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— *vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eingehen (Regel 48 Absatz 2 Buchstabe h)*

[Fortsetzung auf der nächsten Seite]

(54) **Title**: MEDICAMENT FORM FOR RELEASE OF ACTIVE INGREDIENTS

(54) **Bezeichnung** : ARZNEIFORM ZUR FREISETZUNG VON WIRKSTOFFEN

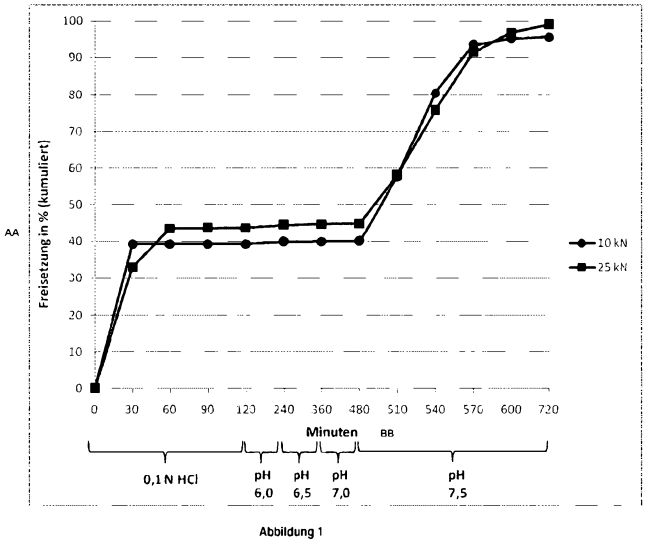

Abbildung 1

FIG. 1:
AA Release in % (cumulated)
BB Minutes

(57) **Abstract**: This invention is concerned with the provision of medicament forms which enable effective administration of a medicament which is usually taken twice or more daily by way of a single daily dose. This is achieved in accordance with the invention by provision of a medicament form comprising a core, a gastric juice-resistant intermediate layer disposed on the surface of the core, and a shell disposed on the opposite side of the intermediate layer from the core. Both the core and the shell comprise a proportion of an active ingredient. The active ingredient is released in at least biphasic form from the medicament form, the first phase relating to the immediate release of the active ingredient after ingestion into the gastric juice. The present invention additionally relates to a process for producing the medicament form and to uses thereof.

(57) **Zusammenfassung**: Diese Erfindung befasst sich mit der Bereitstellung von Arzneiformen, die es ermöglichen, einen Arzneistoff, der üblicherweise zweimal oder mehrmals täglich eingenommen wird, im Wege einer einmal täglichen Gabe wirksam darzureichen. Dies wird erfindungsgemäß erreicht durch Bereitstellung einer Arzneiform umfassend einen Kern, eine magensaftresistente Zwischenschicht, die auf der Oberfläche des Kerns angeordnet ist, und einen Mantel,

der auf der dem Kern gegenüberliegenden

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Seite der Zwischenschicht angeordnet ist. Sowohl der Kern als auch der Mantel enthalten jeweils einen Anteil eines Wirkstoffs. Der Wirkstoff wird aus der Arzneiform in mindestens zweiphasig freigesetzt, wobei die erste Phase die sofortige Freisetzung des Wirkstoffs nach Einnahme in den Magensaft betrifft. Die vorliegende Erfindung betrifft zudem ein Verfahren zur Herstellung der Arzneiform und ihre Verwendungen.

MEDICAMENT FORM FOR RELEASE OF ACTIVE INGREDIENTS

The present invention relates to a medicament form for the release of active ingredients, a method for the production thereof and uses thereof.

This invention is concerned with the provision of medicament forms which enable an effective administration of an active ingredient which is usually taken twice or more daily by way of a single daily dose.

With the development of new medicament forms it is always important that the design of the new medicament form is such that the compliance of the patient can be improved. This for example can be achieved by the reduction of single doses of a medicament which have to be taken daily. The reason for that is that the compliance of the patient often considerably decreases, when several single doses of a medicament have to be taken on one day, in particular, when a combination with further medicaments has to be taken. This is in particular the case with patients with difficulties in swallowing and also elder patients who have to take numerous medicaments due to multimorbidity.

