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(72) Feltalálók(k): <b>Brögmann, Bianca, 64289 Darmstadt (DE)</b> <b>Mühlau, Silke, 88400 Biberach / Riss (DE)</b> <b>Spitzley, Christof, 65627 Elbtal (DE)</b>	(74) Képviselő: <b>SBGK Szabadalmi Ügyvivői Iroda, Budapest</b>

(54) **Oxicodont és naloxont tartalmazó gyógyszerkészítmény**

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(54) **Pharmaceutical preparation containing oxycodone and naloxone**

Pharmazeutische Zubereitung mit Oxycodon und Naloxon

Préparation pharmaceutique contenant de l'oxycodone et de la naloxone

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(73) Proprietor: **EURO-CELTIQUE S.A.**  
**2350 Luxembourg (LU)**

(72) Inventors:  
• **Brögmann, Bianca**  
**64289 Darmstadt (DE)**  
• **Mühlau, Silke**  
**88400 Biberach / Riss (DE)**  
• **Spitzley, Christof**  
**65627 Elbtal (DE)**

(74) Representative: **Bühler, Dirk**  
**Maiwald Patentanwalts GmbH**  
**Elisenhof**  
**Elisenstraße 3**  
**80335 München (DE)**

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**WO-A1-99/32120 DE-A1- 4 325 465**  
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**Description**

**[0001]** The invention concerns an oral sustained release pharmaceutical preparation comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof as claimed for use in the treatment of pain and for use in the concurrent reduction of opioid induced obstipation.

**[0002]** The treatment of severe pain which results from diseases such as cancer, rheumatism and arthritis is central to the treatment of these diseases. The range of pain felt by tumor patients comprises pain of the periosteum and of the bone itself, as well as visceral pain and pain in soft tissues. All such pain forms render the daily life of patients intolerable and often lead to depressive states. Successful pain therapy resulting in a lasting improvement of quality of life for the patients is therefore equally important to the success of a comprehensive therapy, as is the treatment of the actual causes of the disease.

**[0003]** Regarding the importance of a successful pain therapy, the World Health Organization (WHO) has developed a 4-step model for the treatment of patients with tumor pain. This model has proven to be effective in daily routine practice and can be extended to patients suffering from chronic pain or pain forms which result from diseases other than cancer. Depending on the intensity, quality and localization of pain, four steps are distinguished during this therapy, with each next step being indicated if the effect of the pain relief agent used until then is no longer sufficient (Ebell, H. J.; Bayer A. (Ed.): Die Schmerzbehandlung von Tumorpatienten, Thieme 1994 (Supportive Maßnahmen in der Onkologie, Band 3) and Zech, D.; Grond, S.; Lynch, J.; Hertel, D.; Lehmann, K.: Validation of World Health Organisation Guidelines for Cancer Pain Relief: a 10-year prospective study, Pain (1995), 63, 65-76).

**[0004]** According to this 4-step model of the WHO, opioid analgesics take a central role in treating pain. The group of opioid analgesics comprises, besides morphine which represents the prototype of these pharmaceutically active agents, also oxycodone, hydromorphone, nicomorphine, dihydrocodeine, diamorphine, papaveretum, codeine, ethylmorphine, phenylpiperidine and derivatives thereof; methadone, dextropropoxyphene, buprenorphine, pentazocine, tilidine, tramadol and hydrocodone. The ATC-Classification (Anatomical Therapeutic Chemical Classification) of the WHO indicates whether the pharmaceutically active agent represents an opioid analgesic, or not. The pronounced pain-relieving effect of opioid analgesics is due to the imitation of the effect of endogenous, morphine-like acting substances ("endogenous opioids"), whose physiological function is to control the reception and processing of pain stimuli.

**[0005]** Opioids repress the propagation of pain stimuli. Besides the immediate inhibition of neuronal excitatory signal transduction in the spinal cord caused by opioids, an activation of such nerve tracts is relevant, which project from the brainstem into the spinal cord. This activation results in an inhibition of pain propagation in the spinal cord. Moreover, opioids limit the pain reception of the thalamus and by affecting the limbic system they influence the affective pain evaluation.

**[0006]** Opioid receptors are found at different sites in the body. Receptors of the intestine and brain are of particular importance for pain therapy by opioids, especially as their occupation results in different side effects.

**[0007]** Opioid analgesics are considered to be strong agonists if they bind with high affinity to opioid receptors and induce a strong inhibition of pain reception. Substances that also bind with high affinity to opioid receptors, but that do not provoke a reduction of pain reception and which thereby counteract the opioid agonists, are designated as antagonists. Depending on the binding behaviour and the induced activity, opioids can be classified as pure agonists, mixed agonists/antagonists and pure antagonists. Pure antagonists comprise, for example, naltrexone, naloxone, nalmefene, nalorphine, nalbuphine, naloxoneazinen, methylnaltrexone, ketylcyclazocine, norbinaltorphimine, naltrindol, 6- $\beta$ -naloxol und 6- $\beta$ -naltrexol (Forth W.; Henschler, D.; Rummel W.; Starke, K.: Allgemeine und Spezielle Pharmakologie und Toxikologie, 7. Auflage, 1996, Spektrum Akademischer Verlag, Heidelberg Berlin Oxford).

**[0008]** Due to their good analgesic efficiency compounds such as oxycodone, tilidine, buprenorphine und pentazocine, have been used in the form of medicaments for pain therapy. Medicaments such as Oxygesic® (wherein oxycodone is the analgesic active compound) und Valoron® (wherein tilidine is the analgesic active compound) have proven valuable for pain therapy.

**[0009]** However, use of opioid analgesics for pain therapy might go along with undesirable side effects. Thus, long-term use of opioid analgesics can lead to psychological and physical dependence.

**[0010]** Especially the physical dependence of patients suffering from pain to opioid analgesics leads to the development of tolerance, meaning that upon extended intake, increasingly higher doses of the pain relieving agent have to be taken by the patient, in order to experience pain relief. The euphoregenic effect of opioid analgesics often leads to the abuse of pain relievers. Drug abuse and psychological dependence are a common phenomenon, especially among teenagers. These dangerous effects are especially caused by the substances with strong analgesic capacity, and can range from undesired habituation to fully developed addiction. However, these substances are legitimately used for medical purposes and medicine cannot do without them.

**[0011]** Besides the mentioned disadvantages, the use of potent opioid analgesics for pain therapy often also lead to undesirable side effects, such as obstipation, breath depression, sickness and sedation. Less frequently, the urge or the disability to pass water are observed. Different attempts have been made to counteract the habituation processes

and the other side effects occurring during pain therapy. This can be done, e.g. by traditional treatment methods. In the case of drug addiction this might be a drug withdrawal treatment, and in the case of obstipation, this might be done by administration of laxatives.

**[0012]** Other attempts aim at minimizing the addictive and habituation forming potential of opioid analgesics, as well as their other side effects by the administration of antagonists which counteract the opioid analgesic. Such antagonists might be naltrexone or naloxone.

**[0013]** There have been numerous proposals and suggestions, how the application of the aforementioned active compounds could be used to avoid undesired habituation and dependence, or even addiction.

**[0014]** US Patent Nos. 3,773,955 und 3,966,940 suggested to formulate analgesics in combination with naloxone, in order to prevent dependence-promoting effects such as euphoria and the like, upon parenteral application. The avoidance of side effects such as obstipation has not been addressed.

**[0015]** To limit the parenteral abuse of oral application forms, US Patent No. 4,457,933 suggested the combination of morphine with naloxone in defined ranges. The avoidance of side effects such as obstipation has also not been mentioned.

**[0016]** US Patent No. 4,582,835 describes, again in order to avoid abuse, a preparation comprising a combination of buprenorphine and naloxone, that is to be administered either parenterally or sublingually.

**[0017]** European application EP 0 352 361 A1 concerns the treatment of obstipation during pain therapy by the oral application of an opioid analgesic and one antagonist, with the antagonist being a pro-drug form of either naltrexone or naloxone. Avoidance of abuse of the opioid analgesic is not an issue in this application.

**[0018]** German patent application DE 43 25 465 A1 also concerns the treatment of obstipation during pain therapy using a preparation which comprises an opioid analgesic and an antagonist. The characterizing feature of this disclosure is that the antagonist which can be naloxone, has to be present in higher amounts than the opioid analgesic which is preferably morphine. This is to ensure that the antagonist unfolds its anti-obstipation effect without reducing the analgesic activity of the agonist. The avoidance of abuse of the opioid analgesic is not an issue in this application.

**[0019]** In order to avoid side effects such as obstipation and breath depression during pain therapy, preparations have been introduced on the market which can be taken orally and comprise an opioid analgesic and the opioid antagonist, naloxone. The medicament Talwin® of Windrop/Sterling comprises pentazocine and naloxone. The medicament Valoron® of Gödeke comprises a tilidine-naloxone combination.

**[0020]** Besides the potent analgesic effect, the reduction of addictive potential and the avoidance of side effects, medicaments usable for a successful pain therapy should provide for additional characteristics.

**[0021]** Generally, medicaments have to be formulated in a way that the active compounds are stable as long as possible, under standard storage conditions. Medicaments have also to be formulated in a way that the intended release profiles of the active compounds do not change upon long-term storage.

**[0022]** Additionally, (also in the case of agonist/antagonist-combinations) the release profile of each single active compound should be selectable as required. The measures applied in order to achieve this should not hamper or even prevent that the release profiles of additional active compounds (e.g. in the case of combinations of different active compounds) can be chosen as required. Consequently, there should be no mutual dependency of the release profiles.

**[0023]** Medicaments suitable for pain therapy should either contain the active compounds in such amounts or be formulated in such ways that they have to be taken by the patients only rarely. The easier the application scheme for a pain reliever is, and the more evident it is for the patient why and how often he should take which tablet, the more exactly he will adhere to the physician's orders. The necessity to take the pain reliever only infrequently, will result in a high willingness of the patient to take the pain reliever (compliance).

**[0024]** Through the use of so called sustained-release formulations, i.e. formulations of medicaments from which the active compounds are released over an extended period of time, it has been tried to lower the frequency by which pain relieving medicaments have to be taken, and thereby to increase the compliance of patients. Such sustained-release formulations also make sense in that the sustained release of an opioid analgesic reduces the addictive potential of this active compound.

**[0025]** This is due to the fact that the addictive potential of an active compound is not defined by the compound itself, but rather by the way it is administered and the pharmaco-dynamics resulting therefrom. Besides the psychotropic effect of an opioid, the rate by which the brain encounters an opioid, is more decisive criterion for the risk of dependency than the active compound itself (Nolte, T.: STK-Zeitschrift für angewandte Schmerztherapie, 2001, Vol. 2).

**[0026]** The medicament Oxygesic® of Purdue is a preparation from which the opioid analgesic oxycodone is released in a sustained manner. Due to this formulation, the frequency by which the medicament has to be taken as well as the addictive potential is lowered, however the side effects remain and the danger of developing addiction cannot be excluded, as Oxygesic® does not contain opioid-antagonists.

**[0027]** According to the already mentioned European patent application EP 0 352 361 A, neither the opioid analgesic nor the antagonist are formulated to be released in a sustained manner. Accordingly, the time period during which such preparations are effective is limited and preparations have to be taken multiple times per day. The desired compliance of the patient is not achieved. This application also does not disclose the advantages of formulations of preparations

that are characterized by a time-stable and independent release of the active compounds. The storage stability of such preparations is also not addressed by this disclosure.

5 [0028] German patent application DE 43 25 465 A1 discloses formulations according to which obstipation occurring during pain therapy is prevented by the sustained release of the opioid agonist while the antagonist, which is present in excess must not be released in a sustained manner. Due to the high First-Pass-Effect of naloxone, comparably large amounts of this compound have therefore to be used. This application discloses neither the advantages nor the formulations of preparations, which are characterized by time-stable and independent release of the active compounds. The storage stability of such preparations is also not an issue of this disclosure. A doctor using preparations according to this disclosure has therefore to carry out extensive titration experiments each time he wants to increase the dosage.

10 [0029] The company Gödeke offers, under the trademark Valoron®, a pain reliever that comprises a tilidine-naloxone-combination. According to the product literature, a formulation is used from which both active compounds are released in a sustained manner. The matrix used comprises a relevant part of water-swellable material (HPMC) and has therefore to be considered as a swellable (and possibly partially erosive) diffusion matrix. A disadvantage of this known formulation is that tilidine and naloxone, given identical mass ratios but different absolute amounts, show different release profiles. 15 The release rates of the agonist and the antagonist are not independent from each other, which is probably due to the sustained release formulation used. Accordingly, it is necessary for the physician to carry out extensive titration experiments for each individual patient if he wants to increase the dosage even though he does not change the mass ratio of tilidine:naloxone, as he cannot assume that the release profiles of both components will remain constant. The range of therapeutically usable amounts of the analgesic that are available to the doctor is therefore limited.

20 [0030] WO 99/32119 discloses oral dosage forms comprising a combination of an orally analgesically effective amount of an opioid agonist and an orally active opioid antagonist, the opioid antagonist being included in a ratio to the opioid agonist to provide a combination product which is analgesically effective when the combination is administered orally, but which is aversive in a physically dependent subject.

