HU000025739T2

(19) **HU**

(11) Lajstromszám: **E 025 739**

(13) **T2**

MAGYARORSZÁG
Szellemi Tulajdon Nemzeti Hivatala

EURÓPAI SZABADALOM
SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 13 173438**
(22) A bejelentés napja: **2013. 06. 24.**

(51) Int. Cl.: ***A61K 9/24*** *(2006.01)*
C07D 213/38 *(2006.01)*

(96) Az európai bejelentés bejelentési száma:
EP 20130173438
(97) Az európai bejelentés közzétételi adatai:
EP 2679216 A1 **2014. 01. 01.**
(97) Az európai szabadalom megadásának meghirdetési adatai:
EP 2679216 B1 **2015. 05. 27.**

(30) Elsőbbségi adatok:
102012105528 **2012. 06. 25.** **DE**

(72) Feltaláló(k):
Dr. Francas, Gernot, 67551 Worms (DE)
Przyklenk, Karl-Heinz, 64521 Groß-Gerau (DE)

(73) Jogosult(ak):
Hennig Arzneimittel GmbH & Co. KG, 65439 Flörsheim am Main (DE)

(74) Képviselő:
ifj. Szentpéteri Ádám, SBGK Szabadalmi Ügyvivői Iroda, Budapest

(54) **Betahistin módosított kibocsátására szolgáló gyógyszerforma**

European patent application number: 13173438.6
European patent number: 2679216

The present invention relates to a medicament form for the modified release of betahistine, a method for the production thereof and the use of the latter.

Said invention relates to the preparation of medicament forms which make it possible to administer the active ingredient betahistine in the form of only one daily dose, whereas it usually has to be taken at least twice or multiple times daily.

Betahistine is used for the treatment of dizziness relating to Ménière's disease. To ensure that the active ingredient can be effective over the whole day it has to be taken several times a day. Usually betahistine has to be taken three times a day. In some cases it is also necessary to take the currently available betahistine-containing drugs five times a day to ensure its therapeutic effect over 12 to 24 hours. Because of its extremely good water solubility, its hygroscopicity and its acidity it is extremely difficult to formulate the active ingredients in a time-released form.

There is a great deal of interest in creating a medicament form that increases the comfort and the compliance of patients. However, it is very detrimental to the comfort and compliance of patients if several single doses of a medicinal product need to be taken every day. It is important to achieve patient compliance so as to avoid side-effects and the reduced effectiveness of the drug. The lack of compliance of many patients contributes significantly to an increase in healthcare costs.

It is a particular problem for patients who have difficulties swallowing and for older patients who have to take a large number of drugs to treat multimorbidity. The incidence

of Ménière's disease is considerably higher in older patients than younger ones, which means that it would be highly advantageous to reduce the frequency of taking the drug by formulating a new medicament form. In principle, it is known to reduce the number of times a drug needs to be taken by using various delaying mechanisms. This can be achieved for example by means of matrix embedding, so that the active ingredient is released with a time delay.

The reduction of the frequency of administering the drug requires particular medicament formulations which have to meet high technological requirements, as the latter comprise comparatively high amounts of active ingredients. A particular technological challenge is to provide a medicament form that has sufficient stability, exhibits effective time-release behaviour and is of tolerable size. The latter is important to ensure that the medicament form can be easily swallowed. It can also be difficult with large amounts of active ingredients to ensure that the taste is tolerable.

Until now mostly poorly dissolving active ingredients were at the centre of such developments. Numerous medicament forms have been developed for the latter, in particular matrix-based systems. The resorption of such active ingredients is determined by their release from the medicament form so that by developing suitable matrix systems an effective resorption of said active ingredients could be achieved. For highly soluble active ingredients other concepts are necessary. Of course, it is much more difficult to delay the release of a highly soluble active ingredient than a less soluble active ingredient which only dissolves slowly anyway.

Regardless of the solubility of an active ingredient it is very difficult in particular when active ingredients are used which are very difficult to process because of their

instability. In particular, this relates to active ingredients which decompose quickly or are hygroscopic.

Hygroscopic active ingredients tend to absorb moisture from the environment, mostly in the form of water vapour from air moisture. This can be achieved by various mechanisms such as absorption and adsorption. In this case there is a risk of the active ingredient dissolving away or clumping or that undesirable crystals will be formed. The latter makes processing much more difficult so that complex and expensive methods and intermediate steps are necessary to exclude moisture for example. Similarly, this disadvantageous property also makes it more difficult to provide a storable and long-lasting medicament form. Not only is the absorption of moisture from the environment critical but moisture can also be removed from the medicament form itself by the active ingredient. For example, such active ingredients can adsorb moisture from capsule shells resulting in cracks in the capsule shell.

Owing to the hygroscopicity of the active ingredient, in addition to the release of active ingredient from the medicament form, the handling of such medicament forms can also be much more difficult. In general, it would thus be necessary to store the medicament forms in an air-protected environment with the least possible moisture. However, the handling by the patient cannot be controlled and it can be assumed that older people in particular store their tablets outside of blister packs, for example in tablet boxes. Betahistine and the salts thereof are examples of hygroscopic active ingredients, which make their processing and administration much more difficult as described.

There are considerable difficulties in particular with hygroscopic active ingredients which are also highly soluble. The high solubility of the betahistine hinders the already difficult delivery of the active ingredients in medicament forms

with time-delayed release because of the hygroscopicity. Due to the high solubility the generally used delaying formulations for delaying the release of such active ingredients are mostly unsuitable. Additional difficulties are caused by the high acidity of the active ingredient, in particular because the active ingredient is also highly soluble. In this case there is also a risk that the acid active ingredient could attack or decompose the adjuvants. This could result in the decay of the medicament form and a change in the release profile. If a medicament form is to be provided with a suitable release there is a risk that all of the active ingredient will be released rapidly resulting in a high plasma levels and thereby strong side effects.

In this case the formulation of betahistine and the salts thereof as hygroscopic active ingredients, which are also highly soluble and acidic, presents significant difficulties. The hygroscopicity on the one hand and on the other hand the high solubility and high acidity of betahistine and its salts make it difficult to process in general and provide sufficiently stable and storable medicament forms.

Therefore, there is great demand for medicament forms which contain betahistine but can still be stored for a long period and exhibit a releasing behaviour which allows a single daily dose. In particular, there is a need for medicament forms which release betahistine so that it is unnecessary to take the drug several times a day, currently up to five times a day, and can be produced cost-effectively and on a larger scale.

A tablet for releasing betahistine in the form of betahistine dihydrochloride is described in WO 00/53162 A1. The tablet releases the active ingredient with a time delay over a period of mostly 5 to 8 hours. This makes a multiple daily dose unnecessary. Reference is also made to a combined rapid and

delayed release in the form of a two-layered table but its precise structure or production are not disclosed. In particular, it is not clear how the layers hold together and how an acceptable size of the medicament form is ensured. The release behaviour of the medicament form is also unclear. Reference is made only in general terms to the fact that it is possible to take a dose twice or only once daily. To this extent it is not clear whether the medicament form would be at all suitable for imitating a multiple daily dose.

In DE 100 10 509 A1 oral medicament forms are described which contain a sucrose fatty acid ester as the only release-controlling agent in an amount of 1 to 95 % by weight. The medicament forms release the active ingredients rapidly or without delay. A plurality of substances are referred to as possible active ingredients, including practically insoluble active ingredients. Betahistine dimesilate is mentioned as a possible active ingredient. In particular, the medicament form is suitable for administering active ingredients such as flupirtine, tramadol, nifedipine or carbamazepine. The medicament form can be in the form of a tablet. A medicament form which is suitable for releasing the same active ingredient in at least two phases, i.e. imitates a multiple daily dose, is not described in DE 100 10 509 A1. In this way the problem of releasing in particular highly soluble active ingredients which are also acidic and hygroscopic in two phases is not addressed in DE 100 10 509 A1.

WO 98/ 13029 A1 in turn relates to medicament forms for the delayed release of one or more active ingredients, including proteins, enzymes or vaccines sensitive to gastric juices, in order to ensure the therapeutic effect over a sufficient period. Betahistine is described as a possible active ingredient. The formulations contain a coating which tears after a specific

period in the gastrointestinal tract and thus permits the release of active ingredient. A fast-releasing formulation or another delayed releasing formulation can be combined with this formulation, for example in a capsule or as a coating. The precise structure of such a combination of active ingredient-containing formulations, in particular suitable amounts and ratios, are not described. It is also unclear to what extent the acidity and hygroscopicity of the active ingredient betahistine in the medicament form is weakened and to what extent sufficient stability is ensured. The example embodiment which comprises a medicament form with a delayed and rapid releasing unit comprises a capsule. On the one hand, patient compliance is generally reduced with regard to capsules because of their usually relatively large dimensions. On the other hand, there is a risk that that the capsule shell will change during storage and thus have a negative effect on the release when hygroscopic, in particular acidic active ingredients are processed in a capsule.

In DE 101 04 880 A1 multi-particulate medicament forms are described for the multi-phase release of a plurality of active ingredients, in order to ensure a steady release of the active ingredients throughout the bowel area. Betahistine is mentioned as a possible active ingredient. The medicament form here comprises two different pellet forms, which can be combined in a capsule or can be pressed together, wherein a ratio of 1:1 is described. The different pellet forms release the active ingredient or ingredients at different pH values. However, the medicament form does not allow the immediate release of an active ingredient in a first phase. It is thus not possible to achieve therapeutic plasma levels very rapidly in a first phase, and the active ingredients are only released specifically in the small intestine. It is thus still necessary to take several

medicament forms of active ingredients daily where therapeutic plasma levels have to be reached rapidly. Furthermore, the production of the multi-particulate medicament forms is complex and expensive and not suitable for hygroscopic and acidic active ingredients.

Thus there is a great need to provide medicament forms for releasing betahistine which release the active ingredient, so that it is not necessary to take the medicine several times a day, and ensure sufficient stability and storability. Conventional medicament forms have limitations in this regard. In particular, it is only possible to delay the release of betahistine with standard delaying means and conventionally used delaying principles with great amount of effort and at great expense. It is almost impossible to delay the effect by more than 10 hours using conventional delaying principles for the active ingredient betahistine. Conventionally used delaying mechanisms are thus not suitable for the cost-effective and industrial-scale production of betahistine in medicament forms which make it unnecessary to take a multiple daily dose of active ingredient.

The underlying problem of the present invention is addressed by the subject matters of the claims.

The present invention provides oral medicament forms for at least the two-phase release of betahistine, wherein part of the active ingredient is released in the first phase immediately after taking. According to the invention the medicament form is a shell-core tablet. The invention also relates to a production method for such medicament forms and to suitable uses thereof. The concept according to the invention thus does not relate to an extended release in the sense of a conventional delaying formula, but provides the immediate release of a first active ingredient portion immediately after taking and the release of

at least a second active ingredient a certain time after taking. Thus a pulsed release simulates taking the active ingredient twice or multiple times and makes it unnecessary to take the medicament form twice or multiple times.

The medicament form of this invention comprises the active ingredient betahistine in an amount between 1 mg and 200 mg and

- a core which comprises 40% to 60% of the active ingredient,
- an intermediate layer which is arranged on the surface of the core, and
- a shell which comprises 40% to 60% of the active ingredient and is arranged on the side of the intermediate layer opposite the core.