But a sufficient compliance of the patient is constantly necessary for avoiding side effects and reduced effectiveness of the medicament. The lack of compliance of numerous patients is a significant factor for the increasing health expenditures.

In this respect, the reduction of the frequency of use of a medicament from doses which have to be administered a few times daily to a single daily dose has become more important. Normally, in such a case the effect should be comparable with an administration a few times daily. This can be achieved by the use of mechanisms of retardation such as embedment of a drug into a matrix so that the active ingredient is released in a retarded manner, this means uniformly over a longer period of time.

But the reduction of the frequency of use requires special medicament formulations which are associated with high technological requirements, since they comprise relatively high amounts of active ingredient. One technological challenge is the provision of a medicament form with sufficient stability and good release behavior, wherein the size of the medicament form is still is a tolerable range. The latter is important, so that the medicament form can be swallowed easily. Similarly, in the case of high amounts of active ingredient it may be difficult to guarantee a tolerable taste.

Till today, predominantly active ingredients having bad solubility have been the center stage of such developments. For them numerous medicament forms have been developed, in particular matrix-based systems. The resorption of such active ingredients is determined by their release from the medicament form so that by the development of suitable matrix systems a good resorption of these active ingredients could be achieved. For active ingredients having good solubility other concepts are required. Naturally it is much more difficult to retard the release of an active ingredient with good solubility than that of an active ingredient with bad solubility which already dissolves slowly.

Independently from the solubility of an active ingredient there are in particular considerable difficulties, when the processing of the active ingredients in question is difficult due to their instability. Such active ingredients are in particular active ingredients with high decomposition rates or hygroscopy.

Hygroscopic active ingredients have a tendency of taking up humidity from the environment, most often in the form of water vapor from air moisture. This can take place via different mechanisms such as absorption and adsorption. This involves the risk of melting or agglutinating of the active ingredients or of the formation of undesired crystal forms. The latter considerably complicates their processing so that laborious and costly methods and intermediate steps are required, for example for excluding humidity. This disadvantageous property of some active ingredients also complicates the provision of a medicament form with good storability and shelf life. Not only the taking up of humidity from the environment is a critical point, because the active ingredient can also extract humidity from the medicament form itself. For example, such active ingredients can adsorb humidity from the capsule casings, wherein this may result in cracks in the capsule casing.

Due to the hygroscopy of the active ingredient, besides the release of the active ingredient from the medicament form also the handling of such medicament forms can be complicated considerably. Thus in general it would be required that the medicament forms are stored in a manner which guarantees protection from air and smallest amounts of humidity. But the handling during the use of the patient cannot be controlled and it can be assumed that in particular elder humans store their tablets outside the blister, for example in pill organizers.

In this respect it is also problematic that many highly effective active ingredients and active ingredients for which no alternatives are available are hygroscopic. Such active ingredients can for example be found in the classes of active ingredients of antiepileptics, antibiotics,

antidiabetics, cardiovascular agents, gastrointestinal therapeutics, lipid-lowering agents, antidementives, muscle relaxants, analgesics, broncholytic/antiasthmatic agents or also antiallergic agents as well as antiemetic/antivertiginous agents.

As an example, here the antiepileptics valproic acid and carbamazepine are mentioned. Also the antibiotics tetracycline, lincomycin, clindamycin or also rifampicin have hygroscopic properties. Cardiovascular agents with hygroscopic properties are for example atenolol and minoxidil. Betahistine is mentioned as an example for an antiemetic/antivertiginous agent. An example of an antiallergic agent is dexamethasone, and an example of an antidementive is piracetam. An example of a hygroscopic lipid-lowering agent is gemfibrozil.

In therapy it is not possible to dispense with such drugs. So numerous of such active ingredients are also classified by the world health organization as indispensable medicaments. Therefore, there exists a high demand for medicament forms which contain such drugs and are nevertheless storable and are characterized by a good shelf life and which also show a release behavior which enables the single daily intake. In particular, there is a need for medicament forms which release such drugs in a manner so that an intake several times a day is not necessary and which can be manufactured in a cost-effective manner in a larger scale.

