraying solutions thereof in organic solvents.

For further modification of the active substance release profile, the sustained-release forms of administration according to the invention can also contain tramadol saccharinate in a sustained-release matrix, preferably as a uniform distribution.

Matrix materials which can be used are physiologically compatible, hydrophilic materials known to those skilled in the art. The hydrophilic matrix materials used are preferably polymers and particularly preferably cellulose ethers, cellulose esters and/or acrylic resins. The matrix materials used are very particularly preferably ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxymethyl cellulose, poly(meth)acrylic acid and/or derivatives thereof such as their salts, amides or esters.

Other preferred matrix materials are those consisting of hydrophobic materials such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers, or mixtures thereof. The hydrophobic materials used are particularly preferably C_{12}-C_{30} fatty acid mono- or diglycerides and/or C_{12}-C_{30} fatty alcohols and/or waxes, or mixtures thereof.

It is also possible to use mixtures of the above-mentioned hydrophilic and hydrophobic materials as the sustained-release matrix material.

The sustained-release matrix can be prepared by the conventional methods known to those skilled in the art.

In another preferred embodiment, the forms of administration according to the invention contain the active substance tramadol not only in its retarded form but also in its non-retarded form, e.g. as tramadol hydrochloride. By combination with the immediately released active substance, a high initial dose can be achieved for the rapid alleviation of pain. The slow release from the retarded form then prevents the analgesic effect from diminishing.

The amount of tramadol to be administered to the patient varies e.g. as a function of the patient's weight, the indication and the degree of severity of the pain or disease. The amount of tramadol to be administered, and its release, are preferably adjusted so that it has to be taken at most twice a day and preferably only once a day.

If taken once a day, the forms of administration according to the invention preferably contain 10 to 1200 mg, particularly preferably 20 to 1000 mg and very particularly preferably 100 to 800 mg of tramadol.

If taken twice a day, the forms of administration according to the invention preferably contain 5 to 600 mg, particularly preferably 10 to 500 mg and very particularly preferably 50 to 400 mg of tramadol.

The forms of administration according to the invention can preferably be used for the control of pain or for the treatment of urinary incontinence, coughs, inflammatory reactions, allergic reactions, depression, drug abuse, alcohol abuse, gastritis, diarrhoea, cardiovascular disease, respiratory disease, mental illness or epilepsy, and particularly preferably for the control of pain or for the treatment of urinary incontinence or coughs.

According to a second aspect of the invention there is provided a method for controlling pain in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to a third aspect of the invention there is provided a method for treating urinary incontinence in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to a fourth aspect of the invention there is provided a method for treating coughs in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to a fifth aspect of the invention there is provided a method for treating inflammatory and/or allergic reactions in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to a sixth aspect of the invention there is provided a method for treating depression in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to a seventh aspect of the invention there is provided a method for treating drug and/or alcohol abuse in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to an eighth aspect of the invention there is provided a method for treating gastritis in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to a ninth aspect of the invention there is provided a method for treating diarrhoea in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to a tenth aspect of the invention there is provided a method for treating cardiovascular disease in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to an eleventh aspect of the invention there is provided a method for treating respiratory disease in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to a twelfth aspect of the invention there is provided a method for treating mental illness in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to a thirteenth aspect of the invention there is provided a method for treating epilepsy in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to the first aspect of the invention.

According to a fourteenth aspect of the invention there is provided a form of administration according to the first aspect of the invention, when used for one or more of controlling pain, treating urinary incontinence, treating coughs, treating inflammatory and/or allergic reactions, treating depression, treating drug and/or alcohol abuse, treating gastritis, treating diarrhoea, treating cardiovascular disease, treating respiratory disease, treating mental illness, and treating epilepsy.

The forms of administration according to the invention have the advantage that, immediately after preparation, their active substance release profile is stable on storage without the need for tempering, which normally follows drying, or for an expensive coating process. This makes it possible to reduce the production time and hence also the costs of producing the forms of administration according to the invention.

Furthermore, the release of the active substance tramadol from the forms of administration according to the invention, provided with a sustained-release coating applied from an aqueous medium, is surprisingly retarded far more than from the forms of administration, provided with a sustained-release coating of identical composition, which contain the active substance tramadol as tramadol hydrochloride. Application of the sustained-release coating film from an aqueous medium has the further advantage that the expensive recovery or organic solvents is not necessary and that the forms of administration according to the invention no longer contain solvent residues.

A further feature of the forms of administration according to the invention is that the release of the active substance tramadol therefrom is not affected by varying the release conditions within the conventional framework, e.g. by means of the ion concentrations of the buffers, the presence of surface-active substances or the application of different mechanical stresses.

The release profiles of the forms of administration according to the invention were determined as follows:

The form of administration according to the invention was tested in a cage apparatus or in a paddle stirrer, as described in the European Pharmacopoeia, at a release medium temperature of 37 ± 0.5°C and a speed of rotation of 100 rpm or 50 rpm in the case of the paddle stirrer, for 2 hours, in 600 ml of artificial gastric juice at pH 1.2. The form of administration was then tested for a further 8 hours in 900 ml of artificial intestinal juice at pH 7.2. The amount of tramadol saccharinate released at any given time was determined by HPLC. The values shown have been averaged over 3 samples in each case.

The invention is illustrated below with the aid of Examples 1 to 11. These illustrations are given solely by way of example and do not limit the general spirit of the invention.

Examples:

Example 1:

To prepare tramadol saccharinate, equimolar amounts of tramadol hydrochloride - (1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride - and saccharin sodium or saccharin sodium dihydrate are each completely dissolved in the minimum amount of water, with heating. The two solutions are then mixed together, with stirring. On cooling, the tramadol saccharinate crystallizes out of the aqueous solution after only a short time and is isolated by conventional methods and purified with ethanol.

Preparation of pellets:

2500 g of tramadol saccharinate and 2500 g of microcrystalline cellulose (Avicel PH 105®, FMC) are mixed for 10 minutes in a Diosna P25 high-speed mixer and then granulated for 10 minutes with 3300 g of demineralized water. The moist granules are extruded in a NICA E140 extruder with a 1.0 x 2.0 mm extrusion die and the moist extrudate is spheronized in 2.7 kg batches in a NICA spheronizer for 15 minutes at 800 rpm. The pellets are then dried overnight at 50°C in a drying cabinet. The yield of pellets with a particle size in the range 800 to 1250 μm is over 90%.