25 [0031] WO 99/32120 relates to a method of preventing abuse of opioid dosage form and is *inter alia* concerned with a method of reducing the abuse potential of an oral dosage form of an opioid analgesic, wherein an analgesically effective amount of an orally active opioid agonist is combined with an opioid antagonist into an oral dosage form which would require at least a two-step extraction process to be separated from the opioid agonist, the amount of opioid antagonist included being sufficient to counteract opioid effects if extracted together with the opioid agonist and administered parenterally.

30 [0032] WO 01/58447 discloses controlled-release dosage forms containing an opioid agonist and an opioid antagonist and a controlled release material, which, during a dosing interval, releases an analgesic or sub-analgesic amount of the opioid agonist along with an amount of said opioid antagonist effective to attenuate a side effect of said opioid agonist.

35 [0033] US 4 457 933 concerns a method for decreasing both the oral and parenteral abuse potential of strong analgetic agents such as oxycodone, propoxyphene and pentazocine by combining an analgesic dose of the analgetic agents with naloxone in specific, relatively narrow ranges.

[0034] WO 03/007802 discloses a pharmaceutical composition comprising from 10 to 40 mg of oxycodone or a pharmaceutically acceptable salt thereof and 0.65 to 0.90 mg naloxone or a pharmaceutically acceptable salt thereof.

40 [0035] US 3 966 940 relates to orally effective, analgetic compositions which are useful in the prevention of drug abuse because upon parenteral administration, they do not produce analgesia, euphoria, or physical dependence. Composition according to this prior art comprise an orally active, strong analgetic in oral dosage form and contain for each analgetic dose of the analgetic agent an amount of naloxone sufficient, upon parenteral administration of said oral dosage form, to negate the analgetic, euphoretic and dependence producing action of the composition, but insufficient to block the therapeutic effect of the analgetic when the admixture is taken orally.

45 [0036] WO 02/0902060 is concerned with abuse-resistant controlled release opioid tablets in combination containing an opioid antagonist such as naloxone at a level above that needed to suppress the euphoric effect of the opioid, if the combination were crushed to break the controlled release properties causing the opioid and opioid antagonist to be released as a immediate release product as a single dose.

50 [0037] It is one of the objectives of the present invention to provide a pharmaceutical preparation for use in pain therapy that, given a high analgesic activity, is characterized by a reduced abuse potential and for use in the reduction of obstipation, said preparation also being characterized by a reduced administration frequency and therefore providing increased compliance, as well as the ability for individual adaptation of the dosage for each patient. A further objective of the present invention is to provide formulations for pharmaceutical preparations for use in pain therapy and for use in the reduction of obstipation that make sure that the active compounds of said pharmaceutical preparations are stable over a long storage time, and that the release of the active compounds remain reproducibly invariant and independent 55 from each other even after long-term storage.

[0038] The feature combination of the independent claim serves to attain these objectives. Preferred embodiments of the invention are defined in the subclaims.

[0039] According to the invention, the objectives are attained by providing an oral sustained release pharmaceutical

preparation comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof as claimed in independent claim 1 for use in the treatment of pain and for use in the concurrent reduction of opioid induced obstipation.

5 [0040] By the combination of oxycodone (in an analgesically effective amount) and naloxone it is ensured that preparations according to the invention show an efficient analgesic activity and that at the same time, obstipation is reduced. The matrix formulation disclosed herein, which is stable over extended periods of time, ensures permanently that agonist as well as antagonist are always released in predetermined percentages and that their release rates do not influence each other. Thereby, abuse of the medicament, which requires that the oxycodone can selectively be extracted from the formulation, is prevented. The formulation according to the invention disables selective extraction of the agonist from 10 the preparation without the corresponding amount of the antagonist, independent of the absolute and relative amounts of agonist and antagonist chosen.

15 [0041] Moreover, the formulation of a medicament disclosed herein ensures that, given identical relative amounts, the active compounds show equal release profiles, independent of the absolute amount present. Such an independent release behaviour provides a wide range of useable absolute amounts of the analgesic active substance to the physician, given that the optimal agonist/antagonist ratio is known. Thus, it is possible to comfortably adjust the dosage for each individual patient, either by a step-wise dosage increase or, if necessary, a step-wise dosage reduction. This ability to adjust the dosage for the individual patient is extremely useful from a medical point of view.

20 [0042] The formulations for use according to claim 1 are characterized by a low administration frequency, so that high patient compliance is achieved. Furthermore, preparations according to the invention allow the doctor to adjust the dosage for individual patients. Preparations according to the invention enable use over a broad range with respect to the useable absolute amounts of the active compounds and ensure that the active compounds, even after long-term storage, become effective with equal release profiles.

25 [0043] According to the present invention, sustained release of active compounds means that pharmaceutically active substances are released from a medicament over a longer period of time than they are from known formulations for immediate release. Preferably, the release takes place over a time period of two to twenty four hours, of two to twenty hours, especially preferred over a time period of two to sixteen hours or two to twelve hours, with the specifications satisfying the legal and regulating requirements.

30 [0044] According to the invention, formulations of medicaments that ensure such a sustained release of the active compounds from the preparation, are designated as retard formulations, as sustained release formulations or as prolonged release formulations. In the context of the instant invention, "sustained release" does not mean that the active compounds are released from the formulation or the medicament in a pH-dependent manner. According to the invention, the release of the active compounds rather occurs in a pH-independent manner. According to the invention, the term "sustained release" refers to the release of active compounds from a medicament over an extended period of time. It does not imply the controlled release at a defined place; therefore, it does not mean that the active compounds are either 35 released only in the stomach, or only in the intestine (of course, such a release at a defined place could individually be achieved by, e.g., enteric coating of the medicament. However, this presently seems not to be advantageous).

40 [0045] According to the invention, "independent release" means that, given the presence of at least two active compounds, a change of the absolute amount of one compound does not influence the release profiles of the other compounds so that the release profiles of the other compounds are not changed. For formulations according to the invention such an independent release behaviour is independent of the pH value, for which the release is measured, or of the production process. The pH independency particularly applies to the acidic range, i.e. for pH values < 7. The release profile (or release behaviour) is defined as the change of the release of the active compound from the formulation with time, with the amount of each active compound released provided in percents of the total amount of the active compound. The release profile is determined by known tests.

45 [0046] Specifically, this means that for example the release profile of oxycodone, as it is observed for an oxycodone/naloxone-combination with 12 milligrams oxycodone and 4 milligrams naloxone, does not change, if a corresponding preparation with the same formulation contains 12 milligrams oxycodone, but 6 milligrams naloxone.

50 [0047] The independent release feature preferably refers to the situation where preparations of substantially equal composition are compared for the release profile. Preparations of substantially equal composition have different amounts of the active compounds but are otherwise basically the same with respect the components of the composition which essentially influence the release behaviour.

55 [0048] If e.g. the above-mentioned preparations are compared (with the first preparation comprising 12 mg oxycodone and 4 mg naloxone and the second preparation comprising 12 mg oxycodone and 6 mg naloxone) both preparations, provided that they have the same total weight, will provide for the same release profile for oxycodone and naloxone if the difference in the naloxone amount is replaced by a component in the formulation that typically does not influence the release behaviour. As shown in the Example section, the difference in the amount of naloxone may be replaced by a typical pharmaceutically inert filler such as lactose without changing the release profiles.

[0049] The person skilled in the art is well aware that if the amount of the active compound in which two preparations

differ is replaced by a substance that is essential for the release behaviour of the formulation, such as ethylcellulose or a fatty alcohol, differences in the release behaviour may occur. Thus, the independent release feature preferably applies to formulations that have different amounts of the active compounds but are otherwise identical or at least highly similar with respect to the components that essentially influence the release behaviour (given that formulations of the same total weight are compared).

**[0050]** According to the invention, "invariant release behaviour" or "invariant release profile" is defined so that the percentage of the absolute amount of each active compound released per time unit does not significantly change and remains sufficiently constant (and thus does not substantially change) if absolute amounts are changed. Sufficiently constant percentages mean that the percentage released per time unit deviates from a mean value by not more than 20%, preferably by not more than 15% and especially preferably by not more than 10%. The mean value is calculated from six measurements of the release profile. Of course, the amount released per time unit has to satisfy the legal and regulatory requirements.

**[0051]** Specifically, this means for example that given an oxycodone/naloxone combination of 12 mg oxycodone and 4 mg naloxone, during the first 4 hours 25% oxycodone and 20% naloxone are released. If the oxycodone/naloxone combination instead contains 24 mg oxycodone and 8 mg naloxone, during the first 4 hours also 25% oxycodone and 20% naloxone will be released. In both cases the deviation will not be more than 20% from the mean value (which in this case is 25% oxycodone and 20% naloxone).

**[0052]** As outlined for the independent release behaviour, the invariant release feature also preferably refers to a situation where preparations of substantially equal composition are compared. Such preparation differ with respect to the amount of the active compounds, but are of the same or at least highly similar composition with respect to the release-influencing components of the preparation. Typically, the difference in the amount of an active compound will be replaced by the amount of a pharmaceutical inert excipient which does not substantially influence the release behaviour of the preparation. Such a pharmaceutical excipient may be lactose, which is a typical filler in pharmaceutical preparations. The person skilled in the art is well aware that the invariant release feature may not apply to preparations where the difference in the amount of an active compound is replaced by substances that are known to essentially influence the release behaviour of the preparation, such as ethylcellulose or fatty alcohols.

**[0053]** In the Example section it is set out that if one preparation comprises 20 mg oxycodone and 1 mg naloxone or 20 mg oxycodone and 10 mg naloxone, with the difference in naloxone being replaced by lactose, that the two preparations of identical weight provide for the same release profiles, so that they exhibit a sustained, invariant and independent release behaviour.

**[0054]** According to the invention "storage stable" or "storage stability" means that upon storage under standard conditions (at least two years at room temperature and usual humidity) the amounts of the active compounds of a medicament formulation do not deviate from the initial amounts by more than the values given in the specification or the guidelines of the common Pharmacopoeias. According to the invention, storage stability also means that a preparation produced according to the invention can be stored under standard conditions (60% relative humidity, 25°C) as it is required for admission to the market.

**[0055]** According to the invention, "storage stable" or "time stable" also means that after storage under standard conditions the active compounds show release profiles as they would upon immediate use without storage. According to the invention, the admissible fluctuations with respect to the release profile are characterized in that the amount released per time unit fluctuates by no more than 20%, preferably no more than 15% and especially preferably no more than 10%, with respect to a mean value. The mean value is calculated from six measurements of the release profile.

**[0056]** Preferably, the release of the active compounds from a sustained release formulation is determined by the Basket Method according to USP at pH 1.2 or pH 6.5 with HPLC.

**[0057]** Storage stability is preferably determined by the Basket Method according to USP at pH 1.2 with HPLC.

**[0058]** According to the invention, a "non-swellable" or "substantially non-swellable" diffusion matrix is a matrix formulation for which the release of the active compounds is not influenced (or at least not to a relevant degree) by swelling of the matrix (particularly in the physiological fluids of the relevant target sites in the patient's body).

**[0059]** According to the invention, the term "substantially non-swellable" diffusion matrix also refers to a matrix whose volume will increase by approximately 300%, preferably by approximately 200%, more preferably by approximately 100%, by approximately 75% or by approximately 50%, even more preferably by approximately 30% or by approximately 20% and most preferably by approximately 15%, by approximately 10%, by approximately 5% or by approximately 1% in aqueous solutions (and particularly in the physiological fluids of the relevant target sites in the patient's body).

**[0060]** In the context of the present invention, "agonist" or "analgesic" always refers to oxycodone. In the context of the present invention "antagonist" always refers to naloxone.

**[0061]** Preparations produced according to the invention are applied orally. Especially preferred is a formulation for oral application.

**[0062]** Even though this might not be expressly stated, the term "agonist" or "antagonist" always comprises pharmaceutical acceptable salts and the like. If, for example, oxycodone or naloxone is mentioned, this also comprises, besides

the free base, their hydrochloride, sulfate, bisulfate, ttrate, nitrate, citrate, bitrtrate, phosphate, malate, maleate, hydrobromide, hydrojodide, fumarate, succinate and the like.

5 [0063] The application discloses that agonists and antagonists are formulated in a way that they are released from the resulting pharmaceutical preparation in a sustained, independent and invariant manner. This does not mean that the antagonist is in excess compared to the agonist. On the contrary, it is preferred that in formulations comprising an agonist/antagonist combination, the agonist is in excess compared to the antagonist.

[0064] The excess of the agonist is defined based on the amount of the unit dosage of the antagonist present in the combination preparation. The extent of the excess of the opioid agonist is given in terms of the weight ratio of agonist to antagonist.

10 [0065] The formulation comprises oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio of 2:1.

[0066] In an oxycodone and naloxone combination preparation, preferably between 10 and 150 mg, especially preferably between 10 and 80 mg of oxycodone (typical amounts for use) and preferably between 1 and 50 mg naloxone per unit dosage are used.

