



(72) BARTHOLOMÄUS, JOHANNES, DE

(72) BETZING, JÜRGEN, DE

(71) GRÜNENTHAL GMBH, DE

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(54) **ANALGESIQUE A DEGAGEMENT DE SUBSTANCE ACTIVE  
CONTROLE**

(54) **ANALGESIC WITH CONTROLLED ACTIVE SUBSTANCE  
RELEASE**

(57) This invention relates to an orally administered preparation with controlled release of at least one analgesic from microtablets with a diameter of < 3 mm.

### Abstract

This invention relates to an orally administered preparation with controlled release of at least one  
5 analgesic from microtablets with a diameter of  $< 3$  mm.

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**Analgesic with controlled active substance release**

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The present invention relates to a pharmaceutical formulation from which the analgesic active substance is released in a controlled manner.

10 Many formulations of analgesic painkillers which provide controlled release of the active substance are known from the prior art.

EP-A-0647448 *inter alia* has thus already described an  
15 analgesically active preparation with delayed active substance release which consists of a plurality of substrates containing opioid in controlled release form having a diameter of 0.1 to 3 mm as a single daily dose. Substrates suitable for this purpose may assume the form of  
20 spheroids, microbeads, pellets or granules. The production of this type of substrate entails relatively elaborate formulation methods, such as for example layer accretion agglomeration processes for pellets or the extrusion/spheronisation process for spheroids.

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There is furthermore a requirement in many therapeutic applications to provide individual doses of a pharmaceutical containing an analgesic, as is possible with orally administered, liquid dosage forms in the form of  
30 drops and to be able to make use of conventional, uncomplicated formulation methods, such as tableting, during the production thereof.

The object of the present invention was accordingly to  
35 provide an orally administered preparation with controlled release of at least one analgesic, which preparation permits individual, precise dosing, comparable to the administration of drops, for example from storage containers or makes it possible to subdivide a certain

quantity of active substance into a readily and accurately controllable number of substrates, and which may be produced using standard, straightforward formulation methods.

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This object is achieved according to the invention by the provision

of an orally administered preparation with controlled  
10 release of at least one analgesic from a microtablet with a diameter of  $< 3$  mm.

These microtablets preferably have diameters of 1 to 3 mm, particularly preferably of 1.5 to 3 mm.

15

The microtablets according to the invention preferably contain at least one opioid as the analgesic active substance. Hydromorphone, oxycodone, morphine, levorphanol, methadone, dihydrocodeine, codeine, fentanyl, dihydro-  
20 morphine, pethidine, piritramide, buprenorphine, tilidine, tramadol, the particular salts thereof or mixtures thereof are preferably used as the opioid.

Tramadol, tramadol hydrochloride, morphine, morphine  
25 hydrochloride and/or morphine sulfate are very particularly preferably used as the analgesic.

Apart from the stated opioid analgesics, the preparation according to the invention may contain non-opioid  
30 analgesics which optionally exhibit a synergistic action with the opioid analgesics. These non-opioid analgesics include ibuprofen, ketoprofen, flurbiprofen, paracetamol, naproxen, propyphenazone, acematacin, acetylsalicylic acid, metamizol and/or the salts thereof.

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The microtablets used according to the invention are distinguished by controlled release of the analgesic.

Controlled release of the analgesic is taken to mean both non-delayed and delayed release. The opioid active substance is preferably released in a delayed manner.

- 5 Release may be achieved by immobilising the active substance in a controlled release matrix. Incorporation into a matrix material ensures that controlled, delayed release of the active substance is achieved over the desired period of time. It is preferably endeavoured to  
10 adjust the release of the active substance in such a manner that it is sufficient to take the preparation twice, preferably only once, per 24 hours.

Suitable matrix materials are pharmaceutically compatible  
15 hydrophilic materials which are known to the person skilled in the art. Polymers, such as for example cellulose ethers, cellulose esters or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose,  
20 hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters, are very particularly preferred as matrix materials.

The matrix material may, however, also consist of  
25 hydrophobic materials, such as for example hydrophobic polymers, waxes, fats, oils, long-chain fatty acids, fatty alcohols or corresponding esters or mixtures thereof. Mono- or diglycerides of  $C_{12}$ - $C_{20}$  and/or  $C_{12}$ - $C_{20}$  fatty alcohols and/or waxes are preferably used as hydrophobic materials.

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It is also possible to use a mixture of the stated hydrophilic and hydrophobic materials as a controlled release matrix material.