Application of the coating:

3 kg of these pellets (800 - 1250 μm) are coated in a fluidized bed (Hüttlin HKC05) with an aqueous dispersion of the following composition, at a product temperature of 26 to 30°C, until the weight has

increased by 16% (based on the weight of the starting pellets). This coating application corresponds to a polymer application of 13 wt.% (based on the weight of the starting pellets). The pellets are then dried for 10 minutes in the fluidized bed at 45°C.

Aqueous dispersion for 3 kg of pellets:

Eudragit RS 30 D®	1049.0 g
Eudragit RL 30 D®	296.0 g
Triethyl citrate	80.7 g
Glycerol monostearate	20.2 g
Tween 80®	1.9 g
Demineralized water	1074.2 g
Total:	2522.0 g

345 mg of pellets provided with a sustained-release coating contain 149 mg of tramadol saccharinate, corresponding to 100 mg of the active substance tramadol hydrochloride.

The release profile was determined in a cage apparatus by the method indicated above and is shown in Table 1 below and in Figure 3.

Table 1:

Time (min)	Tramadol saccharinate released in % of the total dose of active substance
0	0
60	11
120	32
180	46
240	57
300	67
360	76
480	93
600	105

The active substance release from the pellets produced in this way, provided with a sustained-release coating, was also tested, by the method indicated above, in release media of different composition according to Table 2 below:

Table 2:

a)	2 hours in gastric juice at pH 1.2 and 10 hours in intestinal juice at pH 7.2
b)	10 hours in gastric juice at pH 1.2
c)	10 hours in intestinal juice at pH 6.0
d)	10 hours in intestinal juice at pH 7.2
e)	2 hours in gastric juice at pH 1.2 and 10 hours in intestinal juice at pH 7.2 with 0.1% of Tween 80® in each case

The results of these experiments are shown in Figure 1, where it can be seen that the release profile of the tramadol saccharinate pellets provided with a sustained-release coating is barely affected by the change in composition of the release medium. Neither the pH, nor the ionic strength, nor the presence of surface-active substances affects the release profile of the pellets provided with the sustained-release coating.

Comparative Example 1:

Preparation of pellets containing tramadol hydrochloride:

275 g of tramadol hydrochloride, 75 g of microcrystalline cellulose (Avicel PH 105®, FMC) and 150 g of hydroxypropyl cellulose with a low degree of substitution (1-HPC LH31®) are mixed for 10 minutes in a Kenwood Chef planetary mixer and then granulated for 10 minutes with 250 g of demineralized water. The moist granules are extruded in a NICA E140 extruder with a 1.0 x 2.0 mm extrusion die and the moist extrudate is spheronized in a NICA spheronizer for 15 minutes at 800 rpm. The pellets are then dried overnight at 50°C in a drying cabinet. The yield of pellets with a particle size in the range 800 to 1250 µm is over 90%.

Application of the coating:

320 g of these pellets (800 - 1250 µm) were coated in a fluidized bed (Aeromatic, Strea 1) with an aqueous dispersion of the following composition, at a product temperature of 26 to 32°C, until the weight had increased by 25% (based on the weight of the starting pellets). This coating application corresponds to a

polymer application of 16 wt.% (based on the weight of the starting pellets). The pellets are then dried for 10 minutes in the fluidized bed at 45°C.

Aqueous dispersion for 320 g of pellets:

Eudragit RS 30 D®	152.8 g
Eudragit RL 30 D®	13.9 g
Triethyl citrate	15.0 g
Talcum	15.0 g
Demineralized water	203.3 g
Total:	400.0 g

228 mg of pellets provided with a sustained-release coating contain 100 mg of tramadol hydrochloride.

The release profile was determined in a cage apparatus by the method indicated above. The results of these experiments and of those for the pellets of Example 1 according to the invention are shown in Figure 4.

As can be seen from Figure 4, the tramadol saccharinate pellets provided with a sustained-release coating exhibit active substance release over 10 hours, whereas, after a short delay, the tramadol hydrochloride pellets provided with a sustained-release coating release the active substance almost completely within only 4 hours, despite the thicker polymer coating and the less permeable polymer composition of the coating.

The intrinsic release of the active substances tramadol hydrochloride and tramadol saccharinate was also determined.

The intrinsic active substance release is determined for both tramadol hydrochloride and tramadol saccharinate in demineralized water (37°C ± 0.5°C) using the method "<1087> intrinsic dissolution" published in USP 24-NF19 first supplement (pp. 2706 et seq.). The intrinsic release of each of the two active substances is calculated from the gradient of the cumulative active substance release up to and including the time at which 10% of the pellets have been released. It is given below as the release rate in mg $\cdot$ min^{-1} $\cdot$ cm^{-2}.

Intrinsic release in water:

Tramadol hydrochloride:	21 mg $\cdot$ min^{-1} $\cdot$ cm^{-2}
Tramadol saccharinate:	2 mg $\cdot$ min^{-1} $\cdot$ cm^{-2}

The difference in the intrinsic active substance release clearly shows that tramadol saccharinate is released from pharmaceutical forms considerably more slowly than tramadol hydrochloride and therefore also permeates diffusion barriers more slowly.

Example 2:

Preparation of pellets:

505 g of tramadol saccharinate and 505 g of microcrystalline cellulose (Avicel PH 105®, FMC) are mixed for 10 minutes in a Kenwood Chef planetary mixer and then granulated for 10 minutes with 630 g of demineralized water. The moist granules are extruded in a NICA E140 extruder with a 1.0 x 2.0 mm extrusion die and the moist extrudate is spheronized in a NICA spheronizer for 15 minutes at 800 rpm. The pellets are then dried overnight at 50°C in a drying cabinet. The

yield of pellets with a particle size in the range 800 to 1250 µm is over 90%.