15 [0067] In other preferred embodiments of the invention, the preparations may comprise between 5 and 50 mg of oxycodone, between 10 and 40 mg of oxycodone, between 10 and 30 mg of oxycodone or approximately 20 mg of oxycodone. Preferred embodiments of the invention may also comprise preparations with between 1 and 40 mg naloxone, 1 and 30 mg naloxone, 1 and 20 mg naloxone or between 1 and 10 mg naloxone per unit dosage.

20 [0068] According to the invention, the ratio between oxycodone and naloxone is chosen in such a way that release profiles for both active substances in accordance with the invention are guaranteed and that the agonist can display its analgesic effect while the amount of the antagonist is chosen in such a way that habituation- or addiction-promoting effects and side effects of the agonist are reduced or abolished, without (substantially) affecting the analgesic effect of the agonist. According to the invention, development of habituation and addiction as well as obstipation and breath depression are to be considered as side effects of analgesically effective opioid agonists.

25 [0069] Matrix-based retardation formulations may preferably be used as formulations that provide a release of agonist and antagonist in accordance with the invention. According to the invention, especially preferred are formulations based on a substantially non-swellable diffusion matrix. At the moment, formulations with an erosive matrix or a swellable diffusion matrix are not preferred.

30 [0070] As disclosed in the invention, the matrix that provides the sustained release of the active compounds, has to be chosen in such a way that the release of the active compounds occurs in a sustained, independent and invariant manner. Preferably such matrices comprise polymers based on ethylcellulose, with ethylcellulose being an especially preferred polymer. Specifically preferred are matrices comprising polymers as they are available on the market under the trademark Surelease®. Particularly preferred is the use of Surelease®E-7-7050

35 [0071] Formulations with a release behaviour according to the invention comprise particularly matrices that comprise ethylcellulose and at least one fatty alcohol as the components that essentially influence the release characteristics of the matrix. The amounts of ethylcellulose and the at least one fatty alcohol may significantly vary so that preparations with different release profiles may be achieved. Even though the inventive preparations usually will comprise both of the afore-mentioned components, in some cases it may be preferred that the preparations comprise only ethylcellulose or the fatty alcohol(s) as the release determining components.

40 [0072] Matrices based on polymethacrylate (as, e.g. Eudragit®RS30D and Eudragit®RL30D) or matrices which comprise relevant amounts of water-swellable material, especially of hydroxyalkyl cellulose derivates such as HPMC, are presently preferably avoided according to the invention.

45 [0073] Matrices that are in accordance with the invention can be used to produce preparations that release active compounds in a sustained, independent and invariant manner and that release equal amounts of the active compounds per time unit. Specifically, this means that in the case of a oxycodone/naloxone combination containing 12 mg oxycodone und 4 mg naloxone, 25% oxycodone and 25% naloxone are released within the first 4 hours. Correspondingly, in the case of a oxycodone/naloxone combination containing 24 mg oxycodone and 8 mg naloxone, 25% oxycodone and 25% naloxone are released during the first 4 hours, with the deviation in both cases being no more than 20% of the mean value (which in this case is 25% oxycodone or naloxone).

50 [0074] Such an equal release behaviour for both active compounds may be desirable for medical aspects.

[0075] A preferred embodiment of the invention relates to preparations that release 1% to 40%, preferably 5% to 35%, more preferably between 10% and 30% and even more preferably between 15% and 25% of oxycodone and/or naloxone after 15 minutes. In other preferred embodiments of the invention, 15% to 20%, 20% to 25%, approximately 15%, approximately 20% or approximately 25% of oxycodone and/or naloxone are released after 15 minutes.

55 [0076] Another preferred embodiment of the invention relates to preparations that release between 25% to 65%, preferably between 30% to 60%, more preferably between 35% to 55% and even more preferably between 40% to 50% of oxycodone and/or naloxone after one hour. Preferred embodiments of the invention also relate to preparations that release between 40% to 45%, 45% to 50%, approximately 40%, approximately 45% or approximately 50% of oxycodone



and/or naloxone after one hour.

**[0077]** Yet another preferred embodiment of the invention relates to preparations that release between 40% to 80%, preferably between 45% to 75%, more preferably between 45% to 70% and even more preferably between 45% to 50%, 50% to 55%, 55% to 60%, 60% to 65% or 65% to 70% of oxycodone and/or naloxone after 2 hours. Preferred embodiments also comprise preparations that release approximately 45%, approximately 50%, approximately 55%, approximately 60%, approximately 65% or approximately 70% of oxycodone and/or naloxone after 2 hours.

**[0078]** One preferred embodiment of the invention relates to preparations that release 70% to 100%, preferably between 75% to 95%, more preferably between 80% to 95%, and even more preferably between 80% and 90% of oxycodone and/or naloxone after 4 hours. Preferred embodiments of the invention also relate to preparations that release between 80% to 85%, 85% to 90%, approximately 80%, approximately 85% or approximately 90% of oxycodone and/or naloxone after 4 hours.

**[0079]** One preferred embodiment of the invention also relates to preparations that release between 70% to 100%, preferably between 75% to 100%, more preferably between 80% to 95% and even more preferably between 80% to 85%, between 85% to 90% or between 90% to 95% of oxycodone and/or naloxone after 7 hours. Preferred embodiments of the invention also relate to preparations that release approximately 80%, approximately 85%, approximately 90% or approximately 95% of oxycodone and/or naloxone after 7 hours.

**[0080]** Yet another preferred embodiment of the invention relates to preparations that release between 85% to 100%, preferably between 90% to 100%, more preferably between 95% to 100% and even more preferably approximately 95% or 100% of oxycodone and/or naloxone after 12 hours.

**[0081]** According to the invention, formulations that provide a release of the active compounds in accordance with the invention may comprise, besides the matrix forming polymers, fillers and additional substances, such as granulating aids, lubricants, dyes, flowing agents and plasticizers.

**[0082]** Lactose, glucose or saccharose, starches and their hydrolysates, microcrystalline cellulose, cellatose, sugar alcohols such as sorbitol or mannitol, polysoluble calcium salts like calciumhydrogenphosphate, dicalcium- or tricalciumphosphat may be used as fillers.

**[0083]** Povidone may be used as granulating aid.

**[0084]** Highly-disperse silica (Aerosil®), talcum, corn starch, magnesium oxide and magnesium- or calcium stearate may preferably be used as flowing agents or lubricants.

**[0085]** Magnesium stearate and/or calcium stearate can preferably be used as lubricants. Fatty acids like stearic acid, or fats like hydrated castor oil can also preferably be used.

**[0086]** Polyethylene glycols and fatty alcohols like cetyl and/or stearyl alcohol and/ or cetostearyl alcohol can also be used as additional substances that influence retardation.

**[0087]** If fillers and additional substances such as dyes and the mentioned lubricants, flowing agents and plasticizers are used, care has to be taken that according to the invention only such combinations together with the matrix forming substance and/or the matrix forming substances are used, which ensure release profiles of the active compounds in accordance with the invention.

**[0088]** All these additional components of the formulations will be chosen in such a way that the release matrix receives the character of a substantially non-water- or non-buffer-swellaable and non-erosive diffusion matrix.

**[0089]** According to the invention, a formulation is especially preferred that comprises ethylcellulose or Surelease® E-7-7050 as a matrix-building substance, stearyl alcohol as fatty alcohol, magnesium stearate as lubricant, lactose as filler and povidone as a granulating aid.

**[0090]** Preparations in accordance with the invention can be produced as all common application forms which, on principle, are suitable for retardation formulations and which ensure that the active compounds are released in a manner in accordance with the invention. Especially suitable are tablets, multi-layer tablets and capsules. Additional application forms like granules or powders can be used, with only those applications forms being admissible that provide a sufficient retardation and a release behaviour in accordance with the invention.

**[0091]** Pharmaceutical preparations may also comprise film coatings. However, it has to be ensured that the film coatings do not negatively influence the release properties of the active compounds from the matrix and the storage stability of the active compounds within the matrix. Such film coatings may be colored or may comprise a initial dosage of the active compounds if required. The active compounds of this initial dosage will be immediately released so that the therapeutically effective blood plasma level is reached very quickly.

**[0092]** Pharmaceutical preparations or preliminary stages thereof which are in accordance with the invention can be produced by build-up or break-down granulation. A preferred embodiment is the production by spray granulation with subsequent drying of the granules. Another preferred embodiment is the production of granules by build-up granulation in a drum or on a granulating disk. The granules may then be pressed into e.g. tablets using appropriate additional substances and procedures.

**[0093]** The person skilled in the art is familiar with granulating technology as applied to pharmaceutical technology. The embodiment examples (see below) disclose specific embodiments of the invention. However, it is well within the

scope of the person skilled in the art to adapt the parameters of the process in order to achieve specific purposes.

**[0094]** Production of pharmaceutical preparations or preliminary stages thereof, which are in accordance with the invention, by extrusion technology is especially advantageous. In one preferred embodiment, pharmaceutical preparations or preliminary stages thereof are produced by melt extrusion with co- or counter-rotating extruders comprising two screws. Another preferred embodiment is the production by means of extrusion, with extruders comprising one or more screws. These extruders may also comprise kneading elements.

**[0095]** Extrusion is also a well-established production process in pharmaceutical technology and is well known to the person skilled in the art. The person skilled in the art is well aware that during the extrusion process, various parameters, such as the feeding rate, the screw speed, the heating temperature of the different extruder zones (if available), the water content, etc. may be varied in order to produce products of the desired characteristics. The Example section provides for numerous examples of preparations according to the invention that have been produced by extrusion.

**[0096]** The aforementioned parameters will depend on the specific type of extruder used. During extrusion the temperature of the heating zones, in which the components of the inventive formulation melt, may be between 40 to 120 °C, preferably between 50 to 100 °C, more preferably between 50 to 90 °C, even more preferably between 50 to 70 °C and most preferably between 50 to 65° C, particularly if counter-rotating twin screw extruders (such as a Leistritz Micro 18 GGL) are used. The person skilled in the art is well aware that not every heating zone has to be heated. Particularly behind the feeder where the components are mixed, cooling at around 25 °C may be necessary. The screw speed may vary between 100 to 500 revolutions per minute (rpm), preferably between 100 to 250 rpm, more preferably between 100 to 200 rpm and most preferably around 150 rpm, particularly if counter-rotating twin screw extruders (such as a Leistritz Micro 18 GGL) are used. The geometry and the diameter of the nozzle may be selected as required. The diameter of the nozzle of commonly used extruders typically is between 1 to 10 mm, preferably between 2 to 8 mm and most preferably between 3 to 5 mm. The ratio of length versus diameter of the screw of extruders that may be used for production of inventive preparations is typically around 40:1.

**[0097]** Generally, the temperatures of the heating zones have to be selected such that no temperatures develop that may destroy the pharmaceutically active compounds. The feeding rate and screw speed will be selected such that the pharmaceutically active compounds are released from the preparations produced by extrusion in a sustained, independent and invariant manner and are storage stable in the matrix. If e.g. the feeding rate is increased, the screw speed may have to be increased correspondingly to ensure the same retardation.

**[0098]** The person skilled in the art knows that all the aforementioned parameters depend on the specific production conditions (extruder type, screw geometry, number of components etc.) and may have to be adapted such that the preparations produced by extrusion provide for a sustained, independent and invariant release as well as for the aforementioned storage stability.

**[0099]** The person skilled in the art can infer from the Examples (see below) that by changing the parameters during extrusion and by changing the composition with respect to the compounds that are substantially responsible for the release behaviour of the preparations, preparations with different release profiles may be obtained. Thus, the present invention allows to first produce a preparation with a desired release profile for oxycodone and naloxone by e.g. varying the amount of fatty alcohols or the matrix-forming polymer ethylcellulose as well as production parameters such as temperature, screw speed (during extrusion) or pressure power during tablet production.

**[0100]** Once a preparation with the desired release profile has been obtained, the inventive preparations according to the invention allow the person skilled in the art to change the amounts of the preparations with respect to the active compounds as outlined above. Preparations comprising different amounts of the active compounds but of otherwise substantially equal composition, however, will then provide for the features of sustained, invariant and independent release.

**[0101]** The Example section therefore discloses numerous examples showing that preparations with different release profiles may be obtained by changing the amount of e.g. ethylcellulose. Other examples show that once a preparation has been established with desired release profiles, the change in the amount of naloxone will not influence the release behaviour of such preparations if the difference in the amount of the active compound is replaced by pharmaceutically inert excipients such as lactose.

**[0102]** Examples that display highly advantageous embodiments of the invention are set out below. Additionally examples are given that emphasize the advantages of preparations according to the invention compared to common formulations. Example 1 - Production of tablets with different oxycodone/naloxone amounts in a non-swellable diffusion matrix by spray granulation:

The following amounts of the listed components were used for the production of oxycodone/naloxone tablets according to the invention.