- 35 The microtablets according to the invention may furthermore contain pharmaceutically conventional auxiliaries as additional constituents, such as extenders, for example lactose, microcrystalline cellulose or calcium hydrogen phosphate, as well as slip additives, lubricants and flow

control agents, such as for example highly disperse silicon dioxide, talcum, magnesium stearate and/or stearic acid.

A particularly preferred pharmaceutically compatible matrix material comprises at least one cellulose ether and/or cellulose ester, a 2 wt.% aqueous solution of which has a viscosity at 20°C of 3000 to 150000 mPas, preferably of 10000 to 150000 mPas, optionally in combination with an extender which is not swellable in an aqueous medium, such as for example calcium hydrogen phosphate, or with an insoluble extender swellable in an aqueous medium, such as for example microcrystalline cellulose, or an extender soluble in aqueous media, such as for example lactose.

The content of analgesic, preferably of opioid analgesic, is adjusted as a function of the desired duration of release and quantity of analgesic to be released. The active substance content is preferably between 10 and 85 wt.%, particularly preferably between 25 and 70 wt.%, relative to the complete mixture. On the basis of the action of opioid and non-opioid analgesics, the person skilled in the art is aware of the mixing ratios in which these should be used in order to achieve the desired release of active substances.

In the case of the preparations according to the invention, which comprise microtablets, controlled release of the active substance may also be achieved by coating the individual tablets with at least one coating which permits controlled, generally delayed, release of the active substance in an aqueous medium. Suitable controlled release coatings comprise water-insoluble waxes or polymers, such as for example acrylic resins, preferably poly(meth)acrylates or water-insoluble celluloses, preferably ethylcellulose. These materials are known from the prior art, for example Bauer, Lehmann, Osterwald, Rothgang "Überzogene Arzneiformen", Wissenschaftliche Verlags-gesellschaft mbH, Stuttgart, 1998, pages 69 et seq., and are hereby included by way of reference.

In addition to the water-insoluble polymers, it is optionally possible to adjust the active substance release rate by preferably also using quantities of up to 30 wt.% of non-controlled release, preferably water-soluble polymers, such as for example polyvinylpyrrolidone or water-soluble celluloses, preferably hydroxypropylmethylcellulose or hydroxypropylcellulose, and/or known plasticisers.

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In addition to the controlled release coating, the microtablets according to the invention may additionally be provided with further coatings. It is thus possible to apply a coating containing the active substance, from which coating the active substance is released in a non-controlled manner after oral administration. Such multilayer microtablets may after administration very rapidly provide an initial dose of the analgesic for alleviating the pain, wherein the level of the analgesic may be maintained by the subsequent delayed release of the active substance.

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Apart from the controlled release coating, the microtablets may furthermore also additionally have a coating which dissolves in a pH-dependent manner. It is thus possible, for example, to ensure that a certain number of the microtablets of a preparation pass undissolved through the gastric tract and are not released until they reach the intestinal tract.

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Another preferred embodiment of the preparations according to the invention consists in the microtablets', which are provided with a controlled release and optionally further coatings, already containing the active substance in a matrix which ensures controlled, delayed release of the active substance, or in the matrix controlled release microtablets' having no controlled release coating, but at least one of the stated coatings which ensure an initial dose and/or pH-dependent release.

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The microtablets are produced using known methods, as are described, for example, in EP-A-0166315. The corresponding disclosure is hereby included by way of reference.

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The microtablets are preferably produced by screening all the tablet constituents, preferably through a 0.6 mm screen, and then homogeneously mixing them. The mixture may be converted into granules, wherein the screening step is  
10 then preferably performed after granulation. Where granulation is performed, slip additives and/or lubricants are preferably incorporated before compression. The homogeneous mixture is compression moulded in a tabletting press, preferably a rotary tabletting press, to form  
15 tablets having a diameter of 1 to 3 mm, preferably of 1.5 to 3 mm. This method is preferably also performed when producing microtablets with matrix controlled release, wherein melt granulation is a preferred production process for hydrophobic matrix materials fusible at  $< 100^{\circ}\text{C}$ . Methods  
20 suitable for this purpose are known to the person skilled in the art.

In the event that the preparations according to the invention contain microtablets with coatings, these may be  
25 applied using conventional methods, such as for example by sugar coating, spraying with solutions, dispersions or suspensions, by melt processing or by powder application processes.