Application of the coating:

200 g of these pellets (800 - 1250 µm) are coated in a fluidized bed (Aeromatic, Strea 1) with an aqueous dispersion of the following composition, at a product temperature of 26 to 30°C, until the weight has increased by 27% (based on the weight of the starting pellets). This coating corresponds to a polymer application of 21 wt.% (based on the weight of the starting pellets). The coated pellets are then dried for 10 minutes in the fluidized bed at 45°C.

Aqueous dispersion for 200 g of pellets:

Eudragit RS 30 D®	108.6 g
Eudragit RL 30 D®	30.6 g
Triethyl citrate	8.3 g
Glycerol monostearate	2.1 g
Tween 80®	0.2 g
Demineralized water	111.2 g
Total:	261.0 g

379 mg of pellets provided with a sustained-release coating contain 149 mg of tramadol saccharinate, corresponding to 100 mg of the active substance tramadol hydrochloride.

The release profile was determined in a cage apparatus by the method described above and is shown in Table 3 below and in Figure 3. As a departure from the conditions described above, the coated pellets were tested for 10 hours in artificial intestinal juice at pH 7.2.

Table 3:

Time (min)	Tramadol saccharinate released in % of the total dose of active substance
0	0
60	3
120	14
180	26
240	35
300	46
360	56
480	74
600	91
720	100

Example 3:

Preparation of pellets:

505 g of tramadol saccharinate and 505 g of microcrystalline cellulose (Avicel PH 105®, FMC) are mixed for 10 minutes in a Kenwood Chef planetary mixer and then granulated for 10 minutes with 630 g of demineralized water. The moist granules are extruded in a NICA E140 extruder with a 1.0 x 2.0 mm extrusion die and the moist extrudate is spheronized in a NICA spheronizer for 15 minutes at 800 rpm. The pellets are then dried overnight at 50°C in a drying cabinet. The yield of pellets with a particle size in the range 800 to 1250 µm is over 90%.

Application of the coating:

200 g of these pellets (800 - 1250 µm) are coated in a fluidized bed (Aeromatic, Strea 1) with an aqueous dispersion of the following composition, at a product temperature of 26 to 30°C, until the weight has increased by 21% (based on the weight of the starting pellets). This coating application corresponds to a polymer application of 14 wt.% (based on the weight of the starting pellets). The coated pellets are subjected to the release test either directly after coating and conventional drying or after tempering at 40°C for 15 hours in a drying cabinet.

Aqueous dispersion for 200 g of pellets:

Eudragit RS 30 D®	80.0 g
Eudragit RL 30 D®	20.0 g
Triethyl citrate	6.0 g
Talcum	6.0 g
Demineralized water	88.0 g
Total:	200.0 g

361 mg of pellets provided with a sustained-release coating contain 149 mg of tramadol saccharinate, corresponding to 100 mg of the active substance tramadol hydrochloride.

The release profiles were determined in each case in a cage apparatus by the method described above and are shown in Table 4 below and, for the non-tempered pellets, in Figure 3.

Table 4:

Time (min)	Tramadol saccharinate released in % of the total dose of active substance **without tempering**	Tramadol saccharinate released in % of the total dose of active substance **15 h tempering at 40°C**
0	0	0
60	16	15
120	29	27
180	37	34
240	45	41
360	63	57
480	79	73
600	92	87

The differences of approx. 5% between the values for the active substance release without and with tempering correspond to the usual scatter of experimental values, so tempering after application of the coating has no effect on the release profile.

Example 4:

Preparation of pellets:

252.5 g of tramadol saccharinate and 252.5 g of microcrystalline cellulose (Avicel PH 105®, FMC) are mixed for 10 minutes in a Kenwood Chef planetary mixer and then granulated for 10 minutes with 338.0 g of demineralized water. The moist granules are extruded in a NICA E140 extruder with a 1.0 x 2.0 mm extrusion die and the moist extrudate is spheronized in a NICA spheronizer for 15 minutes at 800 rpm. The pellets are then dried overnight at 50°C in a drying cabinet. The yield of pellets with a particle size in the range 800 to 1250 µm is over 90%.

Application of the coating:

170 g of these pellets (800 - 1250 µm) are coated in a fluidized bed (Aeromatic, Strea 1) with an aqueous dispersion of the following composition, at a product temperature of 26 to 30°C, until the weight has increased by 28% (based on the weight of the starting pellets). This coating application corresponds to a polymer application of 20 wt.% (based on the weight of the starting pellets). The coated pellets are then dried for 10 minutes in the fluidized bed at 45°C.

Aqueous dispersion for 170 g of pellets:

Eudragit RS 30 D®	68.1 g
Eudragit RL 30 D®	45.4 g
Triethyl citrate	6.8 g
Talcum	6.8 g
Demineralized water	99.9 g
Total:	227.0 g

381 mg of pellets provided with a sustained-release coating contain 149 mg of tramadol saccharinate, corresponding to 100 mg of the active substance tramadol hydrochloride.

The release profile was determined in a cage apparatus by the method indicated above and is shown in Table 5 below and in Figure 3. As a departure from the conditions described above, the coated pellets were tested for 6 hours in artificial intestinal juice at pH 7.2.

Table 5:

Time (min)	Tramadol saccharinate released in % of the total dose of active substance
0	0
30	4
120	62
240	94
300	99
480	100

Example 5:

Preparation of pellets:

505.0 g of tramadol saccharinate and 505.0 g of microcrystalline cellulose (Avicel PH 105®, FMC) are mixed for 10 minutes in a Kenwood Chef planetary mixer and then granulated for 10 minutes with 630.0 g of demineralized water. The moist granules are extruded in a NICA E140 extruder with a 1.0 x 2.0 mm extrusion die and the moist extrudate is spheronized in a NICA spheronizer for 15 minutes at 800 rpm. The pellets are then dried overnight at 50°C in a drying cabinet. The yield of pellets with a particle size in the range 800 to 1250 µm is over 90%.

Application of the coating:

200 g of these pellets (800 - 1250 µm) are coated in a fluidized bed (Aeromatic, Strea 1) with an aqueous

dispersion of the following composition, at a product temperature of 26 to 30°C, until the weight has increased by 20% (based on the weight of the starting pellets). This coating application corresponds to a polymer application of 16 wt.% (based on the weight of the starting pellets). The coated pellets are then dried for 10 minutes in the fluidized bed at 45°C.