Preparation (designation)	Oxy/Nal-0	Oxy/Nal-5	Oxy/Nal-10
oxycodone HCl	20.0 mg	20.0 mg	20.0 mg

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(continued)

Preparation (designation)	Oxy/Nal-0	Oxy/Nal-5	Oxy/Nal-10
naloxone HCl	-	5.0 mg	10.0 mg
Lactose Flow Lac 100	59.25 mg	54.25 mg	49.25 mg
Povidone 30	5.0 mg	5.0 mg	5.0 mg
Surelease®	10.0 mg solid material	10.0 mg solid material	10.0 mg solid material
Stearyl alcohol	25.0 mg	25.0 mg	25.0 mg
Talcum	2.5 mg	2.5 mg	2.5 mg
Mg-Stearate	1.25 mg	1.25 mg	1.25 mg

The Surelease® E-7-7050 polymer mixture used had the following composition.

Surelease®
Ethylcellulose 20 cps
Dibutylsebacate
Ammoniumhydroxide
Oleic acid
Siliciumdioxide
Water

**[0103]** For the production of tablets oxycodone HCl, naloxone HCl, Povidone 30 and Lactose Flow Lac 100 were mixed in a tumbling mixer (Bohle) and subsequently spray-granulated with Surelease® E-7-7050 in a fluidized bath granulating device (GPCG3). The material was sieved over a Comill 1.4 mm sieve. An additional granulation step was carried out with melted fatty alcohol in a high-shear mixer (Collette). All tablet cores produced by this approach had a weight of 123 mg, based on dry substance.

Example 2 - Production of tablets with oxycodone and naloxone in a non-swellable diffusion matrix by extrusion:

**[0104]** The following amounts of the listed components were used for the production of the oxycodone/naloxone tablets according to the invention.

Preparation (designation)	Oxy/Nal-Extr
oxycodone HCl	20 mg
naloxone HCl	10 mg
Kollidon 30	6 mg
Lactose Flow Lac 100	49.25 mg
Ethylcellulose 45 cpi	10 mg
Stearyl alcohol	24 mg
Talcum	2.5 mg
Mg-Stearate	1,25 mg

**[0105]** The listed amounts of oxycodone HCl, naloxone HCl, ethylcellulose 45 cpi, Povidone 30, stearyl alcohol and Lactose Flow Lac 100 were mixed in a tumbling mixer (Bohle). This mixture was subsequently extruded with a counter-rotating twin screw extruder of the type Micro 18 GGL (Leistritz AG, Nürnberg, Germany). The temperature of heating zone 1 was 25°C, of heating zone 2, 50°C, of heating zones 3 to 5, 60°C, of heating zones 6 to 8, 55°C, of heating zone

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9, 60°C and of heating zone 10, 65°C. The screw rotating speed was 150 revolutions per minute (rpm), the resulting melt temperature was 87°C, the feed rate was 1.5 kg/h and the diameter of the nozzle opening was 3 mm. The extruded material was sieved with a Frewitt 0.68 x 1.00 mm sieve. The grinded extrudate was then mixed with talcum and magnesium stearate that had been added over a 1 mm hand sieve and was subsequently pressed into tablets. The extruder has a screw geometry, as shown in Fig. 1.

**[0106]** In comparison to the oxycodone/naloxone tablets which also have the Surelease®-based non-swellable diffusion matrix produced by spray granulation (see Example 1), extruded preparations comprise less components.

Example 3 - Release profile of the oxycodone/naloxone tablets from Example 1:

**[0107]** The release of the active compounds was measured over a time period of 12 hours, applying the Basket Method according to USP at pH 1.2 using HPLC. Tablets Ox/Nal-0, Ox/Nal-5 and Ox/Nal-10 were tested.

**[0108]** One recognizes from Fig. 2 and the values listed in the Table that in the case of a non-swellable diffusion matrix based on Surelease®, the release rates of different oxycodone amounts, independent of the naloxone amount, remain equal (invariant). Correspondingly, invariant release profiles are observed for naloxone at different oxycodone amounts.

Time (min)	Ox/Nal-0	Ox/Nal-5-O	Ox/Nal-5-N	Ox/Nal-10-O	Ox/Nal-10-N
	Oxy	Oxy	Nal	Oxy	Nal
0	0	0	0	0	0
15	26.1	24.9	23.5	22.8	24.1
120	62.1	63	61	57.5	60.2
420	91.7	94.5	91.9	89.4	93.5
720	98.1	99.6	96.6	95.7	100.6

**[0109]** The release values refer to oxycodone or naloxone (line 2) and are given as percentages. The mean value for the release of naloxone at e. g. 420 min is 92,7%. The maximal deviation at 420 min is 1%. Oxy and Nal stand for oxycodone and naloxone and indicate the active compound which has been measured.

Example 4 - Release profile of oxycodone/naloxone tablets from Example 2 at different pH-values:

**[0110]** The release of active compounds from the tablets was measured over a time period of 12 hours at pH 1.2 or for 1 hour at 1.2 and subsequently for 11 hours at pH 6.5. Release rates were determined by the basket method according to USP using HPLC.

**[0111]** The following release rates were measured for 12 hours at pH 1.2:

Time (min)	Oxy/Nal-Extr-1,2-O	Oxy/Nal-Extr-1,2-N
	Oxy	Nal
0	0	0
15	24.1	24.0
120	62.9	63.5
420	92.9	93.9
720	96.9	98.1

**[0112]** The following release rates were measured for 1 hour at pH 1.2 and 11 hours at pH 6.5:

Time (min)	Oxy/Nal-Extr-6,5-O	Oxy/Nal-Extr-6,5-N
	Oxy	Nal
0	0	0
60	48.1	49.2

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(continued)

Time (min)	Oxy/Nal-Extr-6,5-O	Oxy/Nal-Extr-6,5-N
	Oxy	Nal
120	65.0	64.7
240	83.3	81.8
420	94.1	92.3

**[0113]** The release rates refer to oxycodone and naloxone (line 2) and are given as percentages. Oxy and Nal stand for oxycodone and naloxone and indicate the active compound measured.

**[0114]** The comparison of the values given in the Tables of Example 4 and the Table of Example 3 make clear that independent of the production process, active compounds are released in equal amounts from the preparations. For example, 89.4% of oxycodone is released from spray-granulated tablets (Ox/Nal-10-tablets, see Example 3) at 420 minutes, while 92.9% is released from extruded tablets (Oxy/Nal-Extr-1.2-O, Example 4) at 420 minutes. The release of oxycodone from extruded tablets thus deviates by 1.1% from the mean value of the release of oxycodone from spray-granulated tablets (91.9% at 420 minutes). 93.5% of naloxone is released from spray-granulated tablets (Ox/Nal-10-tablets, see Example 3) at 420 minutes, while 93.9% is released from extruded tablets (Oxy/Nal-Extr.-1.2-O, Example 4) at 420 minutes. The release of naloxone from extruded tablets thus deviates by 1.3% from the mean value of the release of naloxone from spray-granulated tablets (92.7% at 420 minutes).

**[0115]** Moreover, one can infer from a comparison of the values of the Tables of Example 4 and from Figures 3a and 3b that independent of the pH value at which the release rates have been measured the release of oxycodone and naloxone remain equal and invariant.

Example 5 - Comparative example: release behaviour of Valoron® tablets:

**[0116]** The release of the active substances from tablets was monitored over a time period of 7 hours. Valoron® tablets with 50 mg tilidine and 4 mg naloxone (Ti/Nal-50/4) or 100 mg tilidine and 8 mg naloxone (Ti/Nal-100/8) or 150 mg tilidine and 12 mg naloxone (Ti/Nal-150/12) were tested by the Basket Method according to USP for 1h at pH 1.2 and then for additional 6h at pH 6.5 using HPLC .

**[0117]** One recognizes from Figures 4A and 4B and the values listed in the Table that in case of a swellable (and possibly erosive) diffusion matrix with relevant amounts of HPMC, the release of different amounts of tilidine varies significantly and is not invariant for different amounts of naloxone. This applies in turn to naloxone. This means that for this pH the release of the active compounds is not independent of each other.

Time (min)	Ti/Nal-50/4-T	Ti/Nal-50/4-N	Ti/Nal-100/8-T	Ti/Nal-100/8-N	Ti/Nal-150/12-T	Ti/Nal-150/12-N
	Til	Nal	Til	Nal	Til	Nal
0	0	0	0	0	0	0
60	37.2	27.6	33.9	27.3	29.9	23.3
120	47.6	31.7	46.5	33.4	41.5	28.5
180	54.7	37.4	55	41.2	48.2	35
240	59.7	44	68.2	59.5	54.5	40.1
300	65.2	50.6	82.6	72.9	60.5	47.5
360	70.3	58	85.7	82.7	67.2	56.4
420	74.2	60.8	93.1	90.9	84.9	78.9

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The release values refer to tilidine or naloxone (line 2) and are given as percentages. The mean value for the release of naloxone at e. g. 420 min is 78,87%. The maximal deviation at 420 min is 20,4%. Til und Nal stand for tilidine and naloxone and indicate the active compound tested.

5 Example 6 - Structure comparison of tablets of Examples 1 and 2 with Valoron® N tablets by electron microscopy.

10 [0118] For electron microscopy tablets were used that comprised 20 mg oxycodone and 10 mg naloxone and were produced either by spray granulation according to Example 1 (Ox/Nal-10) or by extrusion according to Example 2 (Oxy/Nal-Extr). Additionally, a Valoron® N tablet with 100 mg Tilidin and 8 mg Naloxone was used. Figures 5A and 5B show different magnifications of scanning electron microscopy pictures of a Ox/Nal-10-tablet with a formulation according to the invention which was produced by spray granulation. Figures 6A and 6B show different magnifications of scanning electron microscopy pictures of a Oxy/Nal-Extr-tablets with a formulation according to the invention, which was produced by extrusion. Figures 7A and 7B show scanning electron microscopy pictures of the Valoron® N-tablet.

15 [0119] From a comparison of the figures one can clearly see that tablets with a formulation according to the invention have a surface which is substantially finer and more homogeneously structured and which shows fewer cracks than the Valoron® tablet, regardless of whether the tablets have been produced by spray granulation or extrusion. The structural difference is possibly the reason for the different release behaviours of the different preparations.

20 Example 7 - Production of tablets with different oxycodone/naloxone amounts in a non-swellable diffusion matrix by extrusion:

[0120] The following amounts of the listed components were used for the production of oxycodone/naloxone tablets according to the invention.

25

Preparation (designation)	OxN20/1-Extr-A	OxN20/1-Extr-B	OxN20/1-Extr-C	OxN20/10-Extr-A
Oxycodone HCl	20 mg	20 mg	20 mg	20 mg
Naloxone HCl	1 mg	1 mg	1 mg	10 mg
Lactose Flow Lac 100	58.25 mg	58.25 mg	58.25 mg	49.25 mg
Kollidon® 30	6 mg	6 mg	6 mg	6 mg
Ethylcellulose	10 mg	10 mg	10 mg	10 mg
Stearly alcohol	24 mg	24 mg	24 mg	24 mg
Talcum	1.25 mg	1.25 mg	1.25 mg	1.25 mg
Mg-Stearate	2.5 mg	2.5 mg	2.5 mg	2.5 mg

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35

40 [0121] Extrusion was performed as described above (Example 2) with the following parameters:

OxN20/1-Extr-A: temperature: 55-63 °C  
rpm (screw): 150 rpm  
feeding rate: 1.5 kg/h

45 OxN20/1-Extr-B: temperature: 55-63 °C  
rpm (screw): 155 rpm  
feeding rate: 1.5 kg/h

50 OxN20/1-Extr-C: temperature: 55-63 °C  
rpm (screw): 1505rpm  
feeding rate: 1.5 kg/h

55 OxN20/10-Extr-A: temperature: 55-63 °C  
rpm (screw): 160 rpm  
feeding rate: 1.75 kg/h

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**[0122]** Tablet production was performed with a common tableting device with the following parameters:

OxN20/1-Extr-A:	rpm:	40 rpm
	Pressure power:	9 kN
OxN20/1-Extr-B:	rpm:	42 rpm
	Pressure power:	8.9 kN
OxN20/1-Extr-C:	rpm:	36 rpm
	Pressure power:	9 kN
OxN20/10-Extr-A :	rpm:	36 rpm
	Pressure power:	7.5 kN

**[0123]** The release of the active compounds was measured over a time period of 12 hours, applying the Basket Method according to USP at pH 1.3 using HPLC. Tablets OxN20/1-Extr-A, OxN20/1-Extr-B, OxN20/1-Extr-C and OxN20/10-Extr-A were tested.

**[0124]** One recognizes from the values listed in the Table that in the case of a non-swellable diffusion matrix based on ethylcellulose, the release rates of different naloxone amounts, independent of the oxycodone amount, remain substantially equal. Correspondingly, the preparations provide for an independent and invariant release of the active compounds.