Considerable difficulties arise in particular with respect to hygroscopic active ingredients which at the same time are also highly soluble. The high solubility of such active ingredients further complicates the already due to hygroscopy very difficult provision of such active ingredients in medicament forms with retarded release. Due to the high solubility normal retardation formulations for the retarded release of such active ingredients are generally unsuitable. Additional difficulties also result from active ingredients which besides high hygroscopy also show high acidity, in particular in the case, when concurrently the active ingredient is characterized by high solubility. So in this case there is the additional risk that the acidic active ingredient attacks or decomposes the adjuvants. This may result in decomposition of the medicament form and in modification of the release profile. If it is desired to provide a medicament form showing the respective release, so there is the risk that the whole proportion of the active ingredient is quickly released, resulting in high plasma levels and thus also strong side effects. Insofar the formulation of such a drug is further complicated. In this connection in particular betahistine, for example in the form of the salts betahistine dimesylate or betahistine dihydrochloride have to be mentioned.

In many cases medicament forms were provided which however are not suitable for the release of hygroscopic drugs, in particular active ingredients with high solubility and/or acidity, and insofar do also not address the problems during their processing as well as the problems, when medicament forms with sufficient stability and storability are provided.

A tablet for the release of betahistine in the form of betahistine dihydrochloride is described in WO 00/53162 A1. Here, the tablet releases the active ingredient in a retarded manner over a period of time of mostly 5 to 8 hours. Thus however, several daily intakes may be become necessary. Also generally a combined quick and retarded release in the form of a two layer tablet is mentioned, but without any disclosure about its exact design or production. In particular there is no disclosure about the cohesion of the layers and how an acceptable size of the medicament form can be guaranteed. Also the release behavior of the medicament form remains unclear. There is only one general note that an intake two times or also one time a day may be possible. Insofar it cannot be deduced, whether in general this medicament form would be suitable for mimicking an intake several times a day.

In DE 100 10 509 A1 oral medicament forms are described which contain a sucrose fatty acid ester in a proportion of 1 to 95 % by weight as the single agent for release control. The medicament forms release the contained active ingredients in a quick or retarded manner. As possible active ingredients a plurality of substances, including virtually insoluble active ingredients are mentioned. For example, also betahistine dimesylate is mentioned as a possible active ingredient. A medicament form which is suitable for releasing one and the same active ingredient in at least two phases, thus mimicking an intake several times a day, is not described in DE 100 10 509 A1. So also the problem of a release in at least two phases of especially hygroscopic active ingredients which possibly in addition are highly soluble and acidic is not solved in DE 100 10 509 A1.

WO 98/13029 A1 on the other hand relates to medicament forms for retarded release of one or more active ingredients, including proteins, enzymes or vaccines which are sensitive to gastric juice, for guaranteeing the therapeutic action over a sufficient time. As a possible active ingredient inter alia betahistine is described. The formulations contain a water-insoluble coating. A gastric juice-resistant coating is not described. A formulation for quick release or another formulation for retarded release may be combined with this formulation, for example in a capsule or as a coating. Exact designs of such a combination of formulations containing active ingredient, in particular suitable proportions and ratios of amounts are not described. Insofar it

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cannot be deduced, whether this medicament form would at all be suitable for optimally mimicking an intake several times a day together with an immediate release of a proportion of the active ingredient in a first phase.

In DE 101 04 880 A1 multi-particulate medicament forms for release in multiple phases of a plurality of active ingredients are described, for guaranteeing a uniform release of the active ingredients over the intestine region. As a possible active ingredient inter alia betahistine is mentioned. The medicament form comprises two different forms of pellets which can be combined in a capsule or can be compressed together, wherein a ratio of 1:1 is described. The different forms of pellets release the active ingredient or the active ingredients at different pH values each. However, this medicament form does not enable an immediate release of an active ingredient in a first phase. So with this medicament form it is not possible to achieve therapeutic plasma levels in a first phase very quickly. Thus with this the daily intake of several medicament forms of active ingredients for which immediately therapeutic plasma levels have to be achieved is not dispensable. In addition, the production of the multi-particulate medicament forms is laborious and expensive and in particular in the case of hygroscopic and possibly also acidic active ingredients less suitable.