30 The orally administered preparations according to the invention consisting of microtablets moreover have the major advantage that the desired dose of analgesic may be subdivided into a straightforwardly countable number of units. In this manner, it is possible to formulate the  
35 orally administered preparation in accordance with individual patient requirements by, for example, taking the desired number of microtablets from a supply of microtablets using a metering unit, preferably a dispenser,

in accordance with the individual duration of release and quantity of analgesic for release which are to be achieved.

- The present invention accordingly also provides
- 5 individually meterable, orally administered preparations, the number of microtablets of which is determined in accordance with the individually desired duration of release and quantity of analgesic for release.
- 10 The present invention also provides the orally administered preparations according to the invention in capsules which contain a defined number of the microtablets with controlled release of the analgesic in accordance with the individual duration of release and quantity of analgesic
- 15 for release which are to be achieved. The number of microtablets in a capsule is preferably selected such that the dose is sufficient for administration once or twice daily. It is advantageous in this dosage form too for the dose of the analgesic to be subdivided between a
- 20 straightforwardly countable number of microtablets, but the patient is relieved of the task of counting by the dose being determined in a capsule.

- The orally administered preparations according to the
- 25 invention may furthermore assume the form of a so-called macrotablet, *i.e.* a tablet of conventional dimensions, into which a defined number of microtablets in accordance with the individual duration of release and quantity of analgesic for release which are to be achieved are
- 30 compression moulded with conventional tablet auxiliaries and additives to form a tablet. In this case, too, it is advantageous if the number of microtablets constituting the macrotablet is selected such that the duration of release and quantity of analgesic for release is sufficient for
- 35 administration once or twice daily.

The present invention accordingly also provides orally administered preparations with controlled release of at least one analgesic comprising microtablets, wherein a

certain number of microtablets in accordance with the individual duration of release and quantity of analgesic for release which are to be achieved are compression moulded with conventional auxiliaries and additives to form  
5 a tablet.

### Examples

The release profile of the preparations produced in the Examples was determined as follows:

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The preparations were placed in 600 ml of artificial gastric juices (pH 1.2) in a rotating basket apparatus (according to the European Pharmacopoeia) at a temperature of the release medium of 37°C and a rotational speed of the  
10 rotating basket of 100 min<sup>-1</sup>. After 120 minutes, the pH value of the release medium was raised to pH 7.2 by addition of phosphate buffer solution. This pH value was maintained until the end of the testing. The quantity of active substance released at a particular point in time is  
15 determined spectrophotometrically.

#### Example 1:

##### Composition:

		per tablet	per capsule containing 10 tablets
Components of the micro- tablets	Tramadol HCl	10.0 mg	100 mg
	Microcrystalline cellulose	4.0 mg	40 mg
	Povidon® K30	0.8 mg	8 mg
	Magnesium stearate	0.2 mg	2 mg
Total		15 mg	150 mg

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The tramadol salt and microcrystalline cellulose were granulated with an aqueous solution of Povidon® K30, dried, screened, mixed with magnesium stearate, compression moulded to form tablets having a diameter of 3 mm and a  
25 height of approx. 2 mm and packaged in capsules each containing 10 tablets.

The release profile was as follows:

after 15 minutes > 80% active substance release.

### Example 2:

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#### Composition:

		per tablet	per capsule containing 10 tablets
Components of the micro- tablets	Tramadol HCl	10.0 mg	100 mg
	Microcrystalline cellulose	4.0 mg	40 mg
	Povidon® K30	0.8 mg	8 mg
	Magnesium stearate	0.2 mg	2 mg
Coating components	Ethylcellulose (Aquacoat®)	0.8 mg	8 mg
	Dibutyl sebacate	0.2 mg	2 mg
Total		16 mg	160 mg

The tramadol salt and microcrystalline cellulose were granulated with an aqueous solution of Povidon® K30 (poly-  
 10 vinylpyrrolidone), dried, screened, mixed with magnesium  
 stearate, compression moulded to form tablets having a  
 diameter of 3 mm and coated with an aqueous ethylcellulose/  
 dibutyl sebacate dispersion in a 4:1 quantity ratio in a  
 fluidised bed apparatus by spraying on the dispersion with  
 15 continuous drying. 10 microtablets were packaged in each  
 capsule.

The average release profile was:

Time after	Active substance release in % of original active substance concentration
30 minutes	1%
240 minutes	18%
480 minutes	29%

### Example 3:

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Microtablets of a diameter of 2 mm and height of approx. 2 mm of the following composition were produced and coated in a similar manner to Example 2. 20 microtablets were packaged in each capsule.