Time (min)	OxN20/1-Extr-A		OxN20/1-Extr-B		OxN20/1-Extr-C		OxN20/10-Extr-A	
	Oxy	Nal	Oxy	Nal	Oxy	Nal	Oxy	Nal
0	0	0	0	0	0	0	0	0
15	21.2	25.8	21.7	21.1	19.7	19.3	23.3	24.3
120	56.6	53.8	58.8	57.3	57.7	56.2	64.5	66.9
420	87.2	84.5	94.2	92.6	93.7	91.5	92.7	96.3
720	99.7	96.8	100.1	98	100.6	97.5	93.6	97.4

**[0125]** The release values refer to oxycodone or naloxone (line 2) and are given as percentages. The mean value for the release of naloxone at e. g. 420 min is 92.3%. The maximal deviation at 420 min is 7.4%. Oxy and Nal stand for oxycodone and naloxone and indicate the active compound which has been measured.

**[0126]** Thus, once a preparation with the desired release profile has been developed, one can change the amount of the active compounds without significantly changing the release profiles of the active compounds. The preparations comprising different amounts of the active compounds still provide for a sustained, independent an invariant release of the active compounds.

**[0127]** Example 8 - Production of tablets with oxycodone/naloxone in a non-swellable diffusion matrix by extrusion:

In the following example it is set out that using formulations according to the present invention, preparations comprising oxycodone and naloxone with particular release behaviours may be obtained.

**[0128]** The following amounts of the listed components were used for the production of oxycodone/naloxone tablets according to the invention.

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10  
15  
20  
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30  
35  
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45  
50  
55

Preparation (designation)	OxN20/1-Extr-D	OxN20/1-Extr-E	OxN20/10-Extr-B	OxN20/10-Extr-C	OxN20/10-Extr-D	OxN20/10-Extr-E
oxycodone HCl	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
naloxone HC1	1 mag	1 mg	10 mg	10 mg	10 mg	10 mg
Lactose Flow Lac 100	56.25 mg	56.25 mg	54.25 mg	65.25 mg	60.25 mg	55.25
Kollidon® 30	7 mg	6 mg	6 mg	7.25 mg	7.25 mg	7.25 mg
Ethylcellulose	11 mg	12 mg	10 mg	12 mg	12 mg	12 mg
Stearyl alcohol	24 mg	24 mg	24 mg	28.75 mg	28.75 mg	28.75 mg
Talcum	1.25 mg	1.25 mg	1.25 mg	1.25 mg	1.25 mg	1.25 mg
Mg-Stearate	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg



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**[0129]** Extrusion was performed as described above (Example 2) with the following parameters:

5	OxN20/1-Extr-D:	temperature:	55-63 °C
		rpm (screw):	150 rpm
		feeding rate:	1.5 kg/h
	OxN20/1-Extr-E:	temperature:	55-63 °C
		rpm (screw):	150 rpm
		feeding rate:	1.5 kg/h
10	OxN20/10-Extr-B:	temperature:	55-63 °C
		rpm (screw):	160 rpm
		feeding rate:	1.75 kg/h
	OxN20/10-Extr-C:	temperature:	55-63 °C
15		rpm (screw):	160 rpm
		feeding rate:	1.75 kg/h
	OxN20/10-Extr-D:	temperature:	55-63 °C
		rpm (screw):	150 rpm
		feeding rate:	1.5 kg/h
20	OxN20/10-Extr-E:	temperature:	55-63 °C
		rpm (screw):	150 rpm
		feeding rate:	1.5 kg/h

**[0130]** Tablet production was performed with a common tableting device with the following parameters:

25	OxN20/1-Extr-D:	rpm:	39 rpm
		Pressure power:	11 kN
	OxN20/1-Extr-E:	rpm:	39 rpm
30		Pressure power:	10.5 kN
	OxN20/10-Extr-B:	rpm:	36 rpm
		Pressure power:	9.5 kN
	OxN20/10-Extr-C:	rpm:	36 rpm
35		Pressure power:	7.8 kN
	OxN20/10-Extr-D:	rpm:	39 rpm
		Pressure power:	9 kN
	OxN20/10-Extr-E:	rpm:	39 rpm
40		Pressure power:	7.5 kN

**[0131]** The release of the active compounds was measured over a time period of 12 hours, applying the Basket Method according to USP at pH 1.2 using HPLC. Tablets OxN20/1-Extr-D, OxN20/1-Extr-E, OxN20/10-Extr-B, OxN20/10-Extr-C, OxN20/10-Extr-D and OxN20/10-Extr-E were tested.

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Time (min)	OxN20/1-Extr-D		OxN20/1-Extr-E		OxN20/10-Extr-B		OxN20/10-Extr-C		OxN20/10-Extr-D		OxN20/10-Extr-E	
	Oxy	Nal	Oxy	Nal	Oxy	Nal	Oxy	Nal	Oxy	Nal	Oxy	Nal
0	0	0	0	0	0	0	0	0	0	0	0	0
15	16.6	16.2	17.4	17.2	26.1	26.8	21.8	21.9	18.5	18.2	18.4	18.2
120	47.6	46.9	49.6	49.7	71.1	73.0	61.2	61.8	52.8	52.8	53.3	53.3
420	82.7	84.5	84.6	85.7	94.3	96.6	93.2	94.7	86.3	86.3	87.2	88.2
720	95	97	95.2	95.8	94.9	97.9	96.4	97.9	94.8	94.8	95.7	96.5

[0132] The release values refer to oxycodone or naloxone (line 2) and are given as percentages. Oxy and Nal stand for oxycodone and naloxone and indicate the active compound which has been measured.

[0133] The example shows that preparations with particular release profiles may be produced if ethylcellulose and fatty alcohols are used as the matrix-components that essentially influence the release characteristics of the preparations. Once a preparation with desired release characteristics has been obtained the amount of the active compounds may be changed. The preparations will still provide for a sustained, independent and invariant release behaviour (see example 7).

## Claims

1. An oral pharmaceutical formulation comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for use in the treatment of pain and for use in the concurrent reduction of opioid induced obstipation, wherein the formulation provides sustained release of oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof, and wherein the formulation comprises oxycodone or a pharmaceutically acceptable salt thereof in a weight ratio of 2:1 to naloxone or a pharmaceutically acceptable salt thereof.
2. Pharmaceutical formulation for use according to claim 1, wherein the formulation comprises naloxone or a pharmaceutically acceptable salt thereof in an amount range of 1 to 50 mg.
3. Pharmaceutical formulation for use according to claim 1 or 2, wherein the formulation comprises oxycodone or a pharmaceutically acceptable salt thereof in an amount range of 10 to 150 mg.
4. Pharmaceutical formulation for use according to any of the preceding claims, wherein the formulation comprises oxycodone and naloxone as the hydrochloride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate or succinate.
5. Pharmaceutical formulation for use according to any of the preceding claims, wherein the formulation corresponds to a tablet.
6. Pharmaceutical formulation for use according to any of the preceding claims, wherein the formulation releases *in vitro* 1% to 40% of oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof after 15 minutes, 40% to 80% of oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof after 2 hours, 70% to 100% of oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof after 7 hours and 85% to 100% of oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof after 12 hours, as determined by the Basket Method according to USP at pH 1.2 with HPLC.

## Patentansprüche

1. Eine orale pharmazeutische Formulierung umfassend Oxycodon oder ein pharmazeutisch annehmbares Salz davon und Naloxon oder ein pharmazeutisch annehmbares Salz davon zu Verwendung bei der Behandlung von Schmerzen und zur Verwendung bei der gleichzeitigen Reduzierung der Opioid-induzierten Verstopfung, wobei die Formulierung eine verzögerte Freisetzung von Oxycodon oder einem pharmazeutisch annehmbaren Salz davon und Naloxon oder einem pharmazeutisch annehmbaren Salz davon zur Verfügung stellt, und wobei die Formulierung Oxycodon oder ein pharmazeutisch annehmbares Salz davon in einem Gewichtsverhältnis von 2:1 zu Naloxon oder einem pharmazeutisch annehmbaren Salz davon umfasst.
2. Pharmazeutische Formulierung zur Verwendung gemäß Anspruch 1, wobei die Formulierung Naloxon oder ein pharmazeutisch annehmbares Salz davon in einem Mengbereich von 1 bis 50 mg umfasst.
3. Pharmazeutische Formulierung zur Verwendung gemäß Anspruch 1 oder 2, wobei die Formulierung Oxycodon oder ein pharmazeutisch annehmbares Salz davon in einem Mengbereich von 10 bis 150 mg umfasst.
4. Pharmazeutische Formulierung zur Verwendung gemäß einem der vorangegangenen Ansprüche, wobei die Formulierung Naloxon und Oxycodon als das Hydrochlorid, Sulfat, Bisulfat, Tartrat, Ziträt, Bitartrat, Phosphat, Malat,

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Maleat, Hydrobromid, Hydrojodid, Fumarat oder Succinat umfasst.

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5. Pharmazeutische Formulierung zur Verwendung gemäß einem der vorangegangenen Ansprüche, wobei die Formulierung einer Tablette entspricht.
  6. Pharmazeutische Formulierung zur Verwendung gemäß einem der vorangegangenen Ansprüche, wobei die Formulierung *in vitro* 1% bis 40% Oxycodon oder ein pharmazeutisch annehmbares Salz davon und Naloxon oder ein pharmazeutisch annehmbares Salz davon nach 15 Minuten, 40% bis 80% Oxycodon oder ein pharmazeutisch annehmbares Salz davon nach 2 Stunden, 70% bis 100% Oxycodon oder ein pharmazeutisch annehmbares Salz davon und Naloxon oder ein pharmazeutisch annehmbares Salz davon nach 7 Stunden, und 85% bis 100% Oxycodon oder ein pharmazeutisch annehmbares Salz davon nach 12 Stunden freisetzt, bestimmt nach der Körbchen Methode gemäß USP bei pH 1,2 mit HPLC (Hochdruckflüssigkeitschromatografie).

### Revendications

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1. Formulation pharmaceutique orale comprenant de l'oxycodone ou un sel pharmaceutiquement acceptable de celui-ci et de la naloxone ou un sel pharmaceutiquement acceptable de celle-ci pour une utilisation dans le traitement de la douleur et pour une utilisation dans la réduction simultanée de la constipation provoquée par les opioïdes, dans laquelle la formulation assure une libération prolongée de l'oxycodone ou d'un sel pharmaceutiquement acceptable de celui-ci et de la naloxone ou d'un sel pharmaceutiquement acceptable de celle-ci, et dans laquelle la formulation contient l'oxycodone ou un sel pharmaceutiquement acceptable de celui-ci dans un ratio pondéral de 2 : 1 par rapport à la naloxone ou à un sel pharmaceutiquement acceptable de celle-ci.
  2. Formulation pharmaceutique pour une utilisation selon la revendication 1, dans laquelle la formulation comprend de la naloxone ou un sel pharmaceutiquement acceptable de celle-ci dans une plage de quantité allant de 1 à 50 mg.
  3. Formulation pharmaceutique pour une utilisation selon la revendication 1 ou 2, dans laquelle la formulation comprend de l'oxycodone ou un sel pharmaceutiquement acceptable de celui-ci dans une plage de quantité allant de 10 à 150 mg.
  4. Formulation pharmaceutique pour une utilisation selon l'une quelconque des revendications précédentes, dans laquelle la formulation comprend de l'oxycodone et de la naloxone sous forme de chlorhydrate, de sulfate, de bisulfate, de tartrate, de nitrate, de citrate, de bitartrate, de phosphate, de malate, de maléate, de bromhydrate, d'iodohydrate, de fumarate ou de succinate.
  5. Formulation pharmaceutique pour une utilisation selon l'une quelconque des revendications précédentes, dans laquelle la formulation correspond à un comprimé.
  6. Formulation pharmaceutique pour une utilisation selon l'une quelconque des revendications précédentes, dans laquelle la formulation libère *in vitro* de 1 % à 40 % de l'oxycodone ou d'un sel pharmaceutiquement acceptable de celui-ci et de la naloxone ou d'un sel pharmaceutiquement acceptable de celle-ci au bout de 15 minutes, de 40 % à 80 % de l'oxycodone ou d'un sel pharmaceutiquement acceptable de celui-ci et de la naloxone ou d'un sel pharmaceutiquement acceptable de celle-ci au bout de 2 heures, de 70 % à 100 % de l'oxycodone ou d'un sel pharmaceutiquement acceptable de celui-ci et de la naloxone ou d'un sel pharmaceutiquement acceptable de celle-ci au bout de 7 heures et de 85 % à 100 % de l'oxycodone ou d'un sel pharmaceutiquement acceptable de celui-ci et de la naloxone ou d'un sel pharmaceutiquement acceptable de celle-ci au bout de 12 heures, comme cela a été déterminé selon l'USP par la méthode du panier à pH = 1,2 et par HPLC (chromatographie en phase liquide à haute performance).