Insofar there is a great need for medicament forms for the release of hygroscopic active ingredients which at least release one active ingredient after intake in such a way that an intake several times a day is dispensable. This in particular relates to active ingredients with high solubility and/or high acidity. Here, conventional medicament forms are stretched to their limits. In particular, a retardation of active ingredients having the above mentioned properties with common retardation means and normally used retardation principles is only possible with great effort and is very costly. For such active ingredients an extension of their action to more than 10 hours with common retardation principles is hardly possible. Thus, normally used retardation mechanisms are not suitable for a cost-effective and thus in an industrial scale realizable formulation of such active ingredients in medicament forms which make an intake of the active ingredient several times a day dispensable. The problem underlying the present invention is solved by the subject matter of the patent claims.

Definitions of the specific embodiments of the invention as claimed herein follow.

According to a first embodiment of the invention, there is provided a medicament form, comprising

a. a core,

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b. a gastric juice-resistant intermediate layer being disposed on the surface of the core, and

c. a shell being disposed on the opposite side of the intermediate layer from the core,

wherein both the core and the shell contain a proportion of an active ingredient each, and wherein the medicament form releases the active ingredient in an at least biphasic form, wherein the first phase relates to the immediate release of the active ingredient after ingestion into the gastric juice, wherein the mass ratio of shell to core has a value of at least 0.5:1.

According to a second embodiment of the invention, there is provided a method for the production of a medicament form according to the first embodiment with the steps

a. preparing the core,

b. preparing the intermediate layer,

c. preparing the shell.

According to a third embodiment of the invention, there is provided use of the medicament form according to the first embodiment in a therapy method.

According to a fourth embodiment of the invention, there is provided a method of treating a disease comprising administration of a medicament form according to the first embodiment.

The present invention provides oral medicament forms for at least biphasic release of at least one active ingredient, wherein a part of the active ingredient in a first phase is immediately released after the intake into the stomach. Furthermore, the invention relates to production methods of such medicament forms as well as suitable uses. Thus, the concept according to the

[Text continues on page 6.]

present invention does not relate to retarded release in the sense of a common retardation formulation, but provides the immediate release of a first proportion of the active ingredient immediately after the intake thereof and the release of at least one second proportion of the active ingredient a certain time after its intake. Such a pulsed release optimally simulates the intake of an active ingredient two or more times a day and makes the intakes of a medicament form two or more times a day dispensable.

The medicament form of this invention comprises

- a core
- a gastric juice-resistant intermediate layer which is disposed on the surface of the core, and
- a shell which is disposed on the opposite side of the intermediate layer from the core,

wherein both the core and the shell each contain a proportion of an active ingredient. In addition, also the intermediate layer may contain an active ingredient. In preferable embodiments the medicament form according to the present invention does not contain any additional constituent which comprises an active ingredient, besides the core, the intermediate layer and the shell, thus in particular no additional layer containing an active ingredient is present. Further preferable, the medicament form according to the present invention consists of the core, the intermediate layer and the shell.

The active ingredient is released from the medicament form in an at least biphasic form. Further phases of release may subsequently follow. A "phase" according to the present invention is a time interval of a release of a proportion of the active ingredient from the medicament form.

In a first phase a first proportion of the amount of active ingredient is released. In a second phase a second proportion of the amount of active ingredient is released. According to the present invention the first phase directly starts after the entry of the medicament form into the stomach. Thus, the first phase relates to the immediate release of the active ingredient after the ingestion into the gastric juice. Preferably, this first phase of the release takes place from the shell, wherein the shell preferably disintegrates in the stomach. Preferably, the second phase of the release takes place from the core. The core preferably does not disintegrate in the stomach and is preferably transported into the small intestine by the so-called "housekeeper waves", thus by contractions of the stomach, for releasing the proportion of the active ingredient of the core there.