In preferred embodiments the medicament form according to the invention does not comprise an additional component which contains active ingredients, in addition to the core, the intermediate layer and the shell, thus in particular does not have an additional active ingredient-containing layer. More preferably, the medicament form according to the invention comprises the core, the intermediate layer and the shell. Preferably, the medicament form according to the invention comprises the active ingredient betahistine in an amount between 1.5 mg and 150 mg, more preferably in an amount between 2 and 120 mg, even more preferably in an amount between 5 and 60 mg.

The active ingredient is released from the medicament form in at least two phases. Additional release phases can follow. A "phase" according to the invention is the time interval for the release of an amount of active ingredient from the medicament form.

In a first phase a first amount of active ingredient is released. In a second phase a second amount of active ingredient is released. According to the invention the first phase begins

directly after the entry of the medicament form into the stomach. The first phase thus relates to the immediate release of the active ingredient after entry into the gastric juices. This first phase of the release is from the shell, the shell preferably decomposing in the stomach. The second phase of the release comes from the core. The core preferably does not decompose in the stomach and is preferably transported by the so-called "housekeeper waves", i.e. by the contractions of the stomach, into the small intestine in order to release an amount of active ingredient from the core.

"Immediate release" means preferably that at least 65% of the first amount of active ingredient, preferably at least 75% and also preferably at least 80% of the first amount of active ingredient is released after 60 minutes into the gastric juices. Particularly preferably, more than 60%, also preferably more than 65% of the first amount of active ingredient is released into the gastric juices after just 30 minutes. This is determined in vitro by using standard apparatus such as rotating basket, stirring blade or flow apparatus in 0.1 N HCl or water as a testing medium under physiological conditions (rotation about 36 to 38°C). The specific conditions are dependent on the specific active ingredient and can be taken from established pharmacopoeia.

The release of the first amount of active ingredient is performed directly after taking the medicament form. Preferably, the release of said amount of active ingredient is not delayed by coatings. Prior to the release of the first active ingredient any coating, for example a film, must not dissolve, tear or swell.

Preferably, the second phase begins at the earliest 4 hours, preferably at the earliest 6 hours and most preferably at the earliest only 7 hours after taking the medicament form. An

early second phase could result in high plasma concentrations which are associated with a risk of side effects and also means there is a risk that the release of active ingredients is not maintained for a sufficiently long period so that the single daily dose is therapeutically sufficient. The second amount of active ingredient is preferably released however at the latest 16 hours after taking, more preferably at the latest 14 hours after taking and most preferably at the latest 12.5 hours after taking. If the release is too late it would mean that the second amount of active ingredient is only released in the deeper parts of the bowel which could mean that the resorption would be reduced significantly because of the reduced resorption area and limited amount of fluid. Particularly preferably, the second amount of active ingredient is released in the colon.

The release in the second phase is preferably performed immediately after reaching a specific pH range. The second amount of active ingredient is preferably released from the core of the medicament form. Thus after reaching a specific pH value within 60 minutes, preferably at least 65% of the second amount of active ingredient, preferably at least 75% and also preferably at least 80% of the second amount of active ingredient, determined in-vitro by using common apparatus in a buffer medium with the respective pH range as a testing medium under physiological conditions (rotation at about 36 to 38°C). The specific conditions are dependent on the specific active ingredient and can be taken from established pharmacopoeia.

Alternatively, the release of the amount of second active ingredient can also be delayed, i.e. extended over a specific time period, preferably over at least 4 hours, more preferably over at least 6 hours. In one embodiment additional release phases can be provided in which portions of the active ingredient are released.

However, the medicament form in addition to the first active ingredient can also comprise further active ingredients, which are released either in a single phase or multiple phases. A multi-phase release is preferred. Particularly preferably, the medicament form according to the invention only comprises one active ingredient, i.e. betahistine. In this way any incompatibilities originating from the production and storage can be avoided.

The medicament form of the present invention is an oral medicament form, this means that it is meant to be taken orally. According to the invention the medicament form consists of a shell-core tablet, which contains the core on the inside and the core is surrounded by the intermediate layer. The latter is in turn surrounded by the shell. The core is "surrounded" by the intermediate layer preferably if at least 95% of the total surface of the core, more preferably at least 98% and more particularly preferably at least 99% of the total surface of the core is covered by the intermediate layer. Even more preferably the total surface of the core is surrounded "completely" by the intermediate layer, whereby "completely" preferably means that more 99.5%, ideally more than 99.8% of the total surface of the core is covered by the intermediate layer. This does not exclude the fact that there are pores in the intermediate layer. The intermediate layer is "surrounded" by the shell preferably if at least 95% of the total surface of the side of the intermediate layer opposite the core, more preferably at least 98% and even more particularly preferably at least 99% of the shell is covered. Even more preferably the total surface of the side of the intermediate layer opposite the core is completely surrounded by the shell, i.e. preferably more than 99.5% and ideally more than 99.8% of the side of the intermediate layer opposite the core is covered by the shell.

The purpose of the medicament form concept according to the invention as a shell-core tablet differs from the purpose usually described in the prior art. Thus shell-core tablets are known as a formulation option for incompatible active ingredients or extremely unpleasant tasting or extremely instable active ingredients. According to the invention the shell-core concept imitates taking at least two tablets daily preferably at an interval of 8 to 12 hours.

The term "betahistine" used here also comprises the pharmaceutically suitable salts of betahistine. The pharmaceutically suitable salts of betahistine are in particular betahistine dihydrochloride, betahistine dimesilate, betahistine methane sulfonate, betahistine fumarate and betahistine citrate. Preferred pharmaceutically suitable salts of betahistine are betahistine dihydrochloride, betahistine dimesilate, betahistine fumarate and betahistine citrate. Particularly preferred salts are betahistine dihydrochloride and betahistine dimesilate. In a particularly preferred embodiment the medicament form comprises betahistine dihydrochloride or betahistine. Preferably between 2 mg and 55 mg relative to the active ingredient base are contained in the medicament form. The active ingredient base is betahistine, i.e. not the salt thereof.

More particularly preferably the medicament form according to the invention contains betahistine dihydrochloride, preferably in an amount between 8 mg and 100 mg, more particularly preferably between 30 and 60 mg, and most preferably 48 mg are contained in the medicament form. When absolute values are specified in the application they always include a tolerance range of +/- 2% around said absolute value.

Betahistine and the pharmaceutically suitable salts thereof are hygroscopic and highly water soluble.

Hygroscopicity exists according to the invention preferably if a material which at 75% relative humidity, preferably at 45% relative humidity and most preferably even at 30% relative humidity, absorbs more than 1 % by weight water from the environment. Particularly preferably, at least 5 % by weight, more preferably at least 8 % by weight water is absorbed from the environment. The amount of water taken up is determined by introducing 0.5 g of a previously only air-tight stored sample of a substance into an atmosphere with a relative air humidity of 75%, 45% or 30% for 24 hours. Afterwards the water content of the substance is determined by the Karl Fischer method in a Karl Fischer titrator by heating up to at most 300°C. The water content is compared with the water content of 0.5 g of the substance from the same sample but which was stored further in an air-tight environment.

The amount of active ingredient in the core is preferably at least 42% and at most 58%, more preferably at least 45% and at most 55% of the total amount of active ingredient in the medicament form. If the amount of active ingredients in the core is too low there is risk that the effect cannot be maintained for a sufficiently long period.

Particularly preferably, the amount of active ingredient in the core and shell is the same. This enables a multi-phase release of the same amounts of active ingredient and is advantageous because this kind of release imitates a multiple daily dose. Preferably, the amount of active ingredient in the shell allows a sufficient therapeutic effect to be maintained for 8 to 12 hours. More particularly, the core and the shell preferably contain 24 mg betahistine dihydrochloride respectively.

In addition to the active ingredient a second and possibly a third active ingredient can be contained in the core, shell

and/or intermediate layer. More particularly preferably the intermediate layer does not contain an active ingredient, i.e. no betahistine.

In addition to the active ingredient the core comprises pharmaceutically acceptable adjuvants. Pharmaceutically acceptable adjuvants are those that with respect to patient safety and processability are generally suitable for use in medicament forms.

The core comprises at least two carrier substances, consisting of at least one disaccharide and at least one polysaccharide with more than 10 monosaccharide components which is preferably swellable on contact with water. By means of this combination optimum breaking resistance and stability are achieved. In addition, the amount of active ingredient is preferably optimally fixed onto the carrier substance. Particularly preferably, the core contains at least three carrier substances. The mass ratio of polysaccharides with more than 10 monosaccharide components to disaccharides is preferably at least 1.1:1, preferably at least 1.25:1 and more preferably at least 1.3:1. These substances can be obtained inexpensively and are easy to process. The latter is particularly advantageous if the active ingredient is to be released from the core straight away. Polysaccharides, which contain glucose units, have proved to be particularly advantageous.

Disaccharides are preferably selected from lactose, sucrose and mixtures thereof.

Preferred polysaccharides with more than 10 monosaccharide components, which are preferably swellable on contact with water, are starch including starch derivatives, cellulose including cellulose derivatives or mixtures thereof. Powdered cellulose such as microcrystalline cellulose is particularly preferred. Likewise starch can be used in a native or pre-

agglutinated form, in particular maize starch. Such carrier substances are better able to absorb water from the active ingredients. However, it has been shown that the breaking resistance of the tablet can decrease with the exclusive use of such polysaccharides as carrier substances as the storage period increases. Therefore, at least two carrier substances are included in the core, consisting of at least one disaccharide and at least one polysaccharide with more than 10 monosaccharide components which is preferably swellable on contact with water.

The carrier substances are sorption-active. A sorption-active carrier substance is able to be deposited on a hygroscopic active ingredient portion, i.e. "carry" the latter and remove the hygroscopicity of the active ingredient to a certain degree. This prevents the dissolving away of the hygroscopic active ingredient which clearly has a positive influence on the breaking resistance and shelf-life of the obtained medicament form.

Surprisingly, in particular carrier substances have proved to be suitable which are themselves hygroscopic, i.e. are suitable for moisture absorption. In fact a poor processability would be expected by the additional moisture absorption of such carrier substances. However, in fact by using such carrier substances together with the active ingredient a solid and stable core can be obtained which can be easily processed and can be compressed.

However, it has been shown that the carrier substances preferably have to be available in excess in relation to the active ingredient. The mass ratio of the carrier substances in the core to the active ingredient in the core is therefore preferably at least 2:1, more preferably at least 3:1, even more preferably at least 3.4:1 and in particularly preferred embodiments at least 5:1. The carrier substances clearly have

the effect that the further absorption of water from the environment can be significantly reduced. The mass ratio should however preferably not be greater than 20:1, preferably not greater than 10:1, more preferably not greater than 7.5:1, as otherwise the processability can be made more difficult. In addition, a mass ratio that is too high is associated with a core that is too large. This can result in too much of an enlargement of the medicament form according to the invention.