Aqueous dispersion for 200 g of pellets:

Eudragit RS 30 D®	106.1 g
Triethyl citrate	6.4 g
Glycerol monostearate	1.6 g
Tween 80®	0.2 g
Demineralized water	84.7 g
Total:	199.0 g

358 mg of pellets provided with a sustained-release coating contain 149 mg of tramadol saccharinate, corresponding to 100 mg of the active substance tramadol hydrochloride.

The release profile was determined in a cage apparatus by the method indicated above and is shown in Table 6 below and in Figure 3. As a departure from the conditions described above, the coated pellets were tested for 14 hours in artificial intestinal juice at pH 7.2.

Table 6:

Time (min)	Tramadol saccharinate released in % of the total dose of active substance
0	0
60	0
120	0
180	0
240	2
300	3
360	5
420	7
480	8
600	10
720	12
840	14
960	15

Example 6:

Testing of the storage stability of tramadol saccharinate pellets provided with a sustained-release coating:

The pellets prepared according to Example 1, provided with a sustained-release coating, were stored in closed glass vessels for 1 week or 2 weeks, either at 30°C and 70% relative humidity, or at 40°C dry, or at 40°C and 75% relative humidity, and in each case the release profile was determined, after storage, by the method described above. As a departure from the conditions described above, the coated pellets were tested for 10 hours in artificial intestinal juice at pH 7.2.

The results of these experiments are shown in Figure 2, where it can be seen that storage at 30°C and 70% relative humidity, and at 40°C dry, has no effect whatsoever on the active substance release profile. Even after storage at 40°C and 75% relative humidity, release from the partially agglutinated pellets is only slowed down very slightly. Immediately after preparation, the forms of administration of tramadol saccharinate according to the invention therefore exhibit a retarded release profile of the active substance which is stable on storage without tempering.

Example 7:

Preparation of pellets:

250 g of tramadol saccharinate and 250 g of microcrystalline cellulose (Avicel PH 105®) are mixed for 10 minutes in a Kenwood Chef planetary mixer and then granulated for 10 minutes with 443 g of demineralized water. The moist granules are extruded in a NICA E140 extruder with a 1.0 x 2.0 mm extrusion die and the moist extrudate is then spheronized in a NICA spheronizer for 15 minutes at 800 rpm. The pellets are then dried overnight at 50°C in a drying cabinet. The yield of pellets with a particle size in the range 800 to 1250 µm is over 90%.

Application of the coating:

170 g of these pellets (800 - 1250 µm) are coated in a fluidized bed (Aeromatic, Strea 1) with an aqueous

dispersion of the following composition, at a product temperature of 35 to 40°C, until the weight has increased by 5% (based on the weight of the starting pellets). The coated pellets are then dried for two hours at 60°C in a drying cabinet.

Aqueous dispersion for 170 g of pellets:

Surelease E-7-7050®*	34.0 g
Demineralized water	23.0 g
Total:	57.0 g

* 25% aqueous ethyl cellulose pseudolatex dispersion. The commercially available ready-to-use dispersion contains dibutyl sebacate as plasticizer and silicon dioxide as lubricant.

313 mg of pellets provided with a sustained-release coating contain 149 mg of tramadol saccharinate, corresponding to a dose of 100 mg of tramadol hydrochloride.

The release profile was determined in a cage apparatus by the method indicated above and is shown in Table 7 below and in Figure 3.

Table 7:

Time (min)	Tramadol saccharinate released in % of the total dose of active substance
0	0
30	15
120	58
240	69
300	71
480	76
600	79

Example 8:

Preparation of tablets:

Composition per tablet:

Tramadol saccharinate	149 mg
Cellactose	146 mg
Magnesium stearate	3 mg

The Cellactose and the magnesium stearate are sieved and then homogeneously mixed with the tramadol saccharinate for 10 minutes in a tumbling mixer (Bohle, LM 40). This mixture is compressed on a Korsch EKO eccentric press with a die to give 10 mm dragee-shaped tablets with a height of approx. 5 mm and a radius of curvature of 8 mm.

Application of the coating:

2000 of these tablets are coated in a fluidized bed (Aeromatic, Strea 1) with an aqueous dispersion of the following composition, at a product temperature of 26 to 30°C, until the weight has increased by 6.5 wt.% (based on the weight of the starting tablet). This coating application corresponds to a polymer application of 5.0 wt.% (based on the weight of the starting tablet). The coated tablets are dried for 10 minutes at 40°C in a drying cabinet.

Aqueous dispersion for 2000 tablets:

Eudragit RS 30 D®	69.7 g
Eudragit RL 30 D®	29.8 g
Triethyl citrate	6.0 g
Glycerol monostearate	1.5 g
Tween 80®	0.1 g
Demineralized water	92.4 g
Total:	199.5 g

The release profile was determined in a paddle stirrer by the method indicated above and is shown in Table 8 below.

Comparative Example 2:

Preparation of tablets:

Composition per tablet:

Tramadol hydrochloride	100 mg
Cellactose	98 mg
Magnesium stearate	2 mg

The Cellactose and the magnesium stearate are sieved and then homogeneously mixed with the tramadol hydrochloride for 10 minutes in a tumbling mixer (Bohle, LM 40). This mixture is compressed on a Korsch EK0 eccentric press with a die to give 9 mm dragee-shaped tablets with a height of approx. 5 mm and a radius of curvature of 8 mm.

Application of the coating:

2000 of these tablets are coated in a fluidized bed (Aeromatic, Strea 1) with an aqueous dispersion of the following composition, at a product temperature of 26 to 30°C, until the weight has increased by 6.5% (based on the weight of the starting tablet). This coating application corresponds to a polymer application of 5.0 wt.% (based on the weight of the starting tablet). The coated tablets are dried for 10 minutes at 40°C in a drying cabinet.

Aqueous dispersion for 2985 tablets:

Eudragit RS 30 D®	69.7 g
Eudragit RL 30 D®	29.8 g
Triethyl citrate	6.0 g
Glycerol monostearate	1.5 g
Tween 80®	0.1 g
Demineralized water	92.4 g
Total:	199.5 g

The release profile was determined in a paddle stirrer by the method indicated above and is shown in Table 8 below.

