Pharmaceutical combinations comprising tramadol

The present invention relates to the use of pharmaceutical combinations which, as active compounds, contain tramadol or one of its enantiomers or one of its pharmaceutically acceptable salts and metoclopramide, domperidone or other prokinetically and antiemetically active substances or one of their pharmaceutically acceptable salts, for the treatment of migraine and migrainoid headaches as well as to the treatment of states of pain which accompany nausea and/or vomiting (for example under chemotherapy) and/or delayed gastric emptying (for example post-operatively, in diabetic gastroparesis).

Migraine is a disorder with recurrent attacks of headache which last between 4-72 hours. Migraine attacks are mainly unilateral, initially dull, then pulsating headaches of medium to severe intensity. Typical concomitant symptoms of migraine are hypersensitivity to light and noise, facial pallor, nausea and vomiting with and without neurological focal deficits as a prodromal stage.

The (usual) migraine without aura is differentiated from the (classical) migraine with aura, which in each case begins with a characteristic scintillating scotoma. A complicated migraine is present if the visual disorders last for days or other neurological focal symptoms occur with the known special forms of retinal, basilar, ophthalmoplegic, aphasic or hemiplegic migraine.

Various ideas exist about the pathogenetic mechanism of migraine. The earlier haemodynamic idea, according to which the initial neurological deficits are induced by regional intracranial vasoconstriction and the subsequent pulsating headache is induced by extra-

cranial vasodilation with pain conduction via the ophthalmic nerve and trigeminal nerve explains the processes in migraine only inadequately.

The regional cerebral blood flow is decreased occipitally in a migraine attack with aura, the slow migration of the cortical oligaemia with overshooting of the supply ranges of individual arteries giving reason to believe that not only vasomotor, but also electrophysiological phenomena corresponding to the so-called "spreading depression" are involved (Spierings ELH (1988); Recent advances in the understanding of migraine. Headache 28: 655-658).

Other findings give reason to believe that the accompanying headache is caused not only by extracranial vasodilation, but also by a central lowering of the pain threshold, so-called immediate early genes (IEGs) being activated in the cells of the spinal cord and of the brain stem after noxious stimulation (Zimmermann, M. (1995); Neurobiologie des Schmerzsystems [Neurobiology of the pain system]. Neuroforum 1/95: 34-45).

Another theory - the model of neurogenic inflammation - offers the possibility of explaining both the blood flow change and the increased pain sensitivity of the vessels during the migraine attack. Accordingly, the increased sensitivity to pain is caused by an increased sensitization of the sensory perivascular fibres of the trigeminovascular system. As a result of this increased sensitization, vascular pulsations, which are normally not able to induce painful sensations, are potent pain stimuli and cause the pulsating throbbing migraine pain. The neurogenic inflammation is induced by noxious stimulation of the perivascular nerve fibres of the meningeal blood vessels. From the nerve ends, which are probably simultaneously nociceptors, neuropeptides such as substance P, neurokinin A and CGRP (calcitonin-gene

related peptide), which are able to induce the neurogenic inflammation, are secreted. CGRP can also be detected to an increased extent in the venous blood of the head during a migraine attack.

As a result of secretion of the neuropeptides, a vicious circle is set in motion: peptide release - vasodilation and capillary permeability increase - increased stimulation of nociceptors - increased peptide release. The active compounds sumatriptan and ergot alkaloids inhibit the release of the neuropeptides and thus interrupt the pain-inducing cycle (Zimmermann, M.: Chronische Schmerzen und ihre Ursachen [Chronic pain and its causes], Deutsches Ärzteblatt 93, Number 43, 1996: A-2749-2752).
Other findings favour a primarily neurogenic hypothalamic dysfunction, the vasoactive serotonin which is secreted in decreased amount from the Raphe's nuclei of the brain stem during the migraine attack having a key role (Ferrari MD et al. (1989): Serotonin metabolism in migraine. Neurology 39: 1239-1242; Pramod R., et al. (1989): 5-HT_1-like receptor agonists and the pathophysiology of migraine, Trends in Pharmacological Sciences 10, 200-204).