Particularly preferably, the core is free of salts comprising calcium phosphate, sodium salts of cellulose and/or magnesium stearate, i.e. such salts are only contained as impurities in an amount of preferably a maximum of 0.5 % by weight, preferably a maximum of 0.1 % by weight in the total mass of the core. If such salts are used in large amounts in the core according to the invention, there can be reaction of the active ingredient in the core with these substances, whereby the stability of the active ingredient in the core can be disadvantageously influenced.

The total amount of carrier substances according to the invention in the total mass of the core is at least 50 % by weight, preferably at least 63 % by weight and more particularly preferably at least 65 % by weight and even more preferably at least 68 % by weight. If too little carrier substance is used the hygroscopicity of the active ingredient can only be compensated insufficiently. Furthermore, the carrier substances have a certain delaying effect on the release of the active ingredient. The core contains a maximum of 90 % by weight carrier substances, preferably a maximum of 85 % by weight carrier substances, more preferably a maximum of 80 % by weight. If the proportions of carrier substance are too high the shaping of the core becomes more difficult. The carrier substances can

also weaken the acidity of the active ingredient. For this a certain amount of carrier substance is required.

In order that the amount of carrier substances remains within sensible limits according to the invention at least one low-molecular organic acid is used as a buffer substance in the core. "Low molecular" acids are organic acids which have molar masses of below 300 g/mol. The mass of organic acid used is preferably less than the mass of the carrier substances. In this case a mass ratio of carrier substances in the core to organic acid in the core is preferably at least 3:1, more preferably at least 4:1 and more particularly preferably at least 4.5:1 and a sufficient compensation of the hygroscopicity and also a sufficient weakening of the acidity could be achieved with good processability of the core. The core contains preferably at least 1 % by weight organic acid, preferably at least 8 % by weight. Preferably, the core contains a maximum of 26 % by weight organic acid, more preferably a maximum of 16 % by weight. The amount of organic acid should not exceed specific values, because said components can worsen the stability of the medicament form.

The organic acid is preferably a carboxylic acid selected from citric acid, lactic acid, tartaric acid, fumaric acid, maleic acid and ascorbic acid as well as mixtures of the latter. Particularly preferred are alpha-hydroxycarboxylic acids, which because of the alpha-hydroxy group show an optimum buffering effect. Preferably, the latter are selected from lactic acid, tartaric acid, citric acid and mixtures thereof. Citric acid is particularly advantageous which can be processed particularly easily and the release of the active ingredient from the core does not change significantly. This is surprising as citric acid in many pharmaceutical forms accelerates the release which would be undesirable here.

The mass ratio of the active ingredient in the core to the organic acid in the core is at least 0.5:1, preferably at least 0.8:1, also preferably at least 0.9:1. The mass ratio according to the invention is a maximum of 1.5:1, preferably a maximum of 1.2:1 and also preferably a maximum of 1.1:1. If there is too little organic acid the acidity of the active ingredient cannot be buffered sufficiently. If there is too much organic acid the acidity increases disadvantageously. The core according to the invention contains preferably at least 8 mg organic acid, preferably at least 15 mg and more particularly preferably at least 20 mg. Preferably, a maximum of 48 mg and more particularly preferably a maximum of 30 mg organic acid are contained in the core.

The core can contain at least one additional pharmaceutically acceptable adjuvant such as for example a filler and/or binding agent. The core can also contain disintegrating agents, selected in particular from alginic acid, calcium carboxymethyl cellulose, cross-linked carboxymethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl starch, cross-linked polyvinyl pyrrolidone and mixtures thereof. The addition of such a disintegrating agent prevents the amount of active ingredient being released from the core only in very deep parts of the bowel. This would result in a much worse resorption of the amount of active ingredient because of the reduced resorption area. It has proved particularly suitable to add cross-linked polyvinyl pyrrolidone.

Preferably, the disintegrating agent has a weight proportion in the core of at least 1 % by weight, more preferably at least 2 % by weight, in order to achieve sufficient decomposition. The maximum content of disintegrating agent is preferably 8 % by weight, preferably a maximum of 6.5 % by weight. If the proportion of disintegrating agent is too high

the release of the active ingredient is too rapid. Alternatively, the core is preferably free of such disintegrating agents, as with the particular core composition according to the invention in most cases surprisingly a sufficiently rapid decomposition is ensured.

The core can comprise at least one granulating agent depending on the manufacturing process. Preferably, the granulating agent contained in the core is in an amount of at least 0.1 % by weight, more preferably at least 0.25 % by weight, even more preferably at least 0.5 % by weight and even more preferably at least 0.75 % by weight. The core contains a maximum of preferably 5 % by weight, more preferably a maximum of 2.5 % by weight granulating agent. Preferred granulating agents in the core are listed below.

According to the manufacturing process the core contains preferably at least one lubricant, preferably in a mass proportion of at most 10 % by weight, preferably at most 8 % by weight of the total mass of the core. Preferably, at least 0.5 % by weight, more preferably at least 1 % by weight lubricants are contained in the core. Preferred lubricants in the core are listed below.

In one embodiment the core contains:

a. betahistine; and

b. at least two carrier substances (in a mass portion of 50 % by weight to 90 % by weight), which are used in particular for "carrying" the active ingredient, for weakening its hygroscopicity and acidity and also for ensuring a certain delaying effect; and

c. at least one low-molecular organic acid (with a mass ratio of active ingredient in the core to organic acid in the core of at least 0.5 to 1 and at most 1.5 to 1 and preferably

with a mass portion of 1 % by weight to 26 % by weight) in particular for weakening acidity of the active ingredient; and

d. optionally a disintegrating agent (preferred mass portion 1 % by weight to 8 % by weight) for accelerating the decomposition of the core; and

e. optionally according to the manufacturing process at least one granulating agent (preferred mass amount of 0.1 % by weight to 5 % by weight); and

f. optionally according to the manufacturing process at least one lubricant (preferred mass portion 0.5 % by weight to 10 % by weight); and

g. optionally additional adjuvants such as for example fillers and/or binding agents.

An intermediate layer is arranged on the surface of the core. A layer of this kind has proved to be advantageous in order to stagger the release of the active ingredient from the core and the shell. Preferably, the intermediate layer is also used to bind the core and shell to one another. Without the intermediate layer the breaking resistance and storable medicament form could mostly not be achieved.

Furthermore, it has been shown that fewer adjuvants are needed in the core, if the intermediate layer exclusively or additionally controls the release of the active ingredient out of the core. In this way the size of the core can be reduced and a suitable size of the entire medicament form can be ensured which is necessary for good patient compliance. Also the release of the active ingredient controlled solely by the core proved difficult because of the high solubility. Thus the release of the active ingredient out of the core with the exclusive use of a delaying matrix could often not be separated in sufficient time before the release of the active ingredient out of the shell. The release could thus not be maintained for a

sufficiently long period. Only with the intermediate layer according to the invention could the release of the active ingredient out of the core and out of the shell be time-staggered sufficiently.

The intermediate layer is preferably resistant to stomach juices. "Resistance to gastric juices" preferably means that the intermediate layer does not dissolve in the pH range of the stomach, and preferably does not dissolve within 120 minutes in 0.1 N HCl at 36°C to 38°C. This preferably means that the core, with the intermediate layer on its surface, does not decompose within 120 minutes in 0.1 N HCl at 36 to 38°C. The decomposition is measured using conventional decomposition apparatus, preferably paddle stirrer apparatus.

The release from the core begins at the earliest on entry into the small intestine milieu by dissolving, decomposition, tearing or other change to the intermediate layer, preferably by dissolving the intermediate layer on reaching a specific pH value. The intermediate layer dissolves preferably on reaching a specific pH value in the aqueous medium of the gastrointestinal tract. The different possible processes are described according to the invention by the term "releasing". The release of the intermediate layer is preferably performed from a pH value of at least 5, more preferably from a pH value of at least 6 and even more particularly preferably from a pH value of at least 6.5. Particularly preferably, the intermediate layer is released from a pH value of at least 7.0 and even more preferably from a pH value of at least 7.2. Releasing at pH values that are too low would cause an early release of the active ingredient in the second phase in the stomach or in the upper duodenum section. Depending on the active ingredient this means that there is a risk of reaching an excessively high plasma level. The intermediate layer should preferably be released at the latest

at a pH value of 7.65, more preferably at the latest at pH 7.5. If the intermediate layer is only released at pH values that are too high, it is no longer possible to ensure a sufficient resorption of the active ingredient.

The intermediate layer comprises at least one film former which preferably ensures gastric juice resistance.

Film formers according to the invention consist of cellulose derivatives, methacrylic acid polymers, polyvinyl derivatives and mixtures thereof. Natural and synthetic polymers have proved to be suitable film formers which have free acid functions. Preferably, said acid functions are highly soluble in salt form. Preferably, each polymer comprises at least 0.1 free acid functions for each monomer component, more preferably at least 0.3 free acid units for each monomer component. Such polymers are suitable for dissolving in the alkali pH range of the bowel, but not in the acidic pH range of the stomach. Preferably such free acid functions are carboxyl groups, as the latter are mostly sufficiently soluble in salt form.

Cellulose derivatives are preferably celluloses that are esterified with organic acids. The organic acids can be aliphatic or aromatic. Preferably, said organic acids comprise at most 10 carbon atoms, more preferably at most 8 carbon atoms. However, they preferably comprise at least 2 carbon atoms. The cellulose derivate is selected particularly preferably from cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate and mixtures thereof.

Preferred polyvinyl derivatives are those that are esterified with organic acids. The latter can be aliphatic or aromatic in nature and preferably comprise at least 2 carbon atoms, preferably however a maximum of 10 carbon atoms.

Preferably, the polyvinyl derivative is esterified both aliphatically and aromatically. A particularly preferred polyvinyl derivative is polyvinyl acetate phthalate.

Suitable methacrylic acid polymers have proved to be those that are composed of methacrylic acid monomers with free carboxyl groups and monomers with esterified carboxyl groups. The monomers with esterified carboxyl groups are preferably selected from methacrylic acid monomers and acrylic acid monomers. The monomers with esterified carboxyl groups are preferably aliphatically esterified, preferably with organic groups. Said organic groups preferably comprise at least 1 carbon atom, preferably a maximum of 5 carbon atoms, more preferably a maximum of 4 carbon atoms. Monomers with esterified carboxyl groups are preferably selected from methylmethacrylate monomers, ethylacrylate monomers and methylacrylate monomers.

Preferred methacrylic acid polymers are polymethacrylic acid/polymethyl methacrylate copolymers, polymethacrylic acid/polyethylacrylate copolymers, polymethacrylic acid/polymethylacrylate/polymethyl methacrylate copolymers and mixtures thereof. The molar ratio of monomers with esterified carboxyl groups to methacrylic acid monomers with free carboxyl groups is preferably at least 0.5:1, particularly preferably at least 0.9:1. The molar ratio is preferably a maximum of 12:1, more preferably a maximum of 10:1 and more particularly preferably a maximum of 2.5:1. More particularly preferred methacrylic acid polymers are polymethacrylic acid/polymethylmethacrylate copolymers. Particularly preferably, the film former comprises at least one methacrylic acid polymer.