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		per tablet	per capsule containing 20 tablets
Components of the micro-tablets	Tramadol HCl	5.0 mg	100 mg
	Microcrystalline cellulose	2.0 mg	40 mg
	Povidon® K30	0.4 mg	8 mg
	Magnesium stearate	0.1 mg	2 mg
Coating components	Ethylcellulose (Aquacoat®)	0.4 mg	8 mg
	Dibutyl sebacate	0.1 mg	2 mg
Total		8.0 mg	160 mg

### Example 4:

Matrix controlled release microtablets were produced by screening tramadol HCl (5 mg/tablet) and glyceryl behenate (Compritol 880 ato®) (5 mg/tablet) through a 0.6 mm mesh screen. The homogenised mixture was then compression moulded with 2 mm punches to form corresponding microtablets. These exhibited the following release profile:

20

Time after	Active substance release in % of original active substance concentration
60 minutes	40%
120 minutes	60%
240 minutes	75%
480 minutes	85%

## Patent Claims

1. Orally administered preparation with controlled  
release of at least one analgesic from microtablets  
with a diameter of  $< 3$  mm.
2. Preparation according to claim 1, characterised in  
that the microtablets have a diameter of 1 to 3 mm,  
preferably of 1.5 to 3 mm.
3. Preparation according to claim 1 or 2, characterised  
in that the analgesic is at least one opioid.
4. Preparation according to claim 3, characterised in  
that hydromorphone, oxycodone, morphine, levorphanol,  
methadone, dihydrocodeine, fentanyl, codeine, dihydro-  
morphine, pethidine, piritramide, buprenorphine,  
tilidine, tramadol, the particular salts thereof or  
mixtures thereof are used as the opioid.
5. Preparation according to claim 4, characterised in  
that tramadol, tramadol hydrochloride, morphine,  
morphine hydrochloride and/or morphine sulfate are  
used as the opioid.
6. Preparation according to one or more of claims 1 to 5,  
characterised in that the microtablets contain the  
analgesic uniformly distributed in a controlled  
release matrix.
7. Preparation according to claim 6, characterised in  
that the matrix comprises at least one polymer, a wax,  
a fat, an oil, a fatty acid, a fatty alcohol or a  
corresponding ester.
8. Preparation according to claim 7, characterised in  
that that cellulose ethers, cellulose esters and/or  
acrylic resins are used as the polymers.

9. Preparation according to one of claims 6 to 8,  
characterised in that ethylcellulose, hydroxypropyl-  
methylcellulose, hydroxypropylcellulose,  
hydroxymethylcellulose, mono- and/or diglycerides of  
5 C<sub>12</sub>-C<sub>18</sub> fatty acids and/or C<sub>12</sub>-C<sub>18</sub> fatty alcohols are  
used as the matrix material.
10. Preparation according to one of claims 1 to 5,  
characterised in that the microtablets are provided  
10 with at least one coating.
11. Preparation according to claim 10, characterised in  
that the coating provides controlled release.
- 15 12. Preparation according to claim 10 or 11, characterised  
in that the coating is based on a water-insoluble  
polymer or wax.
13. Preparation according to claim 12, characterised in  
20 that an acrylic resin or cellulose derivative,  
preferably alkylcellulose, is used as the polymer.
14. Preparation according to claim 13, characterised in  
that ethylcellulose and/or a poly(meth)acrylate is  
25 used as the coating material.
15. Preparation according to one or more of claims 1 to  
14, characterised in that the microtablets are in a  
capsule.  
30
16. Preparation according to claim 15, characterised in  
that the capsules each contain a defined number of  
microtablets in accordance with the individual  
duration of release and quantity of analgesic for  
35 release which are to be achieved.
17. Preparation according to claim 16, characterised in  
that the number of microtablets in the capsule is  
sufficient for administration once or twice daily.

18. Preparation according to one of claims 1 to 14,  
characterised in that the microtablet(s) may be taken  
from a supply of microtablets using a metering unit,  
preferably a dispenser, in a countable number in  
accordance with the individual duration of release and  
quantity of analgesic for release which are to be  
achieved.
19. Preparation according to one or more of claims 1 to  
14, characterised in that a certain number of  
microtablets in accordance with the individual  
duration of release and quantity of analgesic for  
release which are to be achieved are compression  
moulded with conventional auxiliaries and additives to  
form a tablet.
20. Preparation according to one or more of claims 1 to 5,  
characterised in that more than 75% of the analgesic  
is released within 30 minutes.

**Fetherstonhaugh & Co.**  
**Ottawa, Canada**  
**Patent Agents**