In spite of many hypotheses and complicated model ideas, the pathogenetic mechanism of migraine is presently not understood. Migraine has a multifactorial genesis with genetic disposition, external (such as alcohol) and internal (such as hormones) trigger mechanisms. It is not a psychosomatic disorder, although psychological factors can induce an attack.

A large number of preparations which contain individual active compounds or a number of active compounds in fixed combination are known for the treatment of migraine.
In general, antiemetics such as metoclopramide or domperidone on their own or in combination with non-

opioid analgesics such as acetylsalicylic acid, paracetamol, ibuprofen or naproxen are recommended for the treatment of migraine attacks. In the case of medium-severe to severe migraine attacks, antiemetics in combination with ergot alkaloids such as ergotamine or dihydroergotamine or alternatively sumatriptan are agents of choice.

Frequent side effects of ergotamine and dihydroergotamine are nausea, retching, vomiting, headaches, muscle pains and a general sensation of coldness, thus symptoms which under the false assumption of a continued migraine attack can lead to repeated taking of such preparations and thus to overdosage. As a result of frequent use, continual headaches can result which encourage ergotamine abuse. Serious side effects which can occur are circulatory disorders, coronary heart disease (CHD), arterial occlusive disease (AOD), hypertension and anginal symptoms. In pregnancy and the lactation period and in the case of children under 12 years, ergot alkaloids must not be used.

Sumatriptan and its derivatives (almotriptan, eletriptan, naratriptan, rizatriptan, zolmitriptan) are very efficacious migraine agents, which on oral administration are superior to the individual substances ergotamine, acetylsalicylic acid or metoclopramide. Sumatriptan is contraindicated in children, in pregnancy and the lactation period, in patients over 65 years and in patients with coronary heart disease. Undesired effects which can occur are sensations of pressure and heat, general feeling of weakness, a feeling of tightness in the chest, hypertension, coronary heart disease (CHD), myocardial infarct, angina pectoris.

Since, during migraine, gastric emptying is inhibited or considerably slowed and the stomach is of secondary importance as a site of absorption of pharmaceuticals because of the relatively small absorption area and the

significantly smaller vascularization in comparison to the small intestine, in a migraine attack only an inadequate or highly delayed absorption of the analgesic occurs. The emptying time of the stomach therefore plays a great part in the rapidity of the onset of action of the painkiller.

By means of prokinetics such as metoclopramide and domperidone, the gastric emptying and thus the absorption of the painkiller can be accelerated.

Metoclopramide and domperidone have their validity in migraine therapy, however, not only because of their prokinetic actions, but also because of their action against symptoms such as nausea and vomiting, which frequently occur as accompanying symptoms in migraine.

The medicinal therapy of migraine is of symptomatic nature, it does not cure the suffering. Mixed preparations of non-opioid analgesics and mixed preparations of ergot alkaloids are not advised, since on relatively long use, especially on daily use, they in turn cause headaches. In addition, liver and kidney damage, such as the so-called analgesic nephropathy, are possible consequences of the long-term taking of analgesic combinations.
In general, opioid analgesics are not suitable for the therapy of migraine because of their abuse and dependence potential.

The following combinations in particular are known from the patent literature for the treatment of migraine:

- paracetamol and metoclopramide (EP 011 489, EP 011 490, US 5 437 874, EP 695 546, EP 774 253)
- acetylsalicylic acid or the L-lysine acetylsalicylate thereof and metoclopramide (EP 606 031)

- analgesic (such as acetylsalicylic acid), antiemetic (such as metoclopramide) and an antacid (CA 20 20 018)

The analgesic combinations mentioned above in the patent literature are generally suitable for the treatment of migraine attacks. They are not suitable for the treatment of medium-severe to severe migraine. In the case of severe migraine, in general ergot alkaloids in combination with an antiemetic or sumatriptan are indicated.