Particularly preferred film formers are Eudragit® L, Eudragit® S, Eudragit® L 100-55, Eudragit® L30 D-55, Eudragit® L 12.5, Eudragit® S 12.5, Eudragit® FS 30 D and mixtures thereof. More particularly preferred are Eudragit® L, Eudragit® S and

mixtures thereof, in particular Eudragit® L 100, Eudragit® S 100 and mixtures thereof. Eudragit® L100 corresponds to poly(methacrylic acid co-methyl methacrylate) 1:1 (CAS 25086-15-1). Eudragit® S 100 corresponds to poly(methacrylic acid co-methylmethacrylate) 1:2 (CAS 25086-15-1). Eudragit® L-100-55 corresponds to poly(methacrylic acid co-ethylacrylate) 1:1 (CAS 25212-88-8). Eudragit® L 30 D-55 corresponds to poly(methacrylic acid co-ethylacrylate) 1:1 (CAS 25212-88-8). Eudragit® L 12.5 corresponds to poly(methacrylic acid co-methylmethacrylate) 1:1 (CAS 25086-15-1). Eudragit® S 12.5 corresponds to poly(methacrylic acid co-methylmethacrylate) 1:2 (CAS 25086-15-1). Eudragit® FS 30 D corresponds to poly(methylacrylate co-methylmethacrylate-co-methacrylic acid) 7:3:1 (CAS 26936-24-3). In more preferred embodiments methacrylic acid polymers are used which are polyethyl acrylate/polymethylmethacrylate copolymers. Particularly preferred is Eudragit® NE 30 D. Eudragit® NE 30 D corresponds to poly(ethylacrylate co-methylmethacrylate) 2:1 (CAS 9010-88-2).

The film former is particularly preferably a methacrylic acid polymer, more particularly preferably the film former is at least one polymethacrylic acid/polymethylmethacrylate copolymer. In a particular embodiment only methacrylic acid polymers are used as film formers. More particularly preferably a mixture of different methacrylic acid polymers are used. Because of the high solubility of the polymer in the bowel medium it is possible to ensure a targeted release of the active ingredient in the second phase preferably from the core in the small intestine. Furthermore, said film formers can be processed inexpensively and be applied rapidly and easily onto the surface of the core. By mixing different methacrylic acid polymers the pH value from which the intermediate layer should be released can be adjusted specifically. A mixture of Eudragit® S 100 and

Eudragit® L 100 is particularly preferred. The mass ratio of Eudragit® S 100 to Eudragit® L 100 is preferably at least 1.5:1, preferably at least 2.5:1, even more preferably at least 3:1. The mass ratio is preferably a maximum of 10:1, preferably a maximum of 7.5:1 and even more preferably a maximum of 5:1. In alternative embodiments the film former is Eudragit® S 100 or Eudragit® L 100.

The proportion of film former on the intermediate layer according to the invention is at least 35 % by weight and preferably at least 40 % by weight and more preferably at least 45 % by weight. If the content of film formers is too low the intermediate layer may dissolve prematurely in the stomach. The content of film former on the intermediate layer according to the invention is a maximum of 75 % by weight, more preferably a maximum of 70 % by weight and even more preferably a maximum of 65 % by weight. If the content is too high it results in a very brittle intermediate layer without a sufficient bonding effect.

The mass of the intermediate layer is preferably at least 4 mg, more preferably at least 5 mg and particularly preferably more than 5 mg. More particularly preferably the mass of the intermediate layer is at least 8 mg and even more preferably at least 10 mg. If the mass of the intermediate layer is too low the mechanical stability of the core may be reduced. The mass of the intermediate layer is preferably not more than 55 mg, more preferably at most 50 mg and even more preferably at most 35 mg. Particularly preferably the mass of the intermediate layer is not more than 28 mg. If the mass is too high, i.e. there is too much of the intermediate layer, there is a risk that the release of the active ingredient from the core will be impaired. There is also a risk that the medicament form as a whole will be too large and too heavy and thus difficult to swallow. It has proved

to be particularly suitable to have a mass of the intermediate layer of 12 to 25 mg.

The intermediate layer is suitable for bonding the core and shell to one another. The bonding effect of the intermediate layer is preferably achieved by the addition of at least one softening agent. The latter are fluid according to the invention at ambient temperature and under normal pressure. Softening agents that are hygroscopic are particularly preferred. Polyalcohols with at least two hydroxyl groups are particularly preferred. Said polyalcohols contain preferably at least 2 carbon atoms, preferably at most 10 carbon atoms. The hydroxyl groups can be present in free form. Likewise all or a portion of the hydroxyl groups can be esterified, preferably with organic acids. Preferably, said organic acids are aliphatic acids, more preferably the latter comprise at least 2 carbon atoms, preferably at most 24 carbon atoms, most preferably at most 22 carbon atoms.

Particularly preferred softening agents are selected from glycerol, propylene glycol, glycerol triacetate, castor oil, acetylated fatty acid glycerides and mixtures thereof. Polyethers of polyalcohols have also proved to be suitable according to the invention, wherein the polyalcohol components preferably comprise at least 2 carbon atoms and preferably a maximum of 10 carbon atoms. Preferred polyethers are polyethylene glycols, preferably with an average molar mass of up to 600 g/mol. By adding such softening agents a good bonding effect of the intermediate layer could be achieved. Furthermore, said softening agents are useful for ensuring mechanical stability over longer periods.

The amount of softening agent in the intermediate layer is preferably at least 1 % by weight, more preferably at least 5 % by weight, in order to achieve a good bonding effect. Even more

preferably the amount of softening agent on the intermediate layer is at least 8 % by weight and even more preferably at least 12 % by weight. Preferably, there is a maximum of 30 % by weight, more preferably a maximum of 25 % by weight and even more preferably a maximum of 20 % by weight softening agent in the intermediate layer. If the content of softening agent is too high it is not possible to ensure that the intermediate layer will be sufficiently strong and that the gastric juice resistance will be sufficiently high.

The intermediate layer can comprise at least one additional pharmaceutically acceptable adjuvant, which can simplify the processing and application of the layer and/or is suitable for adjusting its consistency. In particular, standard fillers, pore formers and/or additional softening agents can be included. Additional softening agents can be esters of organic acids, preferably said organic acids comprise at least 2 carbon atoms and preferably at most 10 carbon atoms. Citric acid and phthalic acid are preferred. Such softening agents are for example tributyl citrate, triethyl citrate, diethyl phthalate, dibutyl phthalate.

In order to facilitate the application of the intermediate layer, the intermediate layer preferably contains fillers, preferably selected from talc, titanium oxide, magnesium stearate, colorants, glycerol monostearate, lactose, microcrystalline cellulose, polyvinyl pyrrolidone and mixtures thereof. Preferably, the filler is talc. Particularly preferably, the filler is suitable for the perforation of the intermediate layer, so that the release of the active ingredient in the core can also be controlled. However, the mass amount of the filler should preferably be limited to at most 40 % by weight, more preferably at most 35 % by weight, particularly if the intermediate layer is to have a bonding effect. The filler

can reduce the bonding effect of the intermediate layer. The minimum content of filler is preferably at least 5 % by weight, more preferably at least 15 % by weight.

The mass ratio of the core to the intermediate layer should preferably be at least 2:1, more preferably at least 3:1, even more preferably at least 6.5:1 and more particularly preferably at least 7.5:1. The intermediate layer should thus not have too great a mass in relation to the core, in particular if the intermediate layers does not contain an active ingredient. In this way it is ensured that the total weight and thus the dimensions of the medicament form are suitable for taking orally. The mass ratio should be preferably at most 60:1, more preferably at most 45:1. In a preferred embodiment the mass ratio is at most 40:1 and even more preferably at most 30:1 and in particular preferably at most 20:1. If the ratio is too high the intermediate layer is no longer sufficiently thick for the desired function.

In one embodiment the intermediate layer contains:

a. a film former (in a mass amount of 35 % by weight to 75 % by weight), in particular for ensuring the gastric juice resistance of the intermediate layer, and

b. optionally at least one softening agent (preferably a mass amount of 1 to 30 % by weight), which is preferably hygroscopic, in particular in order to ensure a good bonding effect of the intermediate layer; and

c. optionally a filler, in particular talc in a preferred mass amount of 5 % by weight to 40 % by weight; and

d. optionally additional pharmaceutically acceptable adjuvants such as for example additional fillers, pore formers and/or additional softening agents.

The shell contains active ingredient, and thus contains at least the active ingredient. In addition to the active

ingredient it includes at least one pharmaceutically acceptable adjuvant.

The mass ratio of the shell to the core according to the invention is at least 1.8:1, more preferably at least 2:1 and particularly preferably at least 2.2:1. This makes the shell sufficiently processable. The mass ratio according to the invention is a maximum of 5:1, preferably a maximum of 4.5:1 and more preferably a maximum of 4:1. If the mass ratios are too high it cannot be ensured that the size of the medicament form will not be too large to take. Preferably, the shell contains a comparatively higher proportion of pharmaceutically acceptable adjuvants as the core, in order to ensure a specific volume of the shell and also to embed the active ingredient and thereby shield it sufficiently externally, for example from moisture and in particular also light. The mass ratio of the adjuvants in the shell relative to the amount of adjuvant in the core is preferably at least 1.8:1, more preferably even at least 2.5:1.

In the shell according to the invention at least one carrier substance is used as an adjuvant. Preferably, the carrier substance in the shell is hygroscopic. One would have expected that this would worsen the stability of the medicament form, particularly as the shell preferably has no additional coating, and to this extent the shell components are not shielded from moisture and light. The mass ratio of the carrier substance in the shell to the active ingredient in the shell according to the invention is at least 7.5:1, preferably at least 10:1, more preferably at least 14:1 and in more particularly preferred embodiments at least 15:1. The active ingredient is then preferably distributed and embedded in a matrix-like manner in a comparatively greater amount of carrier substance in the shell so that the additional take up of water from the environment can be reduced significantly. The mass

ratio according to the invention is a maximum of 35:1, in order to ensure a suitable size of the medicament form. Even more preferably the mass ratio is a maximum of 30:1 and even more preferably a maximum of 28:1.

Carrier substances in the shell according to the invention are selected from natural or modified polysaccharides consisting of two or more identical or different monosaccharide components. Such substances are inexpensive and can be processed easily. Polysaccharides have proved to be particularly advantageous that include glucose units. A preferred carrier substance is a disaccharide, particularly preferably this is selected from lactose, sucrose and mixtures thereof.

Alternatively, the carrier substance in the shell can be a polysaccharide with more than 10 monosaccharide components, which can preferably swell on contact with water. Particularly preferably the latter is a starch including starch derivatives, cellulose including cellulose derivatives or mixtures thereof. Powdered cellulose such as microcrystalline cellulose is particularly preferred. Likewise starch can be used in a native or pre-agglutinated form, in particular maize starch. Such carrier substances are better able to take up water from the active ingredient. However, it has been shown that with the exclusive use of such polysaccharides as carrier substances in the shell the breaking resistance of the tablet can decrease when using specific active ingredients over an increasing storage period.

In a particularly preferred embodiment therefore at least two carrier substances are included in the shell, more particularly preferably it includes at least one disaccharide and at least one polysaccharide with more than 10 monosaccharide components which is preferably swellable on contact with water. By means of this combination an optimum breaking resistance and

stability was achieved. The amount of active ingredient is preferably fixed optimally on the carrier substance mixture. More particularly preferably the shell contains at least three carrier substances. The mass ratio of polysaccharides with more than 10 monosaccharide components to disaccharides is preferably at least 1.1:1, preferably at least 1.25:1 and more preferably at least 1.3:1.