"Immediate release" preferably means in this case that at least 65 % of the first proportion of the amount of active ingredient, preferably at least 75 % and further preferably at least 80 % of the first proportion of the amount of active ingredient are released into the gastric juice after 60 minutes. Particularly preferably more than 60 %, further preferably more than 65 % of the first proportion of the amount of active ingredient are already released into the gastric juice after 30 minutes. This is determined *in vitro* using common apparatuses such as a bogie basket, stirrer blade or flow apparatus in 0.1 N HCl or water as test medium under physiological conditions (rotation; at about 36 to 38°C). The exact conditions depend on the active ingredient each and the medicament form and can be found in common pharmacopoeias.

Thus, the release of the first proportion of the amount of active ingredient takes place directly after the intake of the medicament form. Preferably, here the release of this proportion of active ingredient is not retarded by coatings. So preferably, before the release of the first proportion of the active ingredient initially no special coating, thus for example a film, has to be dissolved, ruptured or swelled.

Preferably, the second phase only starts at the earliest 4 hours, further preferably only at the earliest 6 hours and most preferably only at the earliest 7 hours after the intake of the medicament form. A second phase which starts too early may result in increased plasma concentrations, and this may involve the respective risk of side effects and further includes the risk that the release of the active ingredient is not sufficiently maintained in order that the intake one time a day is therapeutically sufficient. However, the release of the second proportion of the active ingredient preferably takes place at the latest 16 hours after the intake, further preferably at the latest 14 hours after the intake and most preferably at the latest 12.5 hours after the intake. A release which is too late would result in a release of the second proportion of the active ingredient in sections of the intestine which are too deep so that due to the reduced resorption area and the limited amount of liquid the resorption would considerably be reduced. Particularly preferably, the release of the second proportion of the active ingredient takes place in the colon.

The release in the second phase in this case preferably takes place immediately after achieving a certain pH range. The second proportion of the active ingredient is preferably released from the core of the medicament form. Thus preferably, after achieving a certain pH value within 60 minutes at least 65 % of the second proportion of the amount of active ingredient, preferably at least 75 % and further preferably at least 80 % of the second proportion of the amount of active

ingredient are released, determined *in vitro* using common apparatuses in a buffer medium with the respective pH value as test medium under physiological conditions (rotation; at about 36 to 38°C). The exact conditions depend on the active ingredient each and the medicament form and can be found in common pharmacopoeias.

But in an alternative the release of the second proportion of the active ingredient may also take place in a retarded manner, wherein retarded manner means prolonged over a certain time interval, preferably over at least 4 hours, further preferably over at least 6 hours. In an embodiment further phases of release in which proportions of the active ingredient are released can be provided.

But besides the first active ingredient the medicament form may also comprise further active ingredients which are released in one phase or in more phases. A release in more phases is preferable. Particularly preferably, the medicament form according to the present invention only contains said one active ingredient. So possible incompatibilities during the production and storage thereof can be avoided.

The medicament form of the present invention is an oral medicament form, wherein oral medicament form means that it is intended for oral intake. According to the present invention in this case for example a tablet, caplet, micro-tablet, granules or pellets may be envisaged. The medicament form may also be contained in a multi-particulate medicament form such as a tablet or capsule or in granules, a sachet, stick or bag. Preferably, the medicament form according to the present invention is a tablet.

Exceptionally preferably, the medicament form according to the present invention is a shell-core tablet internally containing the core which is surrounded by the intermediate layer. Said intermediate layer is in turn surrounded by the shell. Preferably, "surrounded" by the intermediate layer with respect to the core means that at least 95 % of the total surface of the core, further preferably at least 98 % and exceptionally preferably at least 99 % of the total surface of the core are covered with the intermediate layer. Still more preferable is, when the total surface of the core is "completely" surrounded by the intermediate layer, wherein "completely" preferably means that more than 99.5 %, ideally more than 99.8 % of the total surface of the core are covered by the intermediate layer. This does not exclude that pores are contained in the intermediate layer. Preferably, "surrounded" by the shell with respect to the intermediate layer means that at least 95 % of the total surface of the intermediate layer on the side which is the opposite side of the intermediate layer from the core, further preferably at

least 98 % and exceptionally preferably at least 99 % are covered by the shell. Still more preferable is, when the total surface of the intermediate layer on the side which is the opposite side of the intermediate layer from the core is completely surrounded by the shell, so preferably more than 99.5 % and ideally more than 99.8 % of the intermediate layer on the side which is the opposite side of the intermediate layer from the core are covered by the shell.