It is disadvantageous that, under the therapy with ergot alkaloids or sumatriptan, a large number of in some cases severe cardiovascular side effects such as angina pectoris, coronary heart disease (CHD), hypertension and myocardial infarct can occur.

There therefore still exists a great need for a reliable painkiller which acts well in moderately severe to severe migraine attacks and has few side effects.

The object of the present invention is therefore in particular the provision of an improved therapeutic for the treatment of medium-severe to severe migraine attacks.

The invention thus relates to the subject matter claimed in the patent claims.

Tramadol (1RS;2RS)-2[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol is an analgesic which is effective in the case of moderately severe to severe pain.
Tramadol belongs to the group of weakly active opioids. Tramadol is distinguished in comparison with other opioids by a lower development of tolerance in respect of the analgesic action, by the significant absence of

opiate-typical side effects, and by a very low dependence potential.

The analgesic action of tramadol includes both opioid and non-opioid components, the latter via the release of serotonin (5-HT) and inhibition of the re-uptake of serotonin and noradrenalin in the central nervous system (CNS).

The non-opioid active components make a significant contribution to the analgesic action of tramadol.

Noradrenalin re-uptake is mainly inhibited by the (-)-enantiomer and serotonin release as well as the inhibition of the re-uptake of serotonin from the synaptic gap is decisively caused by the (+)-enantiomer. Both enantiomers contribute to the analgesic action in man.

Under treatment with tramadol, undesired effects which can occasionally occur are nausea, vomiting, sweating, dryness of the mouth, giddiness and light-headedness. Gastrointestinal symptoms or different psychological side effects are rarely observed.

Prokinetically active compounds, whose main representatives are metoclopramide and domperidone, increase the tone of the lower oesophageal sphincter and accelerate gastric emptying and passage through the small intestine.

At the same time, these active compounds are employed as antiemetics, that is for the suppression of nausea, retching and vomiting.

Metoclopramide and domperidone are indicated in gastroparesis, which can occur post-operatively and in some basic disorders (e.g. diabetes mellitus among others). They are also given in the case of functional dyspepsia, as its cause is suspected to be disorders of gastrointestinal motility.

In addition, they are indicated in migraine and other pain conditions which accompany disorders of gastric emptying.

Surprisingly, it has been found that by the administration of tramadol in combination with prokinetically active antiemetics, an improved agent for the treatment, in particular of medium-severe to severe migraine attacks, is available.

Opioids are in general not suitable for the treatment of migraine, since they are afflicted with a large number of side effects and can lead to physiological and physical dependence.

Moreover, opioids frequently have a constipating action, as a result of which the gastric insufficiency underlying the migraine is increased and thus the absorption and the onset of action of the painkiller is delayed.

An exception among the opioid analgesics is tramadol, which does not exhibit these serious side effects, which are typically seen in the use of opioids.

Surprisingly, it was also found that the migraine attacks are effectively cut short by the combination according to the invention of tramadol and in particular metoclopramide and the occurrence of the symptoms nausea and vomiting can be prevented.

This was all the more surprising, as tramadol itself can induce nausea and vomiting or can increase these accompanying symptoms of migraine.
Therefore tramadol was regarded as unsuitable in the past as a monopreparation for migraine treatment.

By means of combination with metoclopramide, it is also possible to make available tramadol, which is highly

effective in moderately severe and severe pain, for migraine treatment.

Since metoclopramide in migraine has an analgesic effect of its own, as placebo-controlled studies confirm, it is to be expected that a synergistic analgesic effect also occurs on the simultaneous administration of tramadol and metoclopramide.