Preferably, the shell is free of salts comprising calcium phosphate, sodium salts of cellulose and magnesium stearate, i.e. the latter are only present as impurities in an amount of preferably a maximum of 0.5 % by weight, preferably a maximum of 0.1 % by weight of the total mass of the shell. If an excessive amount of such salts are used in the shell according to the invention there may be a reaction of the active ingredient in the shell with said substances, whereby the stability of the active ingredient in the shell may be influenced in a disadvantageous manner.

There are particularly preferably at least two carrier substances in the shell, more particularly preferably three carrier substances. Preferably, the total amount of carrier substances in the total mass of the shell is at least 70 % by weight, preferably at least 77.5 % by weight and more particularly preferably at least 80 % by weight, in order to sufficiently compensate the hygroscopicity of the active ingredient in the shell and at the same time ensure the effective processing of the shell. The shell preferably contains a maximum of 97 % by weight carrier substance, more preferably a maximum of 95 % by weight. If the amount of carrier substance are too high the processability of the shell is made more difficult.

Preferably, the shell contains a buffer substance. Organic acids are particularly good buffer substances and are preferably

low molecular organic acids. Organic acids are referred to as "low molecular" if they have a molar mass of below 300 g/mol. The buffer substance in the shell is preferably a carboxylic acid selected from citric acid, lactic acid, tartaric acid, fumaric acid, maleic acid and ascorbic acid as well as mixtures thereof. Alpha hydroxycarboxylic acids are particularly preferred which because of the alpha hydroxy group show an optimal buffering effect. Preferably, the latter are selected from lactic acid, tartaric acid, citric acid and mixtures thereof. Citric acid is particularly advantageous as it is particularly easy to process and does not significantly change the release of the active ingredient out of the shell. This is surprising as citric acid in many pharmaceutical forms causes an acceleration of the release, which would be undesirable here.

The mass ratio of the active ingredient in the shell to the buffer substance in the shell is preferably at least 0.5:1, preferably at least 0.8:1 and more preferably at least 0.9:1. Said mass ratio is preferably a maximum of 1.5:1, more preferably a maximum of 1.2:1 and particularly preferably a maximum of 1.1 :1. If there is too little buffer substance the acidity of the active ingredient in the shell cannot be sufficiently buffered. If there is too much buffer substance the acidity increases disadvantageously. The shell contains preferably at least 0.5 % by weight, more preferably at least 1 % by weight and even more preferably at least 2.5 % by weight buffer substance. Preferably, the shell contains a maximum of 15 % by weight, more preferably a maximum of 10 % by weight and even more preferably a maximum of 8 % by weight buffer substance.

Surprisingly, citric acid proved to be particularly suitable as a buffer substance even for the shell. Thus it was possible to achieve a sufficient weakening of the acidity

without the release of the active ingredient out of the shell being recognisably accelerated. Thus one would expect that the buffer substance would accelerate the release of the active ingredient. The shell according to the invention contains preferably at least 8 mg buffer substance, preferably at least 15 mg and more particularly preferably at least 20 mg. Preferably, the shell contains a maximum of 48 mg and more particularly preferably a maximum of 30 mg buffer substance.

The shell can contain at least one further pharmaceutically acceptable adjuvant such as for example a filler and binding agent. Preferably however there is no disintegrating agent in the shell, this could lead to a rapid active ingredient release from the shell.

Depending on the manufacture the shell can comprise at least one granulating agent. Preferably, the granulating agent is contained in the shell in an amount of at least 0.02 % by weight, more preferably at least 0.1 % by weight. Preferably, the shell contains a maximum of 2.5 % by weight granulating agent. Preferred granulating means in the shell are preferably specified below.

Depending on the manufacturing process the shell preferably contains at least one lubricant, preferably in a mass amount of at most 5 % by weight, more preferably at most 4.5 % by weight. Preferably, at least 0.25 % by weight, more preferably at least 0.5 % by weight lubricant are contained in the shell. Preferred lubricants in the shell are specified below.

Preferably, the shell itself does not have an additional coating, in particular there is no coating on the shell which would delay or extend the release of the active ingredient. Preferably, no film is applied onto the shell.

In an alternative embodiment however a rapidly decomposing coating on the shell can be advantageous, which preferably

decomposes rapidly in the aqueous medium of the stomach. The latter preferably contains water-soluble polymers as film formers such as cellulose derivatives, polyvinyl pyrrolidone, polyvidone acetate. Cellulose derivatives are preferably selected from methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose and mixtures thereof. Alternatively, the shell can be coated by a sugar-containing pan-coated syrup.

In one embodiment the shell contains:

a. betahistine; and

b. at least one carrier substance (in a mass ratio to the active ingredient in the shell of at least 7.5:1 and at most 35:1 and preferably with a mass of 70 % by weight to 97 % by weight), which is used in particular "to carry" and embed the active ingredient, to weaken its hygroscopicity and acidity and also ensure a certain degree of delay; and

c. optionally at least one buffer substance (preferably with a mass of 0.5 % by weight to 15 % by weight) in particular for weakening the acidity of the active ingredient; and

d. optionally depending on the manufacture at least one granulating agent (preferred amount 0.02 % by weight to 2.75 % by weight); and

e. optionally depending on the manufacture at least one lubricant (preferred amount 0.25 % by weight to 15 % by weight); and

f. optionally additional adjuvants such as for example fillers and binding agents.

The invention also relates to a method of production for the medicament form according to the invention. The latter comprises the steps:

a) preparing the core,

b) preparing the intermediate layer,

c) preparing the shell.

A direct compression of the active ingredient preferably together with adjuvants is often difficult because of the hygroscopicity of the active ingredient. The compression of granulates results in a high strength compressed product with mainly low abrasion. Furthermore, the provision of the mixture to be compressed as a granulate usually only ensure sufficient adhesiveness and flowability. The production of the core thus preferably comprises producing an active ingredient granulate from the active ingredient and preferably the preferred adjuvants for the core. The direct production of the active ingredient granulate was however made much more difficult by the hygroscopicity of the active ingredient. It was particularly difficult with the conventional granulating methods to obtain sufficiently dry and stable active ingredient granulates. Often the active ingredient granulates obtained were too moist, so that during pressing the product had insufficient strength, there were fluctuations in the dose and crusting for example.

A combined granulation has proved to be surprisingly advantageous. The latter comprises according to the invention firstly the production of a pre-granulate which is free of active ingredients according to the invention. The pre-granulate preferably comprises the carrier substance of the cores and the buffer substance of the cores and if necessary additional adjuvants. The active ingredient granulate is produced from the pre-granulate.

Said preferred combined granulation proved itself to be generally more gentle on the active ingredient. Also surprisingly solid and stabile cores could be produced without significant fluctuations in the dosage. "Without significant fluctuations in the dosage" means that the content of active ingredient in the core measured over 5 cores, is preferably at

least 93%, preferably at least 95% and preferably a maximum of 108%, more preferably a maximum of 107% of the theoretical amount of active ingredient per core. This is surprising as a combined granulation is generally associated with the risk of an uneven distribution of the active ingredient and an increased tendency to separate and is therefore usually avoided.

For the production of the pre-granulate moist granulation has proved advantageous, particularly for the production of an adhesive granulate. The production of the pre-granulate thus preferably comprises the step of mixing the carrier substance and preferably buffer substance with a granulating solution. Surprisingly, by means of such a method a stable pre-granulate can be obtained with low residual moisture. As the carrier substance is typically hygroscopic, it should be assumed that a low residual moisture of the adhesive granulate can only be achieved at considerable effort at high drying temperature which is also very expensive.

Preferably, the granulate solution comprises an aqueous solution of a granulating agent. The granulating agent is a substance with adhesive and pasting properties. The latter are preferably synthetic and/or natural polymers. Preferably, the granulating agent is selected from starches, polyvinyl pyrrolidone, gelatines, cellulose ethers and mixtures thereof. More particularly preferably polyvinyl pyrrolidone is used, as a particularly good adhesive effect could be achieved when using hygroscopic active ingredients. However, polyvinyl pyrrolidone is preferably selected so that the average molar mass does not exceed 40,000 g/mol. If the molecular weight is too high the viscosity of the granulate solution is too high and the granulation is made much more difficult. Povidone K25 is particularly suitable.

The production of the pregranulate preferably comprises a drying stage. Drying methods such as spray drying, fluid bed drying, vacuum drying and/or freeze drying are possible.

Preferably, the fluid bed drying takes place at an supply air temperature of at most 75°C, more preferably at most 65°C. The residual moisture of the pregranulate is preferably adjusted to less than 8 % by weight, more preferably to less than 5 % by weight. If the pregranulate has an excessively high residual moisture results in insufficient core strength. Furthermore, fluctuations in the dose are observed.

The preparation of the active ingredient granulate preferably comprises mixing the pre-granulate with an active ingredient solution. In this case the active ingredient is bonded to the pre-granulate. The active ingredient solution preferably comprises the active ingredient and a solvent. The solvent is preferably an alcohol, particularly preferably an aliphatic alcohol. Preferably, the aliphatic alcohol is selected from methanol, ethanol, n-propanol, isopropanol and mixtures thereof. Methanol has good solubility at a low boiling temperature and is therefore particularly preferred. However, the use of methanol has the disadvantage that any residues have to be completely removed because of the toxicity.

The method of preparing the active ingredient granulate preferably comprises a drying stage. In particular fluid bed drying has proved to be particularly advantageous, as rapid drying could be achieved. According to the invention the solvent could thus be removed completely from the active ingredient granulate. The complete removal of the solvent according to the invention means a residual solvent content of below 5000 ppm (m/m), more preferably at most 3000 ppm (m/m), more particularly preferably the residual solvent content is below 3000 ppm (m/m)

relative to the total mass of the dried active ingredient granulate.

The preparation of the core comprises according to the invention preferably compressing the active ingredient granulate. The compression can be performed for example by using a rotary press, eccentric press or other tabletting devices. However, the core can stick to the punch and can crust. Preferably, the active ingredient granulate is therefore mixed with at least one lubricant in order to obtain a compressible core mixture. The procedure has proved to be advantageous and solid cores can be obtained that demonstrate good decomposition. This is surprising as one would have expected separation to occur when mixing the highly compact active ingredient granulate with the lubricant. The addition of the lubricant during the production of the pregranulate and/or active ingredient granulate can result in less solid and less compressible granulates. Therefore, the addition of the lubricant preferably only takes place after the production of the active ingredient granulate.

In particular, fatty acid derivatives have proved to be advantageous lubricants. Fatty acid derivatives according to the invention comprise salts of fatty acids, fatty acid esters, fatty acids and fats as well as mixtures thereof, wherein the fatty acids preferably comprise at least 8 carbon atoms, more preferably at least 12 carbon atoms. However, the use of talc as a lubricant in the method according to the invention can often lead to a suboptimum lubricant effect. The use of fats is particularly advantageous that are liquid at ambient temperature and thus permit simple processing. Cottonseed oil is particularly preferred. When using such fats cores are obtained with an optimum breaking resistance which do not tend to crust.