Figure 1

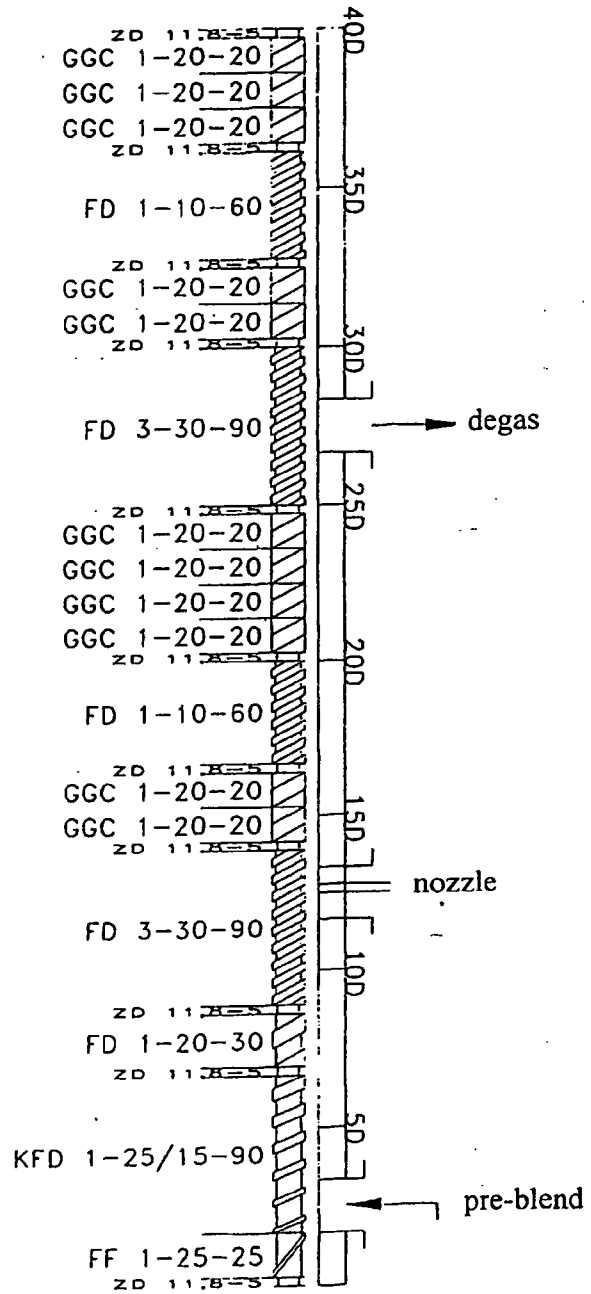


Figure 2

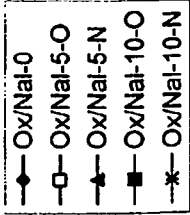
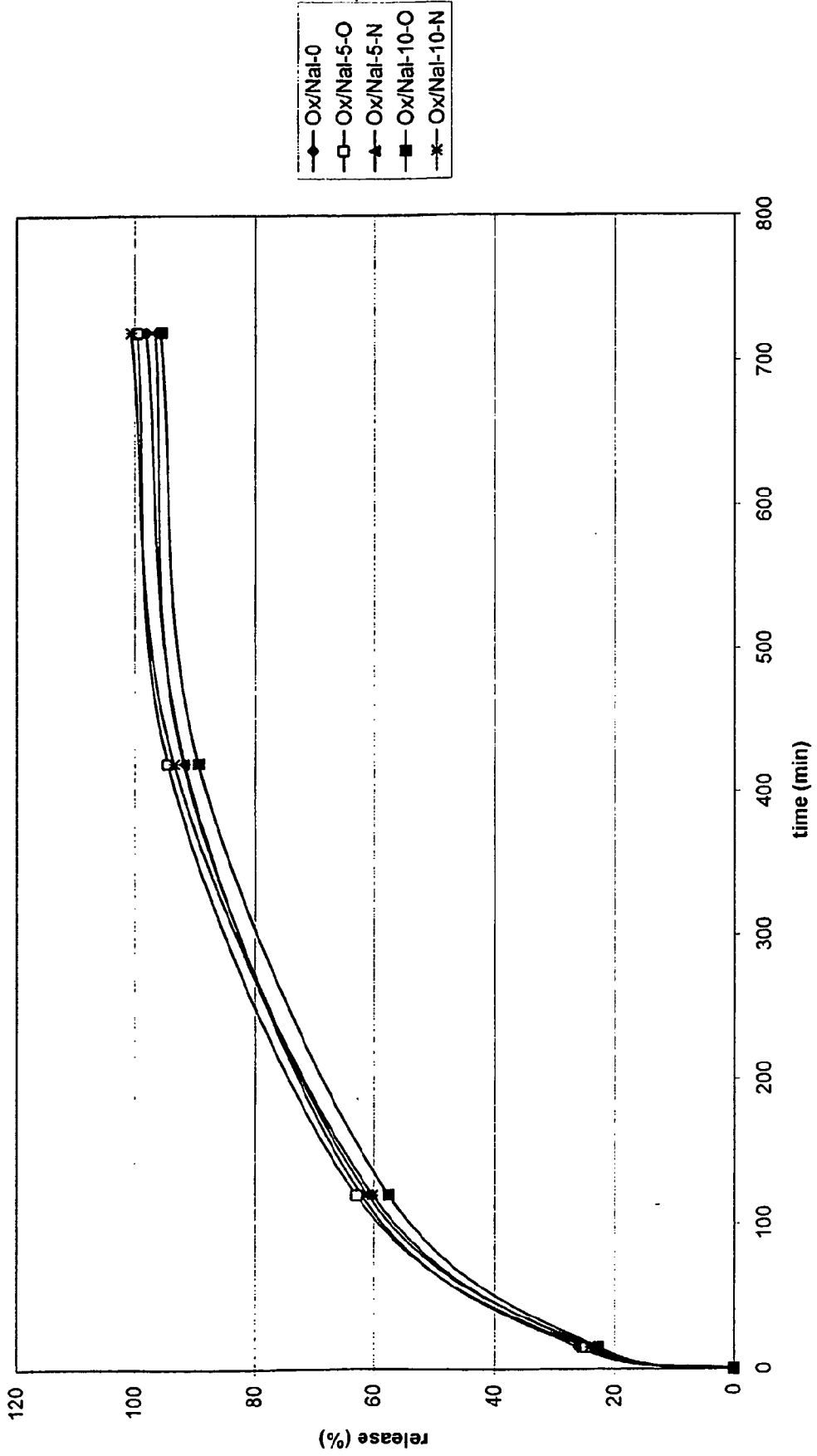