Moreover, the tolerability of tramadol can be improved by the fixed combination, the absorption of tramadol in the gastrointestinal tract accelerated and the occurrence of the concomitant symptoms of migraine, nausea and vomiting, prevented. The substances tramadol and metoclopramide or domperidone are also suitable in respect of their pharmacodynamic and pharmacokinetic properties as combination partners in a fixed pharmaceutical preparation. The analgesic duration of action of tramadol is about 4-7 hours with a terminal elimination half-life of about 5-6 hours. The prokinetic duration of action of metaclopramide and domperidone is approximately 1-2 hours, the antiemetic duration of action approximately 3-5 hours. The half-life is 4-6 hours.

In a further embodiment of the present invention, the combinations can additionally contain non-steroidal anti-inflammatories (NSAID), such as, for example, acetylsalicylic acid, ibuprofen, naproxen or alternatively paracetamol.
As a result, on the one hand an achievement of this is that various analgesic mechanisms of action (central action of tramadol and the peripheral and central analgesic and anti-inflammatory action of the non-steroidal anti-inflammatories) can be utilized for the treatment of medium-severe to severe migraine attacks, which can be important in forms of migraine which are resistant to therapy. On the other hand, the total dose of tramadol or of the additional analgesically active

combination partner can be reduced with identical or improved action on the pain process and undesired effects (e.g. gastrointestinal symptoms with NSAIDs) can be decreased or avoided by a suitable composition of the combination partners.

The combinations indicated are particularly suitable for the treatment of moderate to severe migraine pain or migrainoid headaches.

Moreover, these combinations are suitable for the treatment of:

- moderate to severe acute and chronic pain which is accompanied by nausea and/or vomiting (e.g. vomiting caused by chemotherapy)
- moderate to severe acute and chronic pain with simultaneously present gastric emptying disorders (e.g. post-operatively or in diabetic gastroparesis, inter alia) and
- in nausea or vomiting under tramadol therapy.

Using clinical trials, the activity of the claimed combinations for treating migraine are to be illustrated in more detail using the combination of tramadol and metoclopramide as an example.

Eight patients suffering from moderate to strong migraine headaches which could no longer be treated with weak analgetics (for example acetylsalicylic acid, ibuprofen or paracetamol) were included in the user study.

The intensity of the migraine headaches before the beginning of the treatment and the characteristics of the attendant symptoms were documented, and the efficacy was assessed by the patient during the further course of the treatment.

The pain intensity before and after administration of the medicaments was measured on a VAS scale of a length of 100 mm at the points of time 0, 30 min, 1 h, 2 h, 4 h, 6 h and 12 h. The characteristics of the attendant symptoms of migraine, and their change after administration of the medicaments, were documented on a multi-level verbal rating scale. Furthermore, the patient was asked to assess efficacy and compatibility in a global manner.

Seven of the 8 patients treated were female, and one male. The average age of the patients was 44.7 years (35-63 years). Height and body weight were, on average, 169.3 cm (159-186 cm) and 70.4 kg (55-103 kg), respectively.

All patients conformed with the operational diagnostic criteria of IHS for the diagnosis migraine and had already suffered at least 5 migraine attacks of a duration of 4-72 hours. The headaches were localized strictly hemilateral, and the intensity of the headaches was increased by physical activity.

During the headache attacks, all patients suffered simultaneously from nausea and sensitivity to noise, 28% of the patients additionally suffered from vomiting and 43% from sensitivity to light. On average, the migraine had existed for 15.3 years (2-38 years); the average attack frequency was 4.1 days per month (2-8 days/month).

During the study period, the patients suffered 11 acute migraine attacks which were treated with the free combination of tramadol and metoclopramide.

All patients took the medicaments simultaneously in a single oral dose of 100 mg of tramadol (2 tramadol AWD capsules of 50 mg of tramadol-HCl each) and 10 mg of

metoclopramide solution (30 drops of metoclopramide Temmler 5 mg solution).

Prior to the documented treatment, the migraine pain was stated by the patients as being strong to very strong. On average, the original pain was 75 ± 7 mm (62-83 mm) on the VAS scale.

During the treatment, two patients, who each treated two migraine attacks, did not experience any improvement of the pain, and these patients were declared to be non-responders and excluded from the analysis.