The lubricant is added in such an amount that a proportion of mass of at most 10 % by weight, preferably at most 8 % by weight of the total mass of the mixture of active ingredient granulate and lubricant, i.e. the core mixture, is not exceeded. If the amounts of lubricant are too high it reduces the wettability of the core and can thus have a negative effect on the decomposition of the core. In order to achieve a sufficient lubricating effect, preferably at least 0.5 % by weight, preferably at least 1 % by weight lubricant is used in the total mass of the core mixture, which is then also contained accordingly in the core.

The obtained core preferably has a weight of a maximum of 500 mg, preferably a maximum of 350 mg, more preferably a maximum of 250 mg. The diameter of the core is preferably a maximum of 12 mm, more preferably a maximum of 10 mm and particularly preferably a maximum of 9 mm. If the cores are too large it makes further processing more difficult and medicament forms are then obtained which are difficult to swallow.

The production of the intermediate layer preferably comprises dissolving the film former in a solvent. Likewise the production of the intermediate layer preferably comprises adding the additional adjuvants, in particular the softening agent. This results in an intermediate layer mixture.

The solvent for dissolving the film former is preferably an aliphatic alcohol selected from methanol, ethanol, n-propanol, isopropanol and mixtures thereof. Isopropanol is most preferred. The intermediate layer mixture is applied onto the surface of the core. Possible methods are for example kettle methods in dragee kettles, drum kettles, GS-coaters, and immersion pipe methods or fluid bed methods. It is particularly preferable to use GS coaters, as the latter enable a more rapid and more even coating of the core than for example conventional coating

kettles. The intermediate layer mixture is preferably applied at an air inlet temperature of at most 75°C, more preferably at most 60°C. If the temperatures are too high it can lead to the decomposition of the active ingredient in the core and possibly the intermediate layer.

The production of the shell preferably comprises producing an active ingredient granulate. Preferably, this is produced like the active ingredient granulate for the core. As it is very difficult to directly compress the active ingredient granulate and in order to ensure a suitable volume of the shell, the active ingredient granulate is preferably mixed with at least one pharmaceutically acceptable adjuvant so that a shell mixture is obtained. Preferably, the at least one adjuvant is a carrier substance in the shell.

A mass share of active ingredient granulate on the shell of preferably at least 10 % by weight, preferably at least 20 % by weight has proved to be advantageous. The mass share of the granulate is preferably a maximum of 49 % by weight, preferably a maximum of 42 % by weight.

In such a procedure a tendency to separate would in fact be expected between the comparatively high amount of adjuvant and the compact active ingredient granulate, resulting in poor decomposition. Surprisingly however in this procedure a stabile shell can be obtained with good decomposition properties.

The production of the medicament form according to the invention preferably comprises applying the shell mixture onto the intermediate layer. The term "applying" according to the invention comprises various different methods, preferably pressing the shell onto the intermediate layer preferably by using conventional tablet presses. To ensure that there is no crusting, i.e. the rejection of individual pressed layers, and

thus the adhesion to the punches is prevented, a lubricant is preferably added to the shell mixture.

Preferred lubricants are those that are used during the preparation of the core. It has been shown however that even very small amounts of lubricant can be used to achieve the effective pressing of the shell mixture and an increase in the amount surprisingly quickly has a negative effect on the wettability and decomposition of the shell. Therefore, the lubricant in the shell is preferably limited to 5 % by weight, preferably 4.5 % by weight. Advantageous lubricants have proved in particular to be fats which are liquid at ambient temperature and normal pressure and can thus be processed easily. It is particularly preferable to use cottonseed oil.

The pressing of the shell onto the intermediate layer is preferably performed such that the shell mixture is placed into the press. However, if the core with the intermediate layer is located approximately in the centre of the medicament form to be produced, preferably at least 40 % by weight, more preferably at least 45 % by weight of the shell mixture is placed in a mould. However, preferably at most 65 % by weight, more preferably at most 60 % by weight of the shell mixture is provided. Afterwards the core with the intermediate layer is inserted and the mould is filled with the remaining amount of shell mixture. Afterwards a pressing force is exerted.

When the shell is pressed onto the intermediate layer, preferably a pressing force of at most 35 kN, more preferably at most 30 kN and particularly preferably at most 28 kN is applied. If the pressing forces are too high often medicament forms are obtained that are too compacted and this is associated with an impaired release of the active ingredient. If the pressing forces are too high, particularly with a concave or biplanar form of the core, the core may be deformed. This could cause the

intermediate layer to tear and the mechanism of action could be destroyed. If the pressing forces are too high this could result in the fragmentation of the compacted product. The pressing force should however preferably exceed 7.5 kN, more preferably 8 kN. If the pressing forces are too low it has been found that the resulting medicament form is not sufficiently strong.

The breaking resistance of the medicament form should be preferably at least 60 N, more preferably at least 100 N and even more preferably at least 120 N. The breaking resistance should however preferably not exceed 350 N, preferably 300 N. More particularly preferably the breaking resistance of the medicament form is between 140 N and 280 N, even more preferably between 170 and 270 N. If the breaking resistance is too high the decomposition is more difficult to measure. The breaking resistance of a tablet can be determined by conventional methods under normal conditions by hardness testers by applying a diametrically acting force, generally a pointed or conical test body. According to the invention the breaking resistance was determined by an Erweka TBH-30 hardness tester.

The diameter of the core is preferably at least 3 mm, more preferably at least 4 mm. If the diameter of the core is too small the handling and processability may be more difficult. The diameter of the core is preferably a maximum of 16 mm, more preferably a maximum of 15 mm and particularly preferably a maximum of 14 mm. If the diameter of the core is too large it can be more difficult to swallow the final medicament form. The term "diameter" relates to the diameter of the core at its thickest point.

The thickness of the layer of the shell is preferably at least 0.7 mm, more preferably at least 0.8 mm. If the thickness of the layers is too low the handling of the medicament form and its manufacturing are made more difficult. The thickness of the

layer of the shell is preferably a maximum of 5 mm, preferably a maximum of 3 mm. If the thicknesses of the layer of the shell are too large the medicament form can be too large and can be difficult to swallow. The layer thickness here is the thickness of the shell at the thickness point.

The total diameter of the medicament form corresponds to the respectively used contents, in particular the active ingredients in the core and shell. Likewise the total diameter of the medicament form relates to the diameter of the core. The total diameter of the medicament form is preferably a maximum of 20 mm, more preferably a maximum of 18 mm, more particularly preferably a maximum of 16 mm. If the diameter is too great it can be difficult to swallow. The term "total diameter" relates to the diameter of the medicament form at its thickest point. A diameter of the medicament form of between 8 mm and 14 mm, in particular between 11 mm and 13 mm, has proved particularly effective.

The medicament form preferably has a mass of at most 1100 mg, preferably at most 950 mg and most preferably at most 850 mg, so that the latter can be taken easily. However, the medicament form according to the invention preferably has a minimum weight of 115 mg, also preferably of 225 mg, so that older people can also handle the medicament form easily. The weight of the medicament form is particularly advantageously between 700 mg and 800 mg.

The medicament form according to the invention also preferably has a residual moisture content when stored in air, i.e. an absolute water content of a maximum of 15 % by weight, preferably a maximum of 13 % by weight. More particularly preferably the absolute water content is a maximum of 5 % by weight. This is preferably determined by drying at 105 °C to a

weight constant in a drying chamber or by means of an infrared drier, preferably an infrared drier.

The medicament forms of the invention have the advantage that they are particularly stable when in storage, i.e. the ICH criteria for storage stability are at least met and advantageously exceeded, i.e. the medicament forms according to the invention have more than sufficient levels. Stability when in storage preferably means that when stored under specific storage conditions and for a specific period of time, as specified in the ICH Guideline Q3B (R2) (Impurities in New drug Products), a sufficiently high drug content of preferably more than 90%, relative to the original active amount of ingredient, is still available and decomposition products which could represent a threat to patients do not exceed a specific maximum level. The maximum levels are specified in ICH Guideline Q3B (R2).

The medicament forms according to the invention proved to be extremely stable when in storage during a short stress test in standard blister packs (for example upper film aluminium foil, 20 µm hard and lower film PVC/PVDC film, transparent) at 25°C and 60% relative humidity (corresponds to subtropical Mediterranean climate), 30°C and 65% relative humidity (corresponds to hot and humid climate) and at 40°C and 75% relative humidity (corresponds to very hot and particularly humid climate). The medicament forms according to the invention also still contain after storage at 25°C and 60% relative humidity, 30°C and 65% relative humidity or 40°C and 75% relative humidity after 1 month advantageously between 95% and 105% of the theoretical amount of active ingredient in the medicament form, thus corresponding with the specification. Preferably, the amount of active ingredient after 1 month's storage under one of the specified conditions (25°C and 60%

relative humidity, 30°C and 65% relative humidity or 40°C and 75% relative humidity) is between 96% and 103% and even more preferably between 97% and 102% relative to the amount of active ingredient in the unstored medicament form. The total mass of the stored medicament form differs preferably less than 5%, even more preferably less than 4% and even more preferably less than 2% from the mass of the unstored medicament form during the storage of the medicament form for 1 month at 25°C and 60% relative humidity, 30°C and 65% relative humidity or 40°C and 75% relative humidity. This shows that the take up of water from the environment with the medicament form according to the invention comprising a hygroscopic active ingredient can also be prevented in an extremely moist surrounding atmosphere. Furthermore, the height of the shell-core tablet after storage for 1 month at 25°C and 60% relative humidity, 30°C and 65% relative humidity or 40°C and 75% relative humidity, preferably does not differ by more than 5%, also preferably by more than 4%, also preferably by more than 2% from the height of the shell-core tablet in the unstored state. The medicament form according to the invention thus shows no crusting which usually occurs with hygroscopic active ingredients and influences the release in a disadvantageous manner after storage in a moist environment. The diameter of the medicament form according to the invention also differs after 1 month's storage in one of the said atmospheres preferably by less than 4%, more preferably by less than 3% and even more preferably by less than 2% of the diameter of the unstored medicament form. The medicament forms according to the invention are preferably stable when in storage for more than 6 months, preferably at least 12 months storage under standard conditions according to the international guidelines of the ICH.

The medicament forms according to the invention are characterised by having an excellent uniformity of the mass and content which is ensured by the composition of the medicament forms and the production method. The test was performed according to the relevant methods of the European Pharmacopeia (Ph.Eur. 7). A medicament form preferably has a uniformity of mass such that the mass of 20 such medicament forms preferably does not deviate by more than 5%, also preferably less than 5%, even more preferably less than 4% from the average mass of the medicament form which is produced from the mass of the 20 medicament forms. The medicament form according to the invention preferably has a uniformity of content such that the content of active ingredient of 10 such medicament forms is between 85% and 115%, preferably between 87% and 113% and ideally between 95% and 105%, relative to the average content of the 10 medicament forms of active ingredient.