Table 8:

Time (min)	Tramadol saccharinate released in % of the total dose of active substance	Tramadol hydrochloride released in % of the total dose of active substance
0	0	0
30	1	2
240	9	91
480	17	96
720	25	98

Whereas >90% of the active substance tramadol hydrochloride has already been released from the coated tablets within 4 hours, tramadol saccharinate is released from the coated tablets considerably more slowly and at a constant rate, only 25% of the total dose having been released after 12 hours.
Here again it is clear that the slower rate of dissolution of tramadol saccharinate with identical diffusion barriers results in a greater retardation than in the case of tramadol hydrochloride and, in contrast to the latter, results in zero-order release kinetics even with smaller film layer thicknesses.

Example 9:

Preparation of pellets:

500 g of tramadol hydrochloride, 345 g of sodium saccharinate and 845 g of microcrystalline cellulose (Avicel PH 101®) are mixed for 10 minutes and then granulated for 10 minutes with a sufficient amount of demineralized water for the purpose. After granulation, the granules are extruded in a Nica E140 extruder with a 0.8 x 1.6 mm extrusion die and the extrudate is granulated again with a sufficient amount of water to give a plastic mass. This is extruded again. The moist extrudate is spheronized in a Nica type S450 spheronizer. After drying in a drying cabinet, the pellets are graded, >90% of the pellets having a size in the range 0.63 to 1.0 mm.

Application of the coatings:

1000 g of these pellets are coated in a fluidized bed (Hüttlin HKC05) with an aqueous dispersion of the following composition, at a product temperature of 26 to 30°C, until the weight has increased by 20% (based on the weight of the starting pellets). This coating application corresponds to a polymer application of 16 wt.% (based on the weight of the starting pellets). The pellets are then dried for 10 minutes in the fluidized bed at 45°C.

Aqueous dispersion for 1000 g of pellets:

Eudragit RS 30 D®	499.5 g
Eudragit RL 30 D®	166.5 g
Triethyl citrate	40.0 g
Glycerol monostearate	10.0 g
Tween 80®	1.1 g
Demineralized water	612.9 g
Total:	1330 g

Filling of the coated pellets into capsules:

406 mg of the pellets provided with a sustained-release coating (corresponding to a content of 100 mg of the active substance tramadol hydrochloride) are filled into size 0 hard gelatin capsules on a Zanasi E6 encapsulating machine.

The release profile was determined in a cage apparatus by the method indicated above and is shown in Table 9 below and in Figure 3. As a departure from the conditions described above, the coated pellets were tested for 10 hours in artificial intestinal juice at pH 7.2.

Table 9:

Time in min	Tramadol saccharinate released in % of the total dose of active substance
0	0
60	7
120	22
240	53
480	91
600	99
720	100

Example 10:

The pellets are prepared according to Example 4.

400 g of these pellets (800 - 1250 µm) are coated in a fluidized bed (Aeromatic, Strea 1) with an aqueous dispersion of the following composition, at a product temperature of 26 to 30°C, until the weight has increased by 25% (based on the weight of the starting pellets). This coating application corresponds to a polymer application of 20 wt.% (based on the weight of the starting pellets). The coated pellets are dried for 10 minutes at 40°C in the fluidized bed apparatus.

Aqueous dispersion for 400 g of pellets:

Eudragit RS 30 D®	200.0 g
Eudragit RL 30 D®	66.7 g
Triethyl citrate	16.0 g
Glycerol monostearate	4.0 g
Tween 80®	0.5 g

Demineralized water	212.8 g
Total:	500.0 g

373 mg of pellets provided with a sustained-release coating contain 149 mg of tramadol saccharinate, corresponding to a dose of 100 mg of tramadol hydrochloride.

Preparation of tablets:

Composition per tablet:

Coated pellets	373 mg
Kollidon CL®	22.4 mg
Avicel PH 101®	142.0 mg
Magnesium stearate	2.6 mg
Total:	540 mg

The pellets provided with a sustained-release coating are mixed for 5 minutes in a tumbling mixer (Bohle, LM 40) with Kollidon CL® (crosslinked polyvinylpyrrolidone) and then mixed for a further 10 minutes with microcrystalline cellulose (Avicel PH 101®) and magnesium stearate. This mixture is compressed on a rotary tablet press (Fette, P1200) to round, biplanar tablets each weighing 500 mg, with a diameter of 12 mm and a hardness of 100 to 130 N.

In an aqueous medium, these tablets disintegrate into the individual pellets within 1-2 minutes.

The release profile was determined in a paddle stirrer by the method described above and is shown in Table 10 below and in Figure 3.

Table 10:

Time (min)	Tramadol saccharinate released in % of the total dose of active substance
0	0
30	8
120	22
240	46
300	57
480	86
600	102

Example 11:

The pellets are prepared according to Example 2.

200 g of these pellets (800 - 1250 µm) are coated in a fluidized bed (Aeromatic, Strea 1) with an aqueous dispersion of the following composition, at a product temperature of 35 to 40°C, until the weight has increased by 20% (based on the weight of the starting pellets). This coating application corresponds to a polymer application of 15 wt.% (based on the weight of the starting pellets). The coated pellets are dried for 10 minutes at 45°C in the fluidized bed apparatus.

Aqueous dispersion for 200 g of pellets:

Kollicoat® RS 30 D	100.0 g
Propylene glycol	3.0 g
Talcum	7.0 g
Demineralized water	90.0 g
Total:	200.0 g

358 mg of pellets provided with a sustained-release coating contain 149 mg of tramadol saccharinate, corresponding to a dose of 100 mg of tramadol hydrochloride.

The release profile was determined in a cage apparatus by the method indicated above and is shown in Table 11 below.

Table 11:

Time (min)	Tramadol saccharinate released in % of the total dose of active substance
0	0
30	6
120	37
180	54
240	61
300	71
480	76
600	92
720	98

Figure 3 shows a selection of different profiles for the release of the active substance tramadol saccharinate from extruded pellets which have been coated from aqueous dispersion. Depending on the film composition and the film layer thickness, suitable active substance release profiles can be obtained for formulations to be taken once a day or twice a day, and the release kinetics can be shifted from 1st order to zero order. This shows the great variety of active substance release profiles which can be obtained simply by using commercially available polymer dispersions as recommended by the manufacturer, without further measures or special additives.