Six patients, who treated 7 migraine attacks, remained. In this study, a VAS scale of a length of 100 mm, which is also customarily used in other pain studies, was employed for quantifying headaches.
Here, headaches were evaluated in an approximate manner using the following classification:

0 mm (no headache, **Grade 0**),
1-30 mm (slight headache, **Grade 1**),
31-60 mm (moderate headache, **Grade 2**),
61-100 mm (strong to very strong headache, **Grade 3**).

In most migraine studies, the success criterion is generally the percentage of patients who experience, within a defined period of time (in most cases after 2 or 4 hours) an improvement of the headache intensity from Grade 3 or 2 to 1 or 0.

Table 1: Tramadol/metoclopramide responder: difference between the headache intensity and original pain in mm VAS (the values in brackets are the change of the pain intensity in percent).

Patient	0 h	0.5 h		1 h		2 h		4 h		6 h		12 h	
	mm	mm	%	mm	%	mm	%	mm	%	mm	%	mm	%
1	62	-2	(-3.2)	-14	(-22.6)	-24	(-38.7)	-27	(-43.6)	-28	(-45.2)	-62	(-100)
2	83	-19	(-22.9)	-42	(-50.6)	-60	(-72.3)	-61	(-73.5)	-45	(-54.2)	-43	(-51.8)
3	81	2	(2.5)	-9	(-11.1)	-21	(-25.9)	-37	(-45.7)	-81	(-100)	-81	(-100)
4	70	-37	(-52.9)	-37	(-52.9)	-38	(-54.3)	-30	(-42.9)	-30	(-42.9)	-29	(-41.4)
5	72	-6	(-8.3)	-32	(-44.4)	-67	(-93.1)	-70	(-97.2)	-72	(-100)	-72	(-100)
6	80	-70	(-87.5)	-65	(-81.3)	-59	(-73.8)	-45	(-56.3)	-80	(-100)	-80	(-100)
7	77	2	(2.6)	1	(1.3)	*	*	-77	(-100)	-77	(-100)	-77	(-100)
Mean	**75**	**-18.57**	**(-24.25)**	**-28.29**	**(-37.36)**	**-38.43**	**(-51.15)**	**-49.57**	**(-65.58)**	**-59**	**(-77.46)**	**-63.43**	**(-84.75)**
std.dev.	7	26.66	(34.04)	22.58	(28.27)	24.81	(31.97)	19.88	(25.94)	23.86	(28.32)	20.19	(26.22)

* missing value

Additionally, following the abovementioned convention of the success or efficacy assessment of medicaments for migraine, in Table 2 we additionally state the success of the treatment as the percentage of patients who experienced an improvement of the severity of the headaches from Grade 3 or 2 to Grade 1 or 0 (including non-responders).

Table 2: Improvement of the headache intensity from Grade 3 or 2 to Grade 1 or 0 as a function of time after oral administration of 100 mg of tramadol capsules and 10 mg metoclopramide solution.

Time	**Number of patients (n=8)**	**Improvement from Grade 3-2 to 1-0 (% of patients)**
0.5 h	2	25
1 h	5	62
2 h	6	75
4 h	6	75
6 h	6	75
12 h	6	75

On average, in the group of the responders, the headaches improved after administration of the free combination of tramadol and metoclopramide even within 30 minutes by 24.3% and, after 2 hours, by 51.1%, based on the original pain. After 4 and 6 hours, the reduction in pain intensity was, on average, 65.6% and 77.5%, respectively (see Table 1).

For the entire group of patients treated (including the non-responders), we found an efficacy (improvement of the headaches from strong or moderate to slight or headache-free) of 25% after 30 minutes and 75% after 2 hours (see Table 2).

To recapitulate, it can also be deduced from the present data that the combination of tramadol and

metoclopramide in the dosage administered is a promising alternative to the medicines for migraine currently on the market which are used therapeutically for moderately strong to strong acute migraine headaches.