By means of the medicament form according to the invention and the method of production according to the invention it is thus possible to provide the hygroscopic active ingredient, i.e. an active ingredient that is difficult to process, so that it simulates multiple daily doses. In this case the first amount of active ingredient is released immediately in the first phase. A release of this kind is advantageous in particular for short-term treatments, when the desired plasma level needs to be reached as rapidly as possible and at the same when the effect needs to be prolonged by having subsequent release phases. Such a release system can also be advantageous for long-term treatments, in particular if the concentration of active ingredient falls below the minimum in the case of spaced out dosing interval towards the end of the interval. By means of the rapid initial release of active ingredient of the next medicament form the plasma level is raised rapidly back up to

the necessary level. The particular embodiment of the medicament form according to the invention makes it possible in an optimum manner to imitate taking a dose at least twice a day, in particular taking two medicament forms at an interval of 8 to 12 hours.

The medicament form has a suitable size for taking orally. It is characterised by having high mechanical stability even over a long storage period. Thus the daily dose of betahistine in particular can be reduced to one daily dose which can have a positive effect on patient compliance and indirectly on healthcare costs.

The active ingredient betahistine is used for treating the complex of symptoms of Ménière's disease, the symptoms of which can include dizziness often in connection with nausea and/or sickness, tinnitus and loss of hearing. Therefore, the medicament form according to the invention is used for treating dizziness in connection with the complex of symptoms of Ménière's disease.

The invention also provides a method for treating dizziness in connection with the complex of symptoms of Ménière's disease, wherein the method comprises administering a medicament form according to the invention. Preferably the drug is administered once a day.

Examples

Example 1: Production of a shell-core tablet according to the invention

Element	Constituent	Amount per dosage form (mg	Function

core	betahistine dihydrochloride	24	active ingredient
	lactose monohydrate (Granulac® 230)	53	carrier
	microcrystalline cellulose (Vivapur® 102)	30	carrier
	maize starch	53	carrier
	citric acid, anhydrous	24	buffer substance
	povidone K25 (Plasdone® K25)	2	granulating agent
	hardened cottonseed oil (Lubritab®)	5	lubricant
	total mass	191	
intermediate layer	Eudragit® S 100	6.67	film former
	Eudragit® L 100	1.67	film former
	triacetin	2.50	softening agent
	talc	4.17	filler
	total mass	15.01	
shell	betahistine dihydrochloride	24	active ingredient
	lactose monohydrate (Granulac®	53	carrier

	230)		
	lactose monohydrate (Tablettose® 80)	128.5	carrier
	microcrystalline cellulose (Vivapur® 102)	230	carrier
	maize starch	53	carrier
	citric acid, anhydrous	24	buffer substance
	povidone K25 (Plasdone® K25)	2	granulating agent
	pre-agglutinated maize starch (starch 1500 ®)	30	carrier
	hardened cottonseed oil (Lubritab®)	5.5	lubricant
	total mass	550	
medicament form	Mass	756.01	

First of all the core was made. To produce the core a pregranulate was made. The carrier substances lactose monohydrate, microcrystalline cellulose and maize starch and the buffer substance citric acid were mixed intensively in a mixer/granulator (Diosna P10). The mixture was then granulated in the Diosna P10 mixer with a granulating solution. The granulating solution was produced by dissolving the povidone K25 in purified water so that the solution contained 16 % by weight

povidone K25. The pregranulate was then dried in a fluid bed (GPCG-3) at 60°C to a residual moisture of < 5%. The dried pre-granulate was then sieved (screen width 1 mm).

From the pre-granulate the active ingredient granulate was produced by adding a solution of betahistine hydrochloride to methanol. The clear solution contained 28.5 % by weight betahistine hydrochloride. In addition, the pre-granulate was placed into the Diosna 10 mixer/granulator and granulated with the active ingredient solution. The obtained active ingredient granulate was dried in a fluid bed (GPCG-3) to a residual methanol content of < 3000 ppm. The dried active ingredient granulate was then sieved (screen width 1 mm).

Afterwards hardened cottonseed oil was added to the active ingredient granulate and mixed in a mixer. The obtained core mixture was pressed in a rotary press. Biconvex cores with a diameter of 8 mm were obtained. The obtained cores had a weight of 191 mg and a height of 3.85 mm.

Afterwards the intermediate layer was produced. For this the film formers Eudragit® S 100 and Eudragit® L 100 were dissolved in isopropanol, wherein the content of film formers in the solution was 5.9 % by weight. The softening agent triacetin and the adjuvant talc were stirred into the solution. Water was also added (6.67 ml). The intermediate layer mixture was then applied onto the core so that the latter completely covered the core. The intermediate layer mixture was applied in a GS coater (GS-10) at a supply air temperature of 50°C.

To produce the shell the active ingredient granulate was produced in a similar way to the core, so that there was 186 mg active ingredient granulate. Said active ingredient granulate was mixed with the carrier substances lactose monohydrate, microcrystalline cellulose and pre-agglutinated maize starch and the lubricant hardened cottonseed oil. This produced the shell

mixture. The amount of active ingredient granulate in the shell mixture was thus 33.8 % by weight.

In a final step the shell mixture was pressed onto the intermediate layer in a Syl-one press with tablet supply. In addition, 300 mg of the shell mixture was filled into a mould (round, biconvex, diameter 12 mm, radius of curvature 9.5 mm). Then the core was centred with the intermediate layer. In a second filling step the remaining portion of the shell mixture was filled into the mould. Then a pressing force of 10 kN was applied. The shell-core tablet had a breaking resistance of 140 N, measured with an Erweka TBH-30 hardness measuring device. In a further embodiment with the same starting materials, ratios of amounts and production methods a pressing force of 25 kN was applied while pressing the shell so that a shell-core tablet was obtained with a breaking resistance of 280 N.

Example 2: Production of a shell-core tablet according to the invention

Element	Constituent	Amount per medicament form (mg)	Function
intermediate layer	Eudragit® S 100	8.874	film former
	Eudragit® L 100	2.225	film former
	triacetin	3.331	softening agent
	talc	5.556	filler
	total mass	19.986	

A medicament form was produced with the composition of the core and the shell as in example 1.

However, the composition of the intermediate layer was changed and a greater weight was selected for the intermediate layer. The selected higher weight of intermediate layer contributed to a further increase in the mechanical strength of the core. The selected intermediate layer dissolves at a pH value of 7.0 to 7.2. The intermediate layer thus enables the release of the active ingredient from the core into the central bowel section.

The core and shell were produced as described in example 1. The intermediate layer was produced by dissolving the film former Eudragit® S100 and Eudragit® L 100 in isopropanol, wherein the content of film formers in the solution was 5.9 % by weight. The softening agent triacetin and the adjuvant talc were stirred into the solution. Water was also added (8.86 ml). The intermediate layer mixture was then applied onto the core so that the latter completely covered the core. The application of the intermediate layer mixture was performed in a GS coater (GS-10) at a supply air temperature of 50°C.

Example 3: Production of a shell-core tablet according to the invention

Element	Constituent	Amount per medicament form (mg)	Function
intermediate layer	Eudragit® S 100	11.099	film former
	triacetin	3.331	softening agent
	talc	5.556	filler

	total mass	19.986	

A medicament form was produced with the composition of the core and the shell as in example 1.

However, the composition of the intermediate layer was different, wherein the weight of the intermediate layer was greater, similar to example 2. The selected higher weight of intermediate layer contributed to a further increase in the mechanical strength of the core. The selected intermediate layer dissolves at a pH value of 7.2 to 7.5. The intermediate layer thereby enables the release of the active ingredient from the core in the lower bowel section.

The core and shell were produced as described in example 1. The intermediate layer was produced by dissolving the film former Eudragit® S 100 in isopropanol, wherein the content of film former in the solution was 5.9 % by weight. The softening agent triacetin and the adjuvant talc were stirred into the solution. Water was also added (8.86 ml). The intermediate layer mixture was then applied onto the core so that the latter completely covered the core. The intermediate layer mixture was applied in a GS coater (GS-10) at a supply air temperature of 50°C.

Example 4:

In example 4 a trial was carried to release the active ingredient betahistine dihydrochloride from a core with an intermediate layer with the composition according to example 1, but without a shell. The core and intermediate layer thus comprises 24 mg betahistine dihydrochloride. The release was determined by the paddle apparatus. Figure 2 shows the corresponding results.

Example 5: Stability of the shell-core tablet according to the invention

A medicament form was produced with the same composition of the core and the shell as in example 1. Blister packs (upper film aluminium foil 20 µm hard, lower film PVC/PVDC foil, transparent) comprising the medicament form were subjected to a stress test for 1 month, i.e. at 25°C/60% relative air humidity, 30°C/65% relative air humidity and 40°C/75% relative air humidity. The medicament form after storage had the following parameters. It is clear that the medicament form according to the invention is also stable under extreme storage conditions and despite the hygroscopic active ingredient does not crust or swell. The impurities according to the specification or monography according to Ph. Eur. 7 were below the defined thresholds even after 1 month's storage in extreme conditions or were not available in a measurable amount.

Parameter	Not stored medicament form	Storage for 1 month at 25°C/60% relative humidity	Storage for 1 month at 30°C/65% relative humidity	Storage for 1 month at 40°C/75% relative humidity
height (mm)	7.1	7.1	7.1	7.2
diameter (mm)	12.0	12.0	12.0	12.1
actual weight (mg)	755.7	757.6	757.4	767.0
content (% of the	100.6	101.1	101.5	100.8

theoretical amount of active ingredient)				

Description of the Figures:

Figure 1 shows the curve of the release of two medicament forms according to the invention which are produced according to the example embodiment 1 comprising 24 mg betahistine dihydrochloride in the shell and 24 mg betahistine dihydrochloride in the core. The shell was compressed with a pressing force of 10 kN or 25 kN onto the core with the intermediate layer. This imitates a pH path according to the physiological conditions. A 100% release means the release of 48 mg betahistine dihydrochloride from the medicament form, i.e. 24 mg from the shell and 24 mg from the core. The medicament form according to the invention releases betahistine dihydrochloride in two phases, i.e. firstly pulsed out of the shell and from pH 7.0 (after about 8.5 hours) after releasing the gastric juice resistant intermediate layer from the core. In this way this simulates taking two daily doses, i.e. taking two commercially available medicament forms without any particular release modification at an interval of 8 to 12 hours. By means of the particular structure of the medicament form an optimal release profile is achieved. It is anticipated that this will also be confirmed in-vivo.

Figure 2 shows the curve of the release from the core with the intermediate layer according to example 4. A release of 50% corresponds to the release of 24 mg betahistine dihydrochloride. It can be seen that the intermediate layer only dissolves and the active ingredient is only released from the core from a pH value of 7.0. The core with the intermediate layer is thus

stable in the upper bowel sections; the decomposition only commences from a pH value of 7.0, which corresponds to the bowel section of the ileum to the colon and to a dwelling time in the gastrointestinal tract without release of 7 to 12 hours.