However in an alternative the medicament form can also be a layer tablet in which the intermediate layer may be present between the layers of the layer tablet, wherein in this case the core would be one of the layers and the shell would be the other layer.

It has been shown that the design of a shell-core tablet is particularly advantageous. With the design as a shell-core tablet it was possible to achieve an optimum initiation and an optimal maintenance of the release of the active ingredient over a sufficient period of time. With this shell-core concept it is possible to mimic in a particularly preferable manner the daily intake of at least two tablets, preferably in a time interval of 8 to 12 hours.

The aim of such a design of the medicament form as a shell-core tablet is different from the aim usually pursued in the prior art. So shell-core tablets are known as an option for the formulation of intolerable active ingredients or extremely bad smelling or extremely instable active ingredients.

Preferably, the active ingredient is hygroscopic and shows good solubility in water. Hygroscopic active ingredients and active ingredients with good water solubility in particular profit from the active ingredient design according to the present invention. According to the present invention a hygroscopic active ingredient is an active ingredient if it or the salt of it has the tendency of taking up water from the environment, for example by adsorption or absorption or other mechanisms. So hygroscopic active ingredients are also active ingredients which melt by taking up water (deliquescence).

Preferably, according to the present invention hygroscopy is defined as a property of a substance, when this substance at a relative air humidity of 75 %, preferably at a relative air humidity of 45 % and most preferably already at a relative air humidity of 30 % takes up more than 1 % by weight of water from the environment. Particularly preferably, at least 5 % by weight, further preferably at least 8 % by weight of water are taken up from the environment. The determination of the taking up of water is conducted by placement of 0.5 g of a sample of the substance which before has exclusively been stored airtight, in an atmosphere with relative

air humidity of 75 %, 45 % or 30 % for 24 hours. Subsequently the water content of the substance is determined by the Karl-Fischer method in a Karl-Fischer titrator under heating to a temperature of at most 300°C. The water content is compared with the water content of 0.5 g of the substance originating from the same sample, but which further has been stored airtight.

Preferably, an active ingredient is used which, when a sample thereof is dried under the above mentioned conditions at 105°C until constant weight is achieved, in a drying oven or by means of an infrared dryer, wherein the infrared dryer is preferred, has a water content of at least 0.5 % by weight, based on the total mass of the medicament form, further preferably of at least 1 % by weight. This method determines the proportion of water of the sample which is not chemically bonded. In this case the sample is preferably a medicament form, comprising the active ingredient and adjuvants.

Examples of preferable active ingredients which themselves or in the form of their pharmaceutically acceptable salts are hygroscopic are valproic acid, carbamazepine, tetracycline, lincomycin, clindamycin, rifampicin, erythromycin, metformin, atenolol, ranitidine, minoxidil, acetylsalicylic acid, diclofenac, omeprazole, methyldopa, betahistine, dexamethasone, prednisolone, piracetam, pravastatin and gemfibrozil.

Preferably, the active ingredient has good solubility. According to the present invention, good or high solubility of active ingredients is given, when 1 g of the active ingredient can be dissolved in a maximum of 10 ml of water at 15 to 25°C under normal pressure.

It is particularly preferable, when the active ingredient is an active ingredient of the BCS class I according to the Biopharmaceutics Classification System. Members of the BCS class I are such active ingredients which have high solubility and a high permeation capability, determined for example according to the rules of the FDA ("Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System", 2000).