These combinations can be administered in the form of tablets, effervescent tablets, capsules, granules, powders, delayed-release tablets, delayed-release capsules (single and multiple unit formulations), ampoules for intravenous and intramuscular injection and in the form of infusion solutions, suspensions, suppositories or in other suitable pharmaceutical forms.

The delayed-release pharmaceutical forms can contain the active compounds in completely or partially delayed-release form with or without an initial dose content.

The active compounds can be present together or in formulations which are partly or completely separate from one another, so that a separate administration or one which is graduated in terms of time is also possible.

If such completely separate formulations are present, these are coordinated with one another and contain the respective active compounds in the dose unit in the same amounts and corresponding weight ratios in which they can be present in the combined mixture.
In these pharmaceutical compositions, the active compounds can also be present in the form of their pharmaceutically utilizable salts.

Orally administrable pharmaceutical compositions in which the indicated combinations are contained are preferred.

For the production of the pharmaceutical preparations which contain these combinations, the active compounds are formulated in the indicated amounts with physiologically tolerable excipients and/or diluents and/or auxiliaries in the desired manner.

Examples of the excipients and auxiliaries are gelatin, natural sugars such as cane sugar or lactose, lecithin, pectin, starch (for example maize starch or amylose), cyclodextrins and cyclodextrin derivatives, dextran, polyvinylpyrrolidone, polyvinyl acetate, gum arabic, alginic acid, tylose, talc, lycopodium, silicic acid, calcium hydrogenphosphate, cellulose, cellulose derivatives such as methoxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate, fatty acids having 12 to 22 C atoms, emulsifiers, oils and fats, in particular also vegetable glycerol esters and polyglycerol esters of saturated fatty acids, mono- or polyhydric alcohols and polyglycols such as polyethylene glycols, esters of aliphatic saturated or unsaturated fatty acids [lacuna] 2 to 22 C atoms with monohydric aliphatic alcohols [lacuna] 1 to 20 C atoms or polyhydric alcohols such as glycols, glycerol, diethylene glycol, 1,2-propylene glycol, sorbitol, mannitol.

Further suitable auxiliaries are also substances which cause disintegration (so-called disintegrants), cross-linked polyvinylpyrrolidone, sodium carboxymethylstarch, sodium carboxymethylcellulose, microcrystalline cellulose. Known coating substances can likewise be used. Polymers and copolymers of acrylic acid and/or methacrylic acid and/or their esters, zein, ethylcellulose, ethylcellulose succinate, shellac.

Suitable plastifiers for coating substances can be: citric and tartaric acid esters, glycerol and glycerol esters, polyethylene glycol of various chain lengths. Water or physiologically tolerable organic solvents,

for example, such as alcohols and fatty alcohols, are suitable for the preparation of solutions or suspensions.

For liquid preparations, the use of preservatives such as potassium sorbate, methyl 4-hydroxybenzoate or propyl 4-hydroxybenzoate, of antioxidants such as ascorbic acid and of flavour enhancers such as peppermint oil may be necessary.

In the production of the preparations, known and customary solubilizers, or emulsifiers, such as polyvinylpyrrolidone and polysorbate 80, can be used.

For further examples of suitable excipients and auxiliaries see also Dr. H. P. Fiedler "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete" [Encyclopaedia of auxiliaries for pharmacy, cosmetics and related fields].

In pharmaceutical preparations which contain the combinations of prokinetically active antiemetics and tramadol, the ratio should be 1:4 to 1:10. As individual doses, these pharmaceutical preparations in general contain 5-80 mg of an antiemetic or of one of its salts and 50-400 mg of tramadol or one of its salts. In this case, the daily dose should preferably contain 20 - 80 mg of antiemetic and 200 - 400 mg of tramadol.

Depending on the therapeutic indication, the daily doses mentioned can be employed either in the form of a single administration of the entire amount or in the form of 2 to 4 part doses per day. In general, one administration 2 to 4 times daily is preferred.