The claims defining the invention are as follows:

1. Forms of administration of tramadol, provided with at least one sustained-release coating, which contain the active substance tramadol saccharinate, optionally together with other auxiliary substances.

2. Forms of administration according to claim 1, wherein the tramadol compound is present as a compound formed *in situ*.

3. Forms of administration according to claim 1 or 2, wherein the tramadol compound has been prepared using a water-soluble, pharmaceutically acceptable salt of tramadol, and a water-soluble, pharmaceutically acceptable salt of saccharin.

4. Forms of administration according to claim 3, wherein said pharmaceutically acceptable salt of tramadol is tramadol hydrochloride.

5. Forms of administration according to claim 3 or 4, wherein said pharmaceutically acceptable salt of saccharin is the sodium, potassium, calcium or ammonium salt.

6. Forms of administration according to claim 5, wherein said salt is the sodium salt.

7. Forms of administration according to any one of claims 1 to 6 for oral administration.

8. Forms of administration according to claim 7, in the form of tablets, capsules or suspensions.

9. Forms of administration according to claim 7, wherein said forms are multiparticulate, optionally filled into capsules or compressed to tablets, or in a hydrophilic or lipophilic liquid.

10. Forms of administration according to claim 9, in the form of microtablets, microcapsules, micropellets, granules, active substance crystals or pellets.

11. Forms of administration according to claim 10, wherein the granules or pellets have a size in the range 0.1 to 3 mm.

12. Forms of administration according to claim 11, wherein the granules or pellets have a size in the range 0.5 to 2 mm.

13. Forms of administration according to claim 10, wherein the microtablets have a diameter of 0.5 to 5 mm.

14. Forms of administration according to claim 13, wherein the microtablets have a diameter of 1 to 3 mm.

15. Forms of administration according to claim 14, wherein the microtablets have a diameter of 1 to 2 mm.

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16. Forms of administration according to claim 10, wherein the active substance crystals, microparticles, micropellets or microcapsules have a diameter of 10 μm to 1 mm.

17. Forms of administration according to claim 16, wherein the active substance crystals, microparticles, micropellets or microcapsules have a diameter of 15 μm to 0.5 mm.

18. Forms of administration according to claim 16, wherein the active substance crystals, microparticles, micropellets or microcapsules have a diameter of 30 μm to 200 μm.

19. Forms of administration according to any one of claims 1 to 18, wherein the sustained-release coating is based on a water-insoluble, optionally modified, natural or synthetic polymer, on a natural, semisynthetic or synthetic wax or fat or fatty alcohol, or on a mixture of at least two of these components.

20. Forms of administration according to claim 19, wherein the water-insoluble polymers present as the coating material are poly(meth)acrylates.

21. Forms of administration according to claim 20, wherein said poly(meth)acrylates are selected from poly-(C_{1-4})alkyl(meth)acrylates, poly-(C_{1-4})dialkylamino(C_{1-4})alkyl(meth)acrylates, and/or copolymers thereof.

22. Forms of administration according to claim 21, wherein said copolymers are selected from ethyl acrylate/methyl methacrylate copolymers with a monomer molar ratio of 2:1 (Eudragit NE30D$^{®}$), ethyl acrylate/methyl methacrylate/trimethylammonium ethylmethacrylate-chloride copolymers with a monomer molar ratio of 1:2:0.1 (Eudragit RS$^{®}$), ethyl acrylate/methyl methacrylate/trimethylammonium ethyl methacrylate-chloride copolymers with a monomer molar ratio of 1:2:0.2 (Eudragit RL$^{®}$), or a mixture of at least two of the above-mentioned polymers.

23. Forms of administration according to claim 19, wherein the water-insoluble polymers present as the coating material are cellulose derivatives.

24. Forms of administration according to claim 23, wherein the cellulose derivative is alkyl cellulose or cellulose esters.

25. Forms of administration according to claim 24, wherein said alkyl cellulose is ethyl cellulose.

26. Forms of administration according to claim 24, wherein said cellulose ester is cellulose acetate.

27. Forms of administration according to any one of claims 20 to 26, wherein the polymers have been applied from an aqueous medium.

28. Forms of administration according to claim 27, wherein said aqueous medium is an aqueous latex or pseudolatex dispersions.

29. Forms of administration according to claim 19, wherein the coating polymer which has been used is a mixture of polyvinyl acetate and polyvinylpyrrolidone.

30. Forms of administration according to claim 29, wherein said mixture of polyvinyl acetate and polyvinylpyrrolidone is in the form of aqueous pseudolatex dispersions.

31. Forms of administration according to claim 19, wherein the wax which has been applied as the coating material is carnauba wax, beeswax, glycerol monostearate, glycerol monobehenate (Compritol ATO888®), glycerol ditripalmitostearate (Precirol ATO5®), microcrystalline wax, or a mixture of at least two of these components.

32. Forms of administration according to claim 31, wherein said wax which has been applied as the coating material is applied by the hot-melt coating process.

33. Forms of administration according to any one of claims 20 to 32, wherein the polymers have been used in combination with conventional plasticizers.

34. Forms of administration according to claim 33, wherein the plasticizers which have been used are lipophilic diesters of C_6-C_{40} aliphatic or aromatic dicarboxylic acids and C_1-C_8 aliphatic alcohols.

35. Forms of administration according to claim 33, wherein said plasticizer is selected from dibutyl phthalate, diethyl phthalate, dibutyl sebacate, a hydrophilic or lipophilic citric acid ester, polyethylene glycols, propylene glycols, glycerol esters, acylated mono- and diglycerides, medium-chain triglycerides, oleic acid, or a mixture of at least two of these plasticizers.

36. Forms of administration according to claim 35, wherein said hydrophilic or lipophilic citric acid ester is triethyl citrate, tributyl citrate, acetyltributyl citrate, or acetyltriethyl citrate.