Betahistin módosított kibocsátására szolgáló gyógyszerforma

Szabadalmi igénypontok

1. Mag-héj szerkezetű tabletta betahistin legalább két fázisban történő kibocsátására, amely tabletta hatóanyag-tartalma 1 mg és 200 mg közötti, és amely tabletta az alábbiakat tartalmazza:

a) egy mag, amely a hatóanyag-mennyiség 40-60%-át tartalmazza
b) egy közbenső réteg, amely a mag felületén helyezkedik el és 35-75 tömeg %-ban legalább egy filmképző anyagot tartalmaz,
c) egy héj, amely a hatóanyag-mennyiség 40-60 %-át tartalmazza és a közbensö rétegnek a maggal ellentétes oldalán helyezkedik el,

ahol a héj és a mag tömegaránya legalább 1,8 az 1-hez és legfeljebb 5 az 1-hez; és ahol a mag legalább egy 300 g /mól-nál alacsonyabb molekulatömeggel rendelkező szerves savat tartalmaz pufferanyagként, olyan mennyiségben, hogy a magban található hatóanyag és a magban található szerves sav tömegarány 0,5:1-1,5:1 legyen; valamint, ahol a mag továbbá legalább két hordozóanyagot tartalmaz, amelyek legalább egy diszacharid és legalább egy, több mint 10 monoszacharid-egységből álló poliszacharid lehetnek, és ahol a mag hordozóanyag-tartalma 50-90 tömeg %; valamint, ahol a filmképző anyag egy cellulóz-származék, metakrilsav-polimer, polivinil-származék vagy ezek keveréke; valamint, ahol a héj legalább egy hordozóanyagot tartalmaz, amely természetes vagy módosított poliszacharid lehet, amely két vagy több, azonos vagy eltérő monoszacharid-egységből áll; és ahol a héjban található hordozóanyag és a héjban található hatóanyag tömegaránya 7,5:1-35:1.

2. Az 1. igénypont szerinti mag-héj tabletta, ahol a mag és a közbenső réteg tömegaránya legfeljebb 40 az 1-hez.

3. Az 1. vagy 2. igénypont szerinti mag-héj tabletta, ahol a mag tömege legfeljebb 350 mg.

4. Az előző igénypontok legalább egyike szerinti mag-héj tabletta, ahol a héj nem rendelkezik bevonattal.

5. Az előző igénypontok legalább egyike szerinti mag-héj tabletta, ahol a gyógyszerforma össztömege legfeljebb 1100 mg és legalább 225 mg.

6. Az előző igénypontok legalább egyike szerinti mag-héj tabletta, ahol a mag átmérője legalább 4 mm és ahol a mag-héj tabletta átmérője legfeljebb 18 mm.

7. Az előző igénypontok legalább egyike szerinti mag-héj tabletta, ahol a magban található szerves sav egy alfa-hidroxisav és ahol a magban található hordozóanyagok és a magban található sav tömegaránya legalább 3 az 1-hez.

8. Az előző igénypontok legalább egyike szerinti mag-héj tabletta, ahol a filmképző anyag szabad savfunkciókkal rendelkezik, és ahol a közbenső réteg 5-30 tömeg % mennyiségű lágyítót tartalmaz.

9. Az előző igénypontok legalább egyike szerinti mag-héj tabletta, ahol a közbenső réteg tömege 12-25 mg.

10. Az előző igénypontok legalább egyike szerinti mag-héj tabletta, ahol a hatóanyag betahistin-dihidroklorid vagy betahistin-dimezilát, amelyek a gyógyszerformában a hatóanyag-bázisra vonatkoztatott 2 mg és 55 mg közötti mennyiségben vannak jelen.

11. Az előző igénypontok legalább egyike szerinti mag-héj tabletta, ahol a hatóanyag betahistin-dihidroklorid, és ahol a hatóanyag összmennyisége a mag-héj tablettában 30 és 60 mg közötti.

12. Az előző igénypontok legalább egyike szerinti mag-héj tabletta, ahol a hatóanyag mennyisége a magban és a héjban azonos.

13. Az előző igénypontok legalább egyike szerinti mag-héj tabletta, ahol a mag-héj tabletta a magból, a közbenső rétegből és a héjból áll.

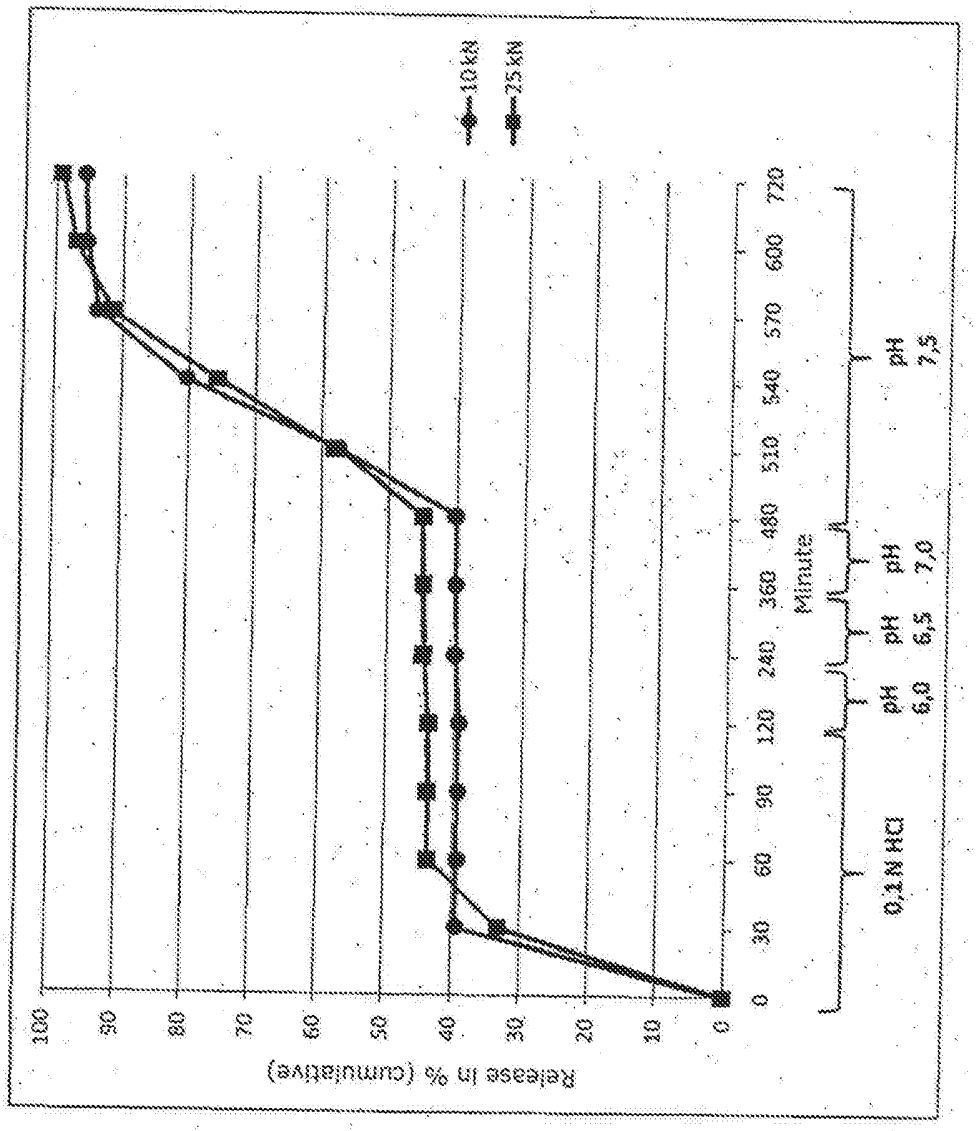
14. Eljárás az 1-13. igénypontok legalább egyike szerinti mag-héj tabletta előállítására, amely az alábbi lépéseket tartalmazza:

a) a mag előállítása;
b) a közbenső réteg előállítása;
c) a héj előállítása.

15. Az 1-13. igénypontok bármelyike szerinti mag-héj tabletta Menière-féle tünetegyüttessel kapcsolatos szédülés kezelésénél történő alkalmazásra.

Dr. Szentpéteri Ádám
szabadalmi ügyvivő
SBGK Szabadalmi Ügyvivői Iroda
H-1062 Budapest, Andrássy út 113.
Telefon: 461-1000 Fax: 461-1099
E-mail: szentpeteri@sbgk.hu

A meghatalmazott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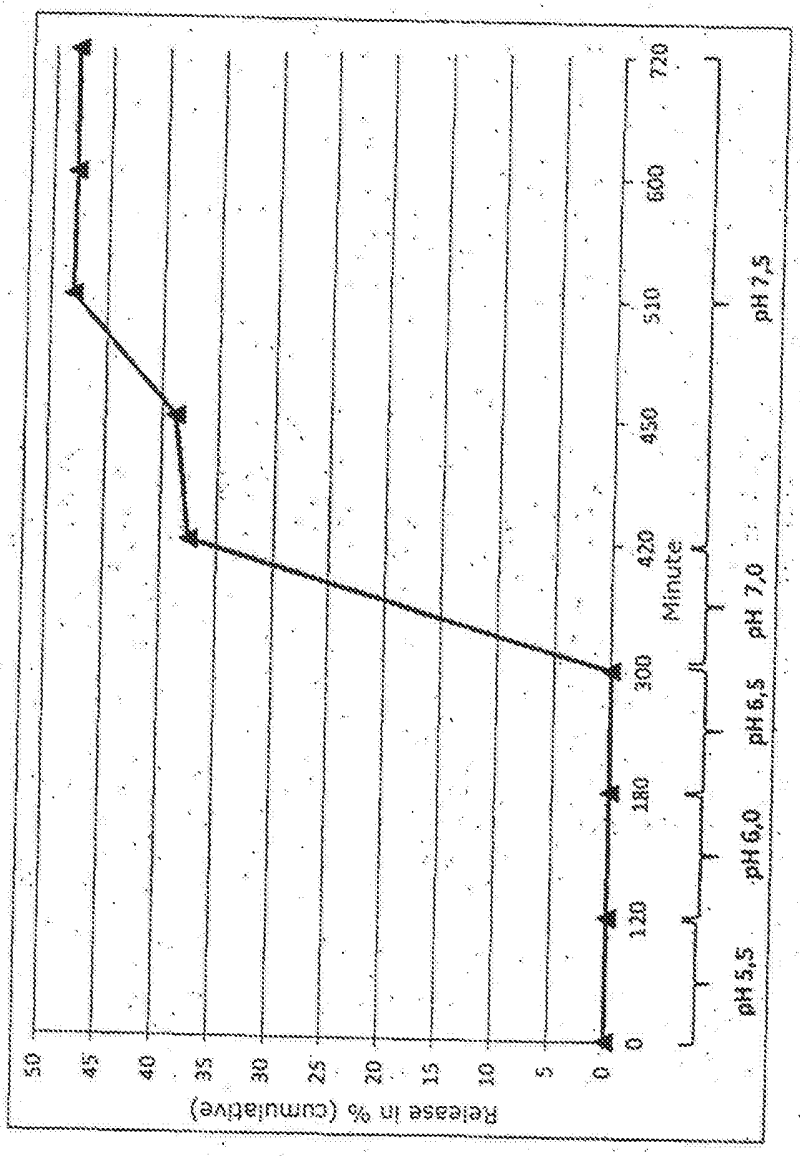
pH 7,0
pH 7,5

Figure 1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Minute
pH 5,5
pH 6,0
pH 6,5
pH 7,0
pH 7,5

Figure 2