The following examples are intended to illustrate the invention in greater detail and are thus not a conclusive list.

Example 1

Preparation of a metoclopramide solution

802.4 g of purified water are introduced into a suitable container and 4.7 g of metoclopramide hydrochloride monohydrate, 0.1 g of ascorbic acid, 170.1 g of sorbitol, 2.8 g of potassium sorbate and a presolution of 18.9 g of ethanol 96% (v/v), 0.7 g of methyl 4-hydroxybenzoate and 0.3 g of propyl 4-hydroxybenzoate are added with stirring and the mixture is stirred until all constituents are dissolved. The solution is filtered through a suitable filter.

Recipe	Parts by weight (%)
Metoclopramide hydrochloride monohydrate	0.47
Ascorbic acid	0.01
Sorbitol	17.01
Potassium sorbate	0.28
96% (v/v) Ethanol	1.89
Methyl 4-hydroxybenzoate	0.07
Propyl 4-hydroxybenzoate	0.03
Purified water	80.24

Filling of the solution:

The solution is filled into suitable dropping bottles in a suitable filling machine.

Example 2

Preparation of the tramadol solution

484.2 g of purified water are introduced into a suitable container and 100.0 g of tramadol hydrochloride, 1.5 g of potassium sorbate, 161.8 g of ethanol 96% (v/v), 124.5 g of 1,2-propylene glycol, 200.0 g of granulated sugar, 1.0 g of polysorbate 80 and 1.0 g of peppermint oil are added with stirring and the mixture is stirred until all constituents are dissolved. The solution is filtered through a suitable filter.

Recipe	Parts by weight (%)
Tramadol hydrochloride	9.3
Potassium sorbate	0.1
96% (v/v) Ethanol	15.1
1,2-Propylene glycol	11.6
Granulated sugar	18.6
Polysorbate 80	0.1
Peppermint oil	0.1
Purified water	45.1

Filling of the solution:

The solution is filled into suitable dropping bottles in a suitable filling machine.

Example 3

Tramadol-metoclopramide delayed-release pellets

Preparation of the active compound-containing cores

4824 g of tramadol hydrochloride-metoclopramide hydrochloride monohydrate-Aerosil® 200 mixture are applied in a coating pan to 1000 g of neutral pellets of suitable size (e.g. having a diameter of between 0.5 and 0.6 mm) using about 2200 g of a 15% strength solution of ethylcellulose/shellac (6:4) in an about 96% (v/v) ethanol-water mixture. The cores obtained are then dried and screened (0.8-1.4 mm).

Application of the membrane

A membrane is applied to 6.15 kg of the active compound-containing cores prepared in this way by adding 470 g of a 15% strength solution of ethylcellulose/shellac (6:4) in an about 96% (v/v) ethanol-water mixture. 700 g of talc are introduced in powder form as a release agent.

Recipe	Parts by weight (%)
Tramadol hydrochloride	57.8
Metoclopramide hydrochloride monohydrate	11.6
Neutral pellets	14.4
Ethylcellulose	3.5
Shellac	2.3
Aerosil 200	0.3
Talc	10.1
About 96% (v/v) ethanol/water mixture	q.s.

Active compound release

The in-vitro release of tramadol hydrochloride from the delayed-release pellets according to Example 3 is determined according to USP 23/NF in apparatus 3. The temperature of the release medium is 37°C, the stroke

rate of the sample tubes 20 strokes/minute and the amount of test solution per investigation interval 175 ml.