37. Forms of administration according to claim 35, wherein said glycerol ester is triacetin.

38. Forms of administration according to any one of claims 33 to 37, wherein the plasticizer is present in amounts of 5 to 50 wt.%, based on the polymeric coating material.

39. Forms of administration according to claim 38, wherein said plasticizer is present in amounts of 10 to 40 wt.%, based on the polymeric coating material.

40. Forms of administration according to claim 38, wherein said plasticizer is present in amounts of 10 to 30 wt.%, based on the polymeric coating material.

41. Forms of administration according to any one of claims 1 to 40, wherein said forms have a sustained-release matrix.

42. Forms of administration according to claim 41, wherein the matrix is based on a hydrophilic matrix material.

43. Forms of administration according to claim 42, wherein said hydrophilic matrix material is a hydrophilic polymer.

44. Forms of administration according to claim 43, wherein said hydrophilic polymer is cellulose ethers, cellulose esters and/or acrylic resins and/or salts, amides and/or esters thereof.

45. Forms of administration according to claim 44, wherein said hydrophilic polymers are ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxymethyl cellulose, poly(meth)acrylic acid and/or salts, amides and/or esters thereof.

46. Forms of administration according to claim 41, wherein the matrix is based on a hydrophobic matrix material.

47. Forms of administration according to claim 46, wherein said hydrophobic matrix material is hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or esters or ethers, or mixtures thereof.

48. Forms of administration according to claim 47, wherein said hydrophobic matrix material is C_{12}-C_{30} fatty acid mono-diglycerides and/or C_{12}-C_{30} fatty alcohols and/or waxes, or mixtures thereof.

49. Forms of administration according to any one of claims 1 to 48, wherein said forms have an enteric coating as an additional coating.

50. Forms of administration according to claim 49, wherein the enteric coating consists of methacrylate acid/methyl methacrylate copolymers with a monomer molar ratio of 1:1 (Eudragit L®), methacrylic acid/methyl methacrylate acrylate copolymers with a monomer molar ratio of 1:2 (Eudragit S®), methacrylic acid/ethyl acrylate copolymers with a monomer molar ratio of 1:1 (Eudragit L30-D55®), methacrylic acid/methyl acrylate/methyl methacrylate with a monomer molar ratio of 7:3:1 (Eudragit FS®), shellac, hydroxypropyl methyl cellulose acetate-succinate, cellulose acetate-phthalate or a mixture of at least two of these components, optionally also in combination with poly(meth)acrylates.

51. Forms of administration according to claim 50, wherein said poly(meth)acrylates is Eudragit NE30D®, and/or Eudragit RL® and/or Eudragit RS®.

52. Forms of administration according to any one of claims 1 to 51, wherein said forms additionally contain the active substance tramadol in non-retarded form.

53. Forms of administration according to any one of claims 1 to 52, wherein their retarded release profile for the active substance tramadol immediately after preparation is stable on storage without tempering.

54. Forms of administration according to any one of claims 1 to 53, wherein the sustained-release coating has been applied from aqueous media and not tempered after conventional drying.

55. Forms of administration according to any one of claims 1 to 54 to be taken once a day, wherein said forms contain 10 to 1200 mg of tramadol.

56. Forms of administration according to claim 55, containing 20 to 1000 mg of tramadol.

57. Forms of administration according to claim 56, containing 100 to 800 mg of tramadol.

58. Forms of administration according to any one of claims 1 to 57 to be taken twice a day, wherein said forms contain 5 to 600 mg of tramadol.

59. Forms of administration according to claim 58, containing 10 to 500 mg of tramadol.

60. Forms of administration according to claim 59, containing 50 to 400 mg of tramadol.

61. Forms of administration of tramadol, provided with at least one sustained-release coating, substantially as hereinbefore described with reference to any one of the examples, but excluding the comparative examples.

62. A method for controlling pain in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

63. A method for treating urinary incontinence in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

64. A method for treating coughs in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

65. A method for treating inflammatory and/or allergic reactions in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

66. A method for treating depression in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

67. A method for treating drug and/or alcohol abuse in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

68. A method for treating gastritis in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

69. A method for treating diarrhoea in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

70. A method for treating cardiovascular disease in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

71. A method for treating respiratory disease in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

72. A method for treating mental illness in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

73. A method for treating epilepsy in a subject, said method comprising administering to said subject a therapeutically effective amount of a form of administration according to any one of claims 1 to 61.

74. A form of administration according to any one of claim 1 to 61, when used for one or more of controlling pain, treating urinary incontinence, treating coughs, treating inflammatory and/or allergic reactions, treating depression, treating drug and/or alcohol abuse, treating gastritis, treating diarrhoea, treating cardiovascular disease, treating respiratory disease, treating mental illness, and treating epilepsy.