The active ingredient may also be acidic. According to the present invention, preferably an active ingredient is acidic, when its solution in water with a mass proportion of the active ingredient of 10 % by weight at standard conditions (DIN 1343) has a pH value of at most 5, further preferably a pH value of at most 4 and exceptionally preferably a pH value of at most 3.

The medicament form according to the present invention in total comprises preferably between 1 mg and 200 mg of active ingredient. Preferably, the medicament form according to the

present invention comprises the active ingredient in an amount of between 1.5 mg and 150 mg, further preferably in an amount of between 2 mg and 120 mg, even more preferably in an amount of between 5 mg and 60 mg.

Preferably, the active ingredient is betahistine or a pharmaceutically acceptable salt of betahistine. Pharmaceutically acceptable salts of betahistine are in particular betahistine dihydrochloride, betahistine dimesylate, betahistine methane sulfonate, betahistine fumarate and betahistine citrate. Further preferable are betahistine dihydrochloride, betahistine dimesylate, betahistine fumarate and betahistine citrate. Exceptionally preferable are betahistine dihydrochloride and betahistine dimesylate. In a particularly preferable embodiment the medicament form comprises betahistine dihydrochloride or betahistine dimesylate. In this case preferable between 2 mg and 55 mg, based on the base of the active ingredient, are contained in the medicament form. The base of the active ingredient is betahistine, thus not the salt.

It is exceptionally preferable, when the medicament form according to the present invention contains betahistine dihydrochloride, preferably in an amount of between 8 mg and 100 mg, exceptionally preferably between 30 and 60 mg, and most preferably 48 mg are contained in the medicament form. When in this application absolute values are mentioned, then this always also comprises values in a tolerance range of ± 2 % around the mentioned absolute value.

Here, the active ingredient may be contained in the core, in the intermediate layer and in the shell. And in this case it is preferable that the proportion of the active ingredient in the core and in the shell each amounts to 40 % to 60 % of the total amount of the active ingredient in the medicament form. The proportion of the active ingredient in the core preferably amounts to at least 42 % and at most 58 %, further preferably at least 45 % and at most 55 % of the total amount of the active ingredient in the medicament form. When the amounts of the active ingredient in the core are too low, then there is the risk that the effect cannot be maintained for a period of time which is sufficiently long.

Preferably, the proportions of the active ingredient in the core and in the shell are the same. This enables a multiphasic release of equal amounts of active ingredient and is advantageous, because this kind of release optimally mimics an intake of a medicament several times a day. In an alternative the distribution of the active ingredient in the core and in the shell may also be different. According to the present invention, “the same” preferably means that the mass ratio of the amount of active ingredient in the core to the amount of active ingredient in the shell

preferably amounts to at least 1 to 1.1 and at most 1.1 to 1, further preferably at least 1 to 1.05 and at most 1.05 to 1.

Besides the active ingredient also a second, optionally also a third active ingredient may be contained in the core, the shell and/or the intermediate layer. It is especially preferable that the intermediate layer does not contain any active ingredient.

The core contains an active ingredient, thus comprises at least the active ingredient. Besides the active ingredient, preferably there is contained at least one pharmaceutically acceptable adjuvant. Pharmaceutically acceptable adjuvants are substances which with respect to the safety of the patient and the processability are generally suitable for the use in medicament forms.

It has been shown that it is advantageous, when the core at least comprises a carrier which is preferably sorption-active. A sorption-active carrier has the capability of being adsorbed to a hygroscopic proportion of an active ingredient, thus "carry" it, and of removing the hygroscopy of the active ingredient up to a certain degree. Thereby, the melting of the hygroscopic active ingredient is avoided which results in a distinct positive influence onto the breaking strength and the shelf life of the achieved medicament form.

Surprisingly it was found that for that in particular carriers are suitable which themselves are hygroscopic, thus have a tendency for taking up humidity. Normally it would be expected that by the additional uptake of humidity of such carriers the processability would be compromised. But in reality it was possible to obtain by the use of such carriers together with the active ingredient a hard and stable core which can easily be processed and compressed.