The investigation is begun with test solution of pH 1.5, after the first hour change the rotors with the samples into 175 ml in each case of test solution tubes of pH 4.5, after the 2nd hour into a test solution of pH 6.9, after the 4th hour into a new test solution of pH 6.9, after the 6th hour into a test solution of pH 7.2 and after the 8th hour into a test solution of pH 7.5. The amount of active compound released found in the solution medium at the abovementioned times is determined spectrophotometrically. The following release rates are determined for tramadol hydrochloride:

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

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

Example 4

Tramadol-metoclopramide capsules

Preparation of the capsule filling material

323 g of tramadol hydrochloride, 6.5 g of metoclopramide hydrochloride monohydrate, 597 g of calcium hydrogen phosphate, 0.5 g of Aerosil® 200 and 1.0 g of magnesium stearate are screened and mixed in a suitable mixer.

Recipe	Parts by weight (%)
Tramadol hydrochloride	32.3
Metoclopramide hydrochloride monohydrate	6.5
Calcium hydrogenphosphate	59.7
Aerosil® 200	0.5
Magnesium stearate	1.0

Preparation of the capsules:

The capsule filling material is filled into hard gelatin capsules of suitable size with a nominal filling weight of 155 mg on a suitable capsule filling machine.

Example 5

Tramadol + metoclopramide soluble tablets

Preparation of the power mixture:

251 g of tramadol hydrochloride, 25 g of metoclopramide hydrochloride $1H_2O$, 4 g of Aerosil® 200, 50 g of Aspartam®, 100 g of crospovidone, 700 g of microcrystalline cellulose, 819.5 g of lactose monohydrate, 37.5 g of flavouring (for example strawberry), 10 g of sodium dodecyl sulphate and 3 g of magnesium stearate are screened and mixed in a suitable mixer.

Recipe	Parts by weight (%)
Tramadol hydrochloride	12.55
Metoclopramide hydrochloride 1-water	1.25
Aerosil® 200	0.20
Aspartam®	2.50
Crospovidone	5.00
Microcrystalline cellulose	35.00
Lactose	40.98
Flavouring	1.88
Sodium dodecyl sulphate	0.50
Magnesium stearate	0.15

Preparation of the tablets:

The powder mixture is tabletted using a suitable tabletting machine (400 mg nominal weight).

Patent Claims:

1. Use of pharmaceutical combinations of at least one prokinetically active antiemetic or pharmaceutically acceptable salts thereof and tramadol, its enantiomers or pharmaceutically acceptable salts for the production of a medicament for the treatment of migraine or migrainoid headaches.

2. Use of pharmaceutical combinations of at least one prokinetically active antiemetic or pharmaceutically acceptable salts thereof and tramadol, its enantiomers or pharmaceutically acceptable salts for the production of a medicament for the treatment of states of pain which accompany nausea or vomiting and/or delayed gastric emptying.

3. Use according to Claim 1 or 2, characterized in that the pharmaceutical combinations contain metoclopramide, domperidone or 5-HT_3 antagonists as antiemetic.

4. Use according to Claim 1 or 2, characterized in that the pharmaceutical combinations contain 5-80 mg of an antiemetic or of one of its salts and 50-400 mg of tramadol or one of its salts.

5. Use according to Claim 1 or 2, characterized in that the pharmaceutical combinations are preferably administered orally.

6. Pharmaceutical combinations comprising at least one prokinetically active antiemetic or pharmaceutically acceptable salts thereof and tramadol, its enantiomers or pharmaceutically acceptable salts and a non-steroidal anti-inflammatory (NSAID) or paracetamol.

7. Pharmaceutical combinations according to Claim 6, characterized in that the NSAID employed is preferably acetylsalicylic acid, ibuprofen or naproxen.

8. Use of the pharmaceutical combinations according to Claim 6 for the production of a medicament for the treatment of migraine or migrainoid headaches.

9. Use of the pharmaceutical combinations according to Claim 6 for the production of a medicament for the treatment of states of pain which accompany nausea or vomiting and/or delayed gastric emptying.

10. Medicament comprising pharmaceutical combinations according to Claim 6 and, if appropriate, pharmaceutically suitable excipients and/or auxiliaries.

11. Process for the production of a medicament according to Claim 10, characterized in that pharmaceutical combinations according to Claim 6 are processed using excipients and/or auxiliaries.