Dated 24 February, 2005
Grunenthal GmbH

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Figure 1

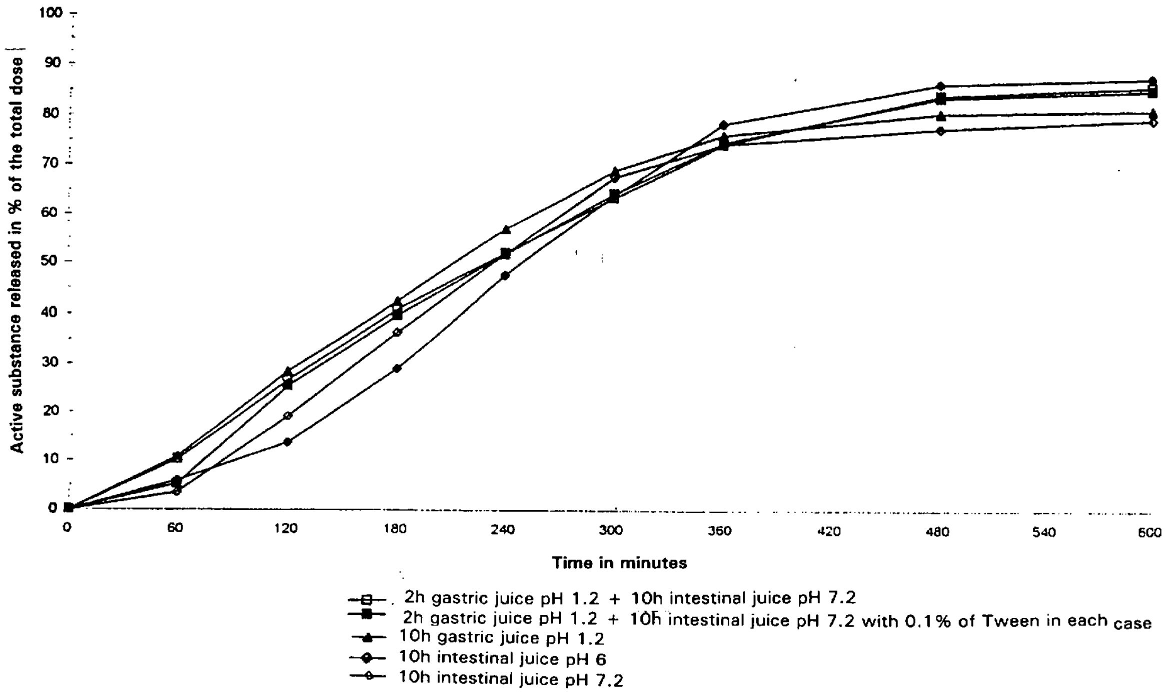

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Figure 2

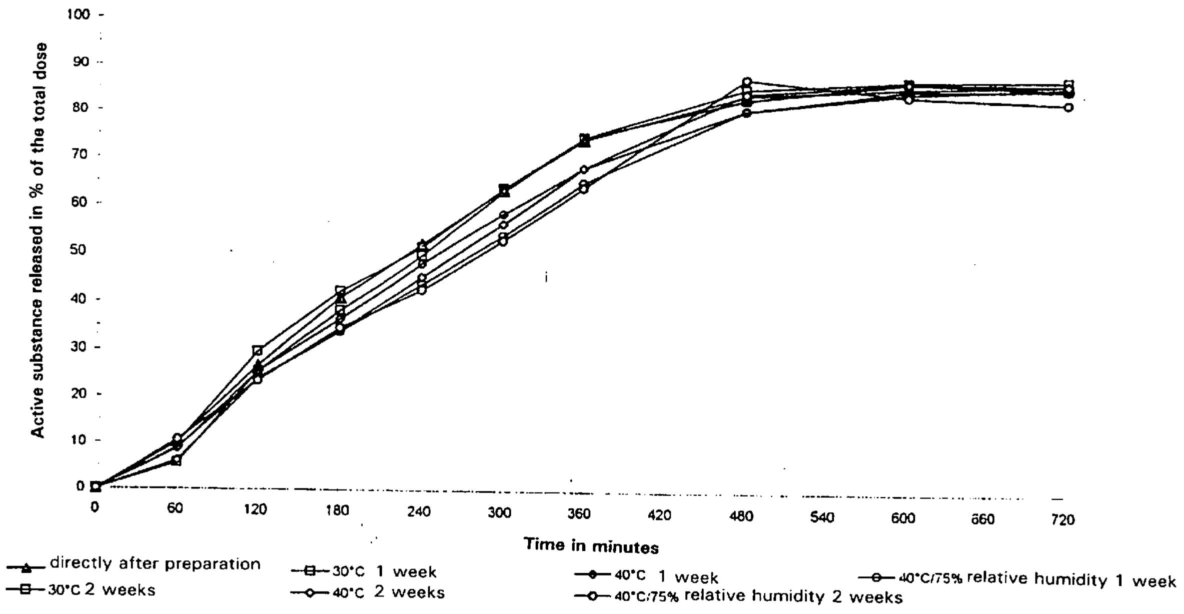

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Figure 3

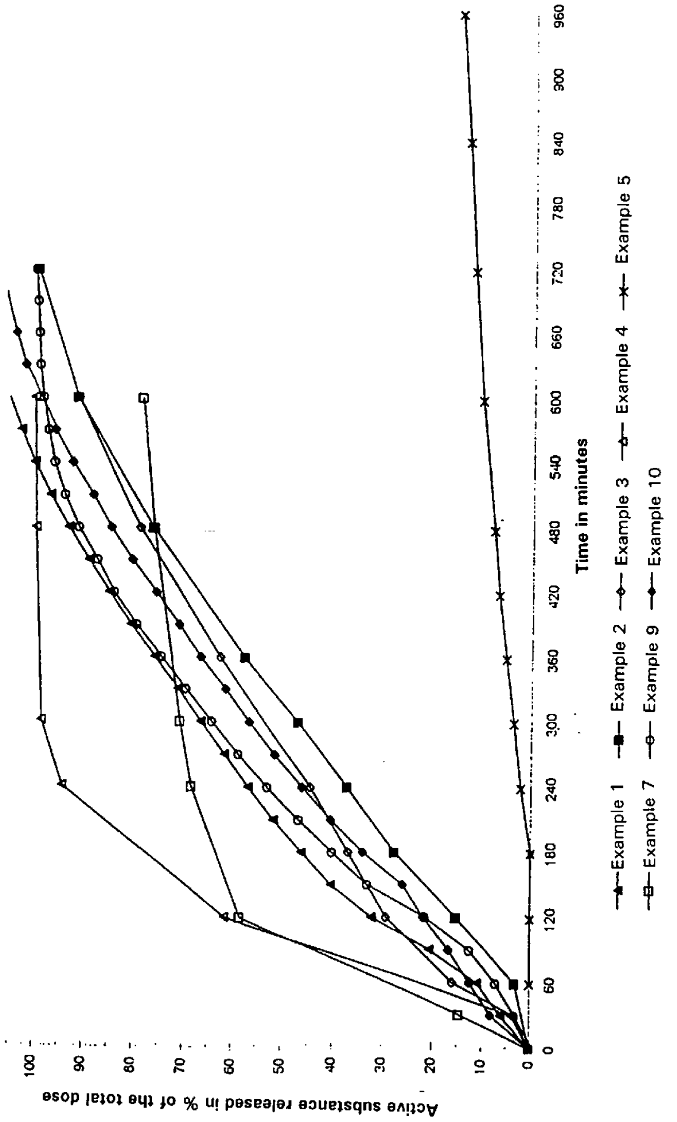

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Figure 4