But it has been shown that for that the carrier or the carriers preferably have to be present in an excess with respect to the active ingredient. Therefore preferably, the mass ratio of the carrier or the carriers in the core to the active ingredient in the core is at least 2:1, further preferably at least 3:1, further preferably at least 3.4:1 and in exceptionally preferable embodiments at least 5:1. Obviously the carrier in this case has the effect that a further up-take of water from the environment can be considerably reduced. But the mass ratio should preferably not be higher than 20:1, preferably not higher than 10:1, further preferably not higher than 7.5:1, because otherwise the processability may be complicated. A mass ratio which is too high is also connected with a core which is too big. This may result in an enlargement of the medicament form according to the present invention which is too high.

Suitable carriers may be of inorganic or organic kind. Preferable carriers are selected from natural and synthetic polymers. Preferably, they are natural or modified polysaccharides, preferably consisting of two or more equal or different monosaccharide entities. Such substances can be obtained cheaply and can be easily processed. The latter is in particular advantageous, when the release of the proportion of the active ingredient from the core should take place immediately. It has been shown that polysaccharides containing glucose units are particularly advantageous. In this case the natural or modified polysaccharide is preferably a disaccharide, particularly preferably this is selected from lactose, sucrose and mixtures thereof.

In an alternative this carrier may be a polysaccharide with more than 10 monosaccharide entities which in contact with water is preferably swellable. Particularly preferably, here starch including starch derivatives, cellulose including cellulose derivatives or mixtures thereof are used. Powdered cellulose such as microcrystalline cellulose is exceptionally preferable. Also starch in native or pre-gelatinized form, in particular corn starch can be used. Such carriers are still more capable of taking up water from the proportion of the active ingredient.

But it has been shown that the breaking strength of the tablet may decrease with increasing storage time, when in the case of the use of certain active ingredients exclusively only such polysaccharides are used as carriers. Therefore, in a particularly preferable embodiment in the core are contained at least two carriers, wherein in this case exceptionally preferably at least one disaccharide and at least one polysaccharide with more than 10 monosaccharide entities which in contact with water is preferably swellable are used. With this combination an optimal breaking strength and an optimal stability were achieved. Also the proportion of the active ingredient is optimally fixed, preferably at the mixture of the carriers. And it is exceptionally preferable, when the core contains at least three carriers. The mass ratio of polysaccharides with more than 10 monosaccharide entities to disaccharides is preferably at least 1.1:1, preferably at least 1.25:1 and particularly preferably at least 1.3:1.

There may also be used inorganic carriers, preferably ones having hygroscopic properties. Inorganic carriers may also be contained in addition to the above mentioned organic carriers.

Preferably, the core contains salts of the above mentioned organic or inorganic substances in a proportion of at most 5 % by weight, preferably at most 2 % by weight and exceptionally preferably in a proportion of at most 1 % by weight. When salts of the above mentioned organic substances or salts of inorganic substances are used in the core according to the present invention in high amounts, then this may result in reaction of the active ingredient in the core

with these substances, by what the stability of the active ingredient in the core can be negatively influenced. In this case salts in particular comprise alkali and alkaline earth metal salts of such substances. Particularly preferably, the core is free of salts of the above mentioned organic or inorganic substances, i.e. salts of such substances, in particular comprising calcium phosphate, sodium salts of celluloses and/or magnesium stearate, are only contained as impurities in a proportion of preferably at most 0.5 % by weight, preferably at most 0.1 % by weight of the total mass of the core.

Preferably, the total proportion of the carriers according to the present invention, based on the total mass of the core, is at least 50 % by weight, preferably at least 63 % by weight and exceptionally preferably at least 65 % by weight as well as further preferably at least 68 % by weight. When the amount of the carrier(s) is too low, then the hygroscopy of the active ingredient can only be compensated to an insufficient extent. Furthermore, the carrier(s) result(s) in a certain retardation effect with respect to the release of the active ingredient. Preferably, the core contains at most 90 % by weight of carrier respectively carriers, preferably at most 85 % by weight and further preferably at most 80 % by weight. Mass proportions of the carrier(s) which are too high complicate the forming operation of the