Figure 3A

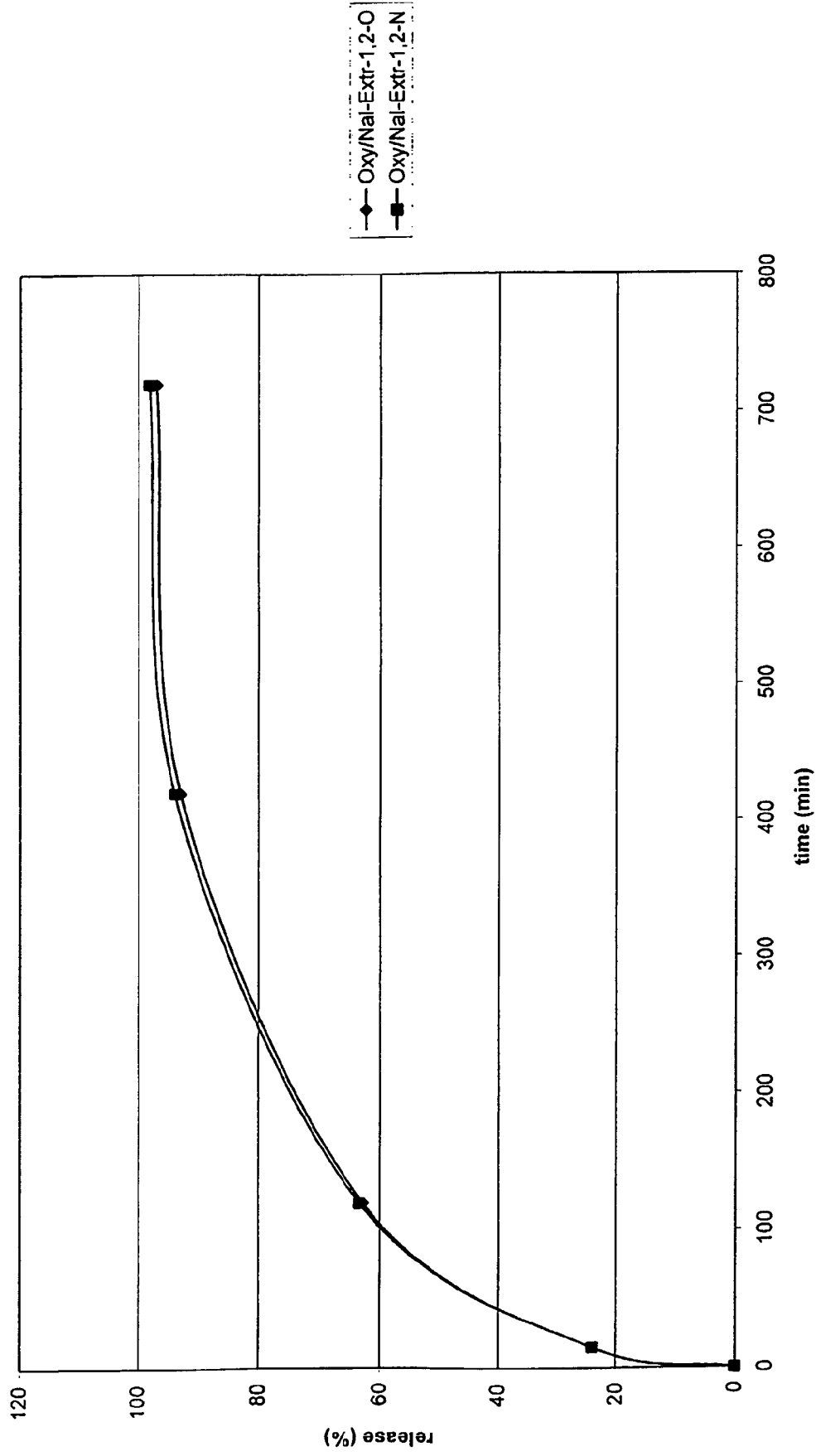


Figure 3B

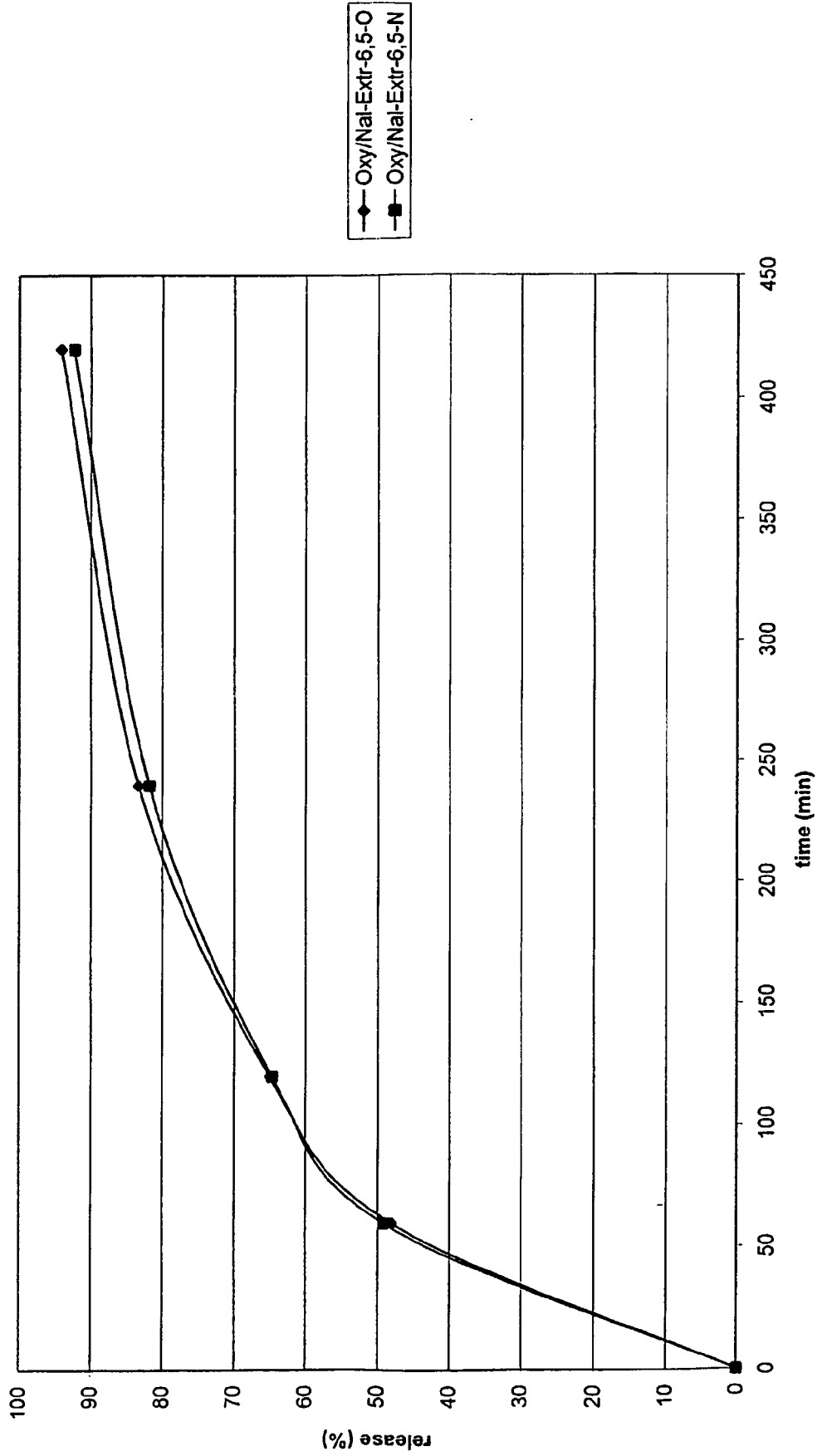




Figure 4A

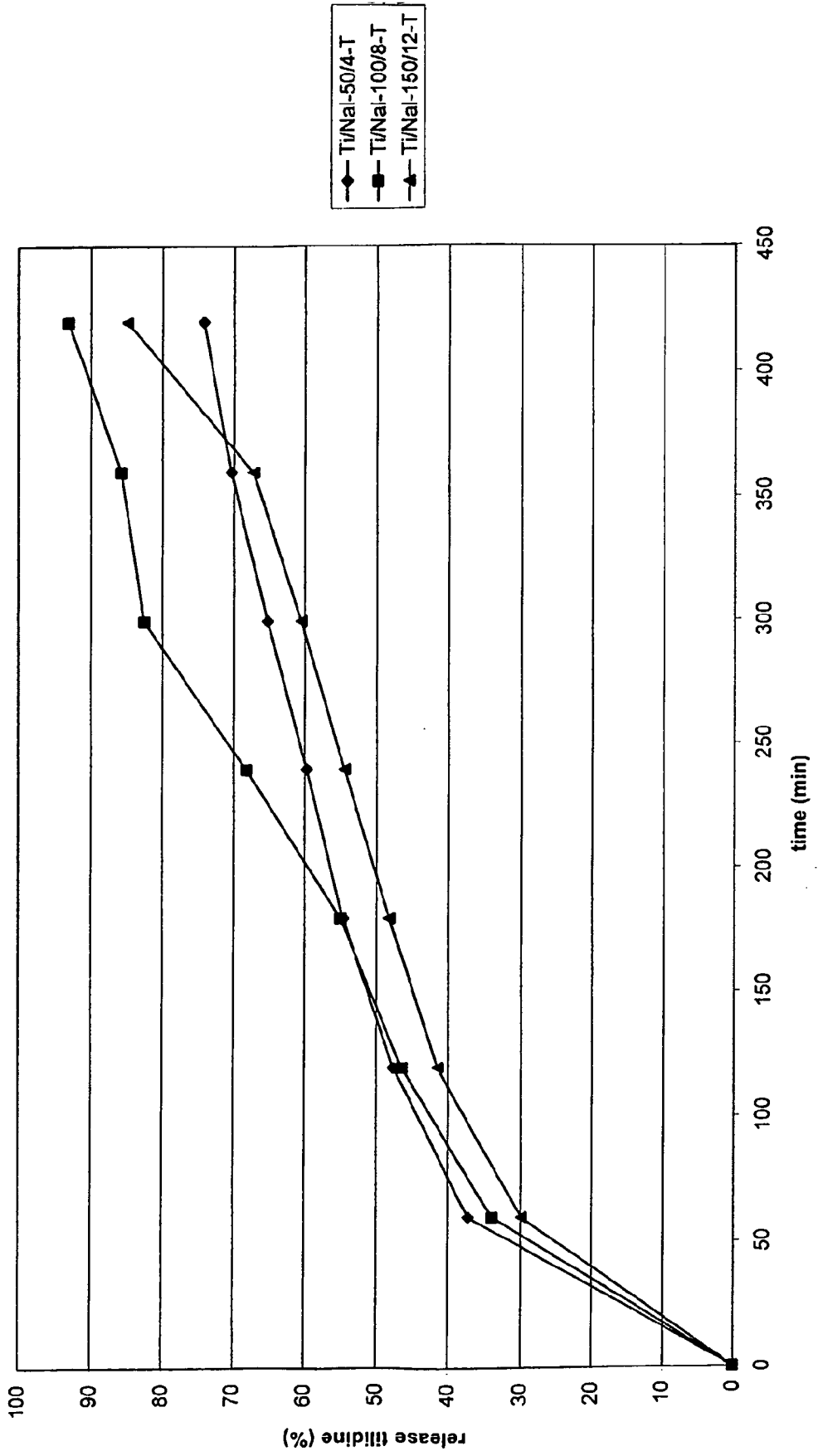


Figure 4B

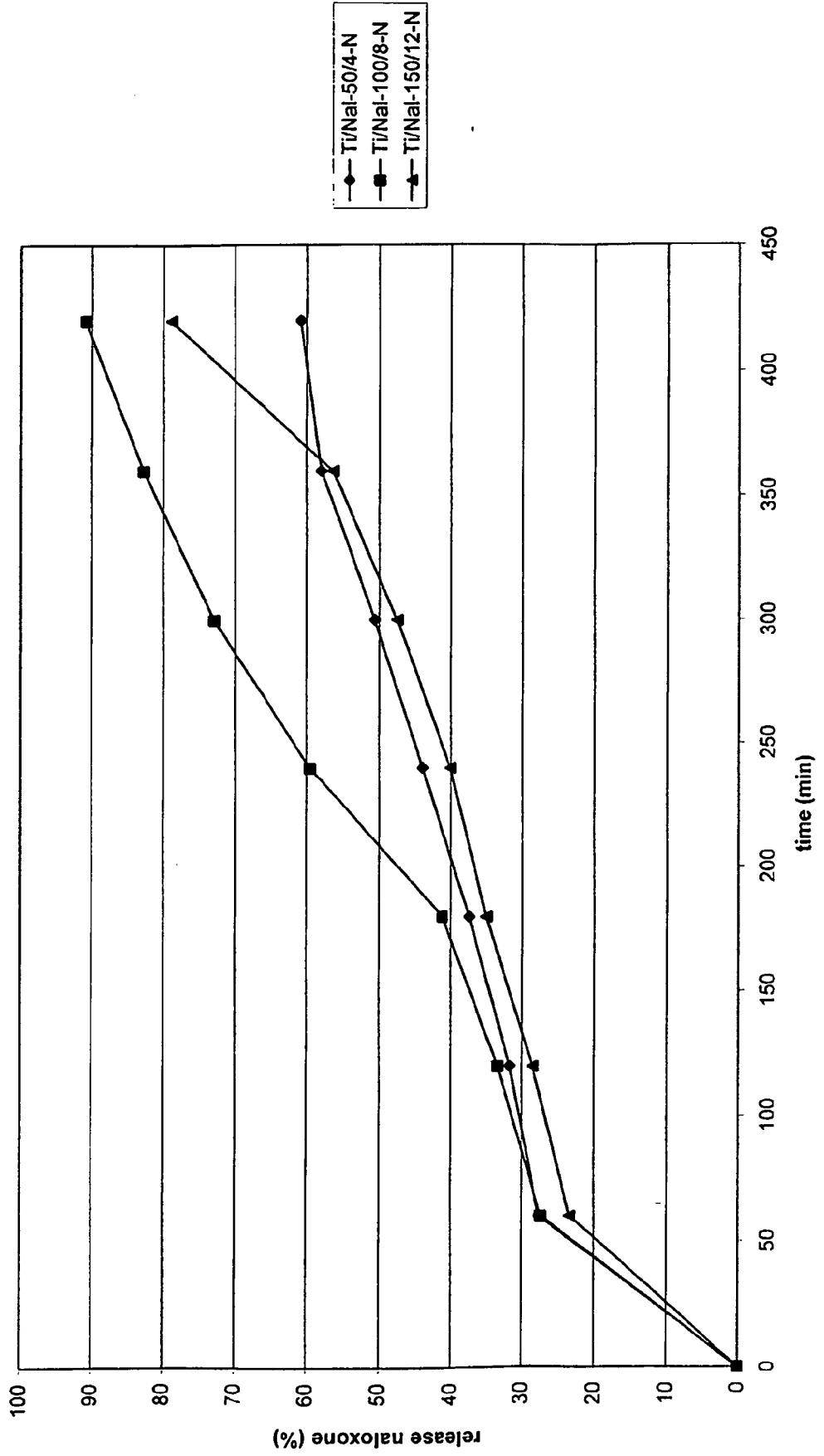


Figure 5A: Surface of the Ox/Nal-10 tablet at 25x magnification. The voltage was 10 kV. The bar length corresponds to 2 mm.

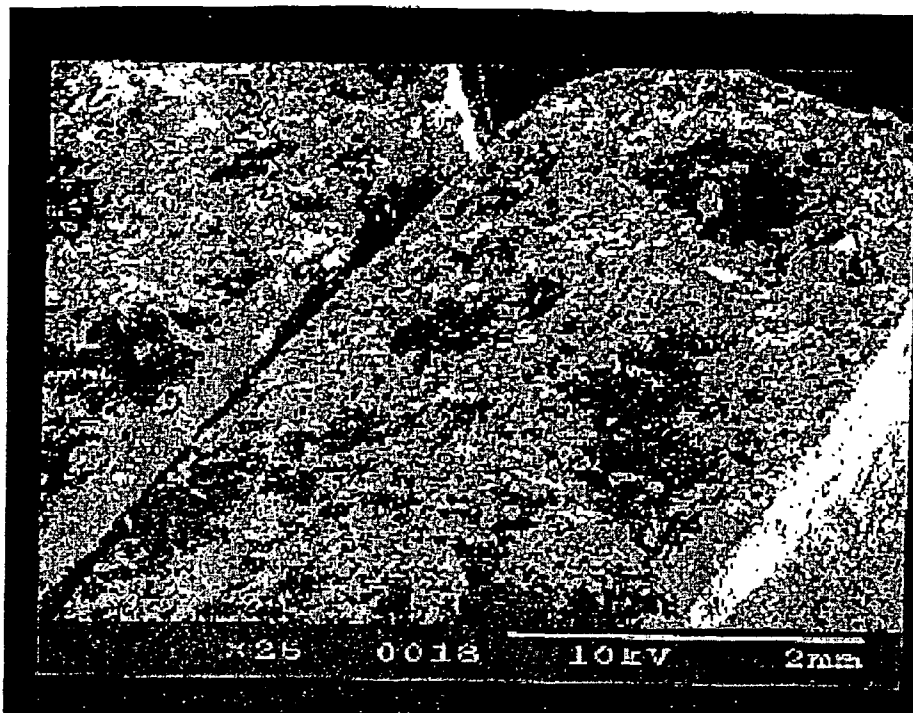


Figure 5B: Surface of the Ox/Nal-10 tablet at 200x magnification. The voltage was 10 kV. The bar length corresponds to 200  $\mu$ m.

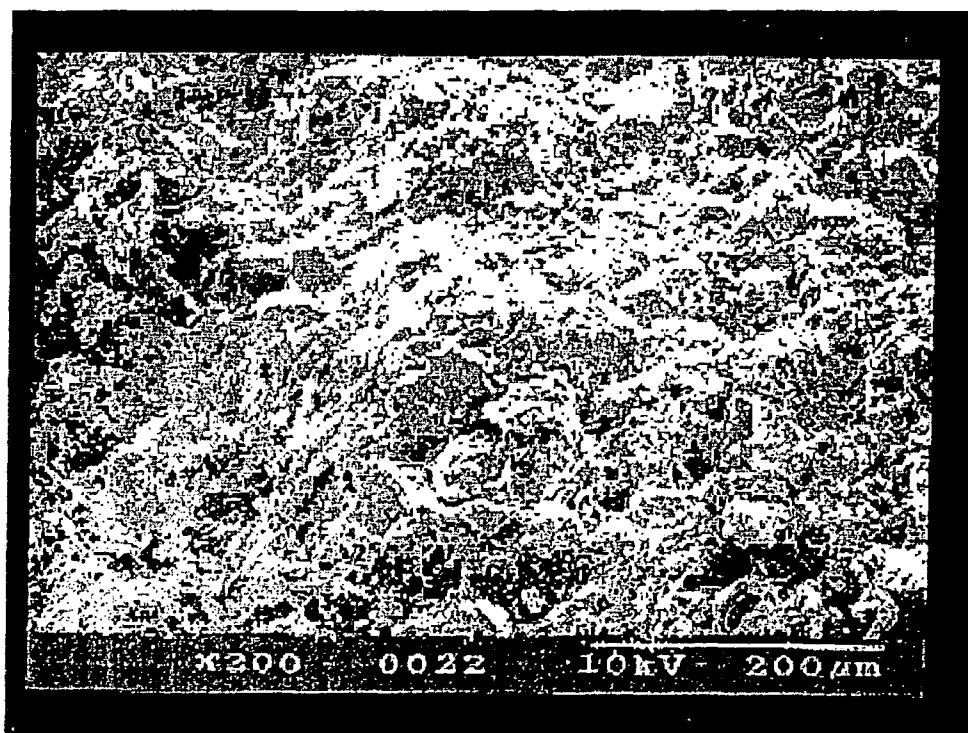


Figure 6A: Surface of the Oxy/Nal-Extr tablet at 40x magnification. The voltage was 10 kV. The bar length corresponds to 700  $\mu\text{m}$ .

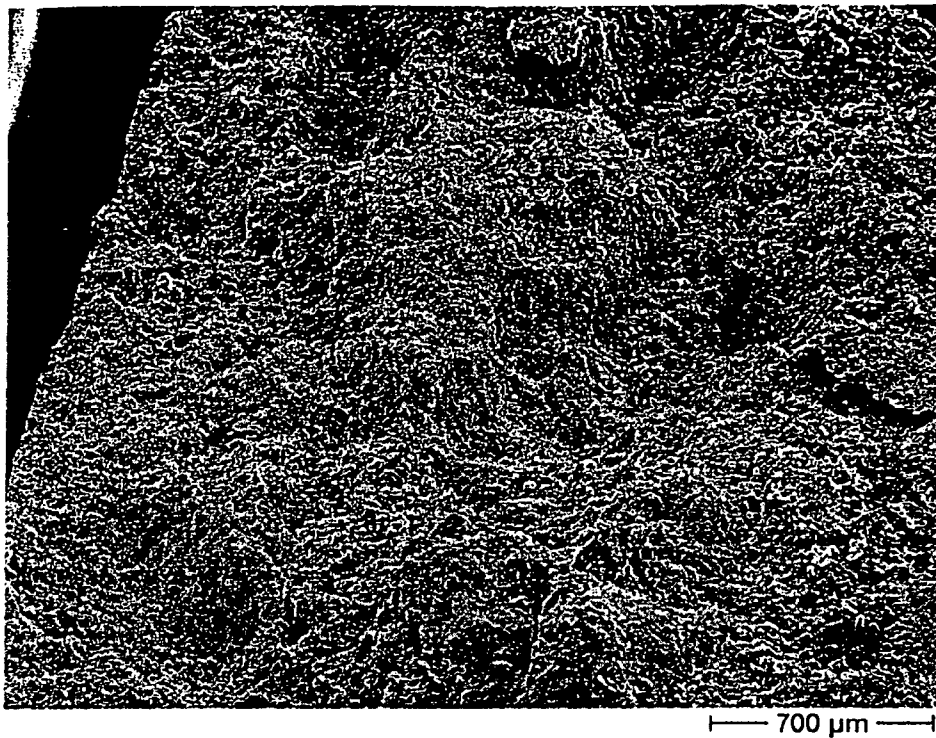


Figure 6B: Surface of the Oxy/Nal-Extr tablet at 100x magnification. The voltage was 10 kV. The bar length corresponds to 300  $\mu\text{m}$ .

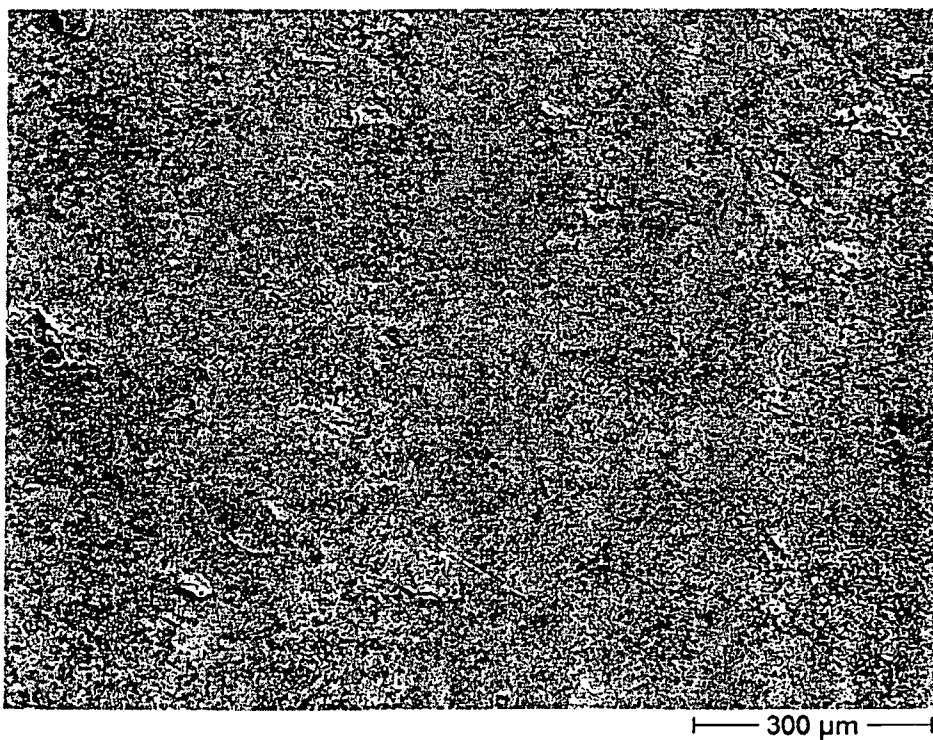


Figure 7A: Surface of the Valoron® N tablet at 25x magnification. The voltage was 10 kV. The bar length corresponds to 2 mm.

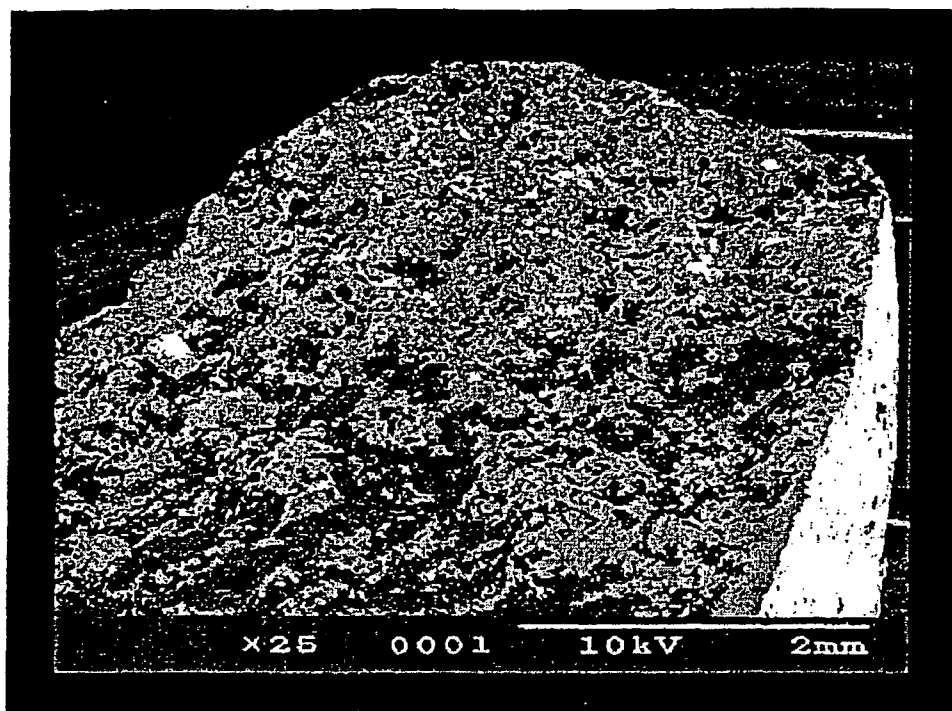
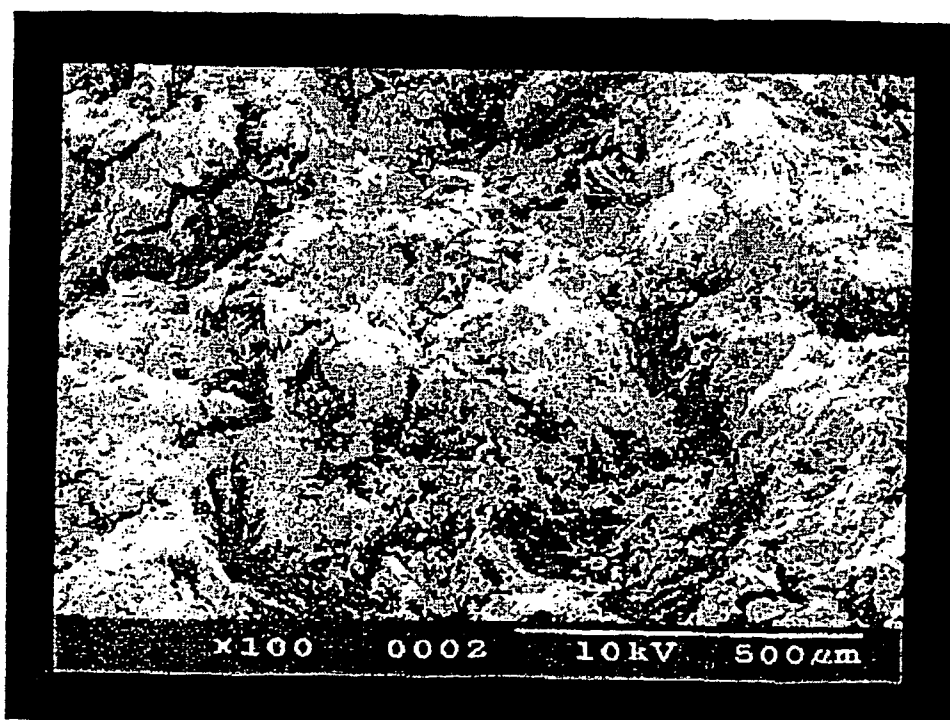


Figure 7B: Surface of the Valoron® N tablet at 100x magnification. The magnification shows a crystal of tilidine (down left). The voltage was 10 kV. The bar length corresponds to 500  $\mu$ m.



**REFERENCES CITED IN THE DESCRIPTION**

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## Oxicodont és naloxont tartalmazó gyógyszerkészítmény

### SZABADALMI IGÉNYPONTOK

1. Oxicodont vagy ennek gyógyszerészetileg elfogadható sóját és naloxont vagy ennek gyógyszerészetileg elfogadható sóját tartalmazó gyógyszerkészítmény fájdalom kezelésében való alkalmazásra és opioid-indukált székrekedés egyidejű csökkentésében való alkalmazásra, ahol a készítmény az oxicodonnak vagy gyógyszerészetileg elfogadható sójának és a naloxonnak vagy gyógyszerészetileg elfogadható sójának elnyújtott kibocsátását biztosítja, és ahol a készítmény az oxicodont vagy gyógyszerészetileg elfogadható sóját a naloxonhoz vagy gyógyszerészetileg elfogadható sójához viszonyítva 2:1 tömegarányban tartalmazza.

2. Gyógyszerkészítmény az 1. igénypont szerinti alkalmazásra, ahol a készítmény a naloxont vagy gyógyszerészetileg elfogadható sóját 1-50 mg tartományba eső mennyiségben tartalmazza.

3. Gyógyszerkészítmény az 1. vagy 2. igénypont szerinti alkalmazásra, ahol a készítmény az oxicodont vagy gyógyszerészetileg elfogadható sóját 10-150 mg tartományba eső mennyiségben tartalmazza.

4. Gyógyszerkészítmény az előző igénypontok egyike szerinti alkalmazásra, ahol a készítmény az oxicodont és a naloxont hidrokloridként, szulfátként, biszulfátként, tartarátként, nitrátként, citrátként, bitartarátként, foszfátként, malátként, maleátként, hidrobromidként, hidrojodidként, fumarátként vagy szukcinátként tartalmazza.

5. Gyógyszerkészítmény az előző igénypontok egyike szerinti alkalmazásra, ahol a készítmény egy tablettának felel meg.

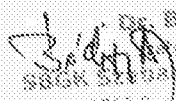
6. Gyógyszerkészítmény az előző igénypontok egyike szerinti alkalmazásra, ahol a készítmény, 1,2-es pH-n HPLC-vel az USP-nek megfelelő Basket-eljárással meghatározva, az oxicodonnak vagy gyógyszerészetileg elfogadható sójának és a naloxonnak vagy gyógyszerészetileg elfogadható sójának 1-40 %-át 15 perc elteltével, az oxicodonnak vagy gyógyszerészetileg elfogadható sójának és a naloxonnak vagy gyógyszerészetileg elfogadható sójának 40-80 %-át 2 óra elteltével, az oxicodonnak vagy gyógyszerészetileg elfogadható sójának és a naloxon-nak vagy gyógyszerészetileg elfogadható sójának 70-100 %-át 7 óra elteltével és az oxicodonnak vagy gyógyszerészetileg elfogadható sójának és a naloxonnak vagy



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gyógyszerészetileg elfogadható sójának 85-100 %-át 12 óra elteltével bocsátja ki *in vitro* módon.

A meghatalmazott:

  
Dr. Bódix Árpád  
Sóközvetítő Iroda  
Sóközvetítő Iroda  
n. 1063 S. János, Aranyos út 113.  
Telefon: 461-1000 Fax: 461-1098  
Email: sodix@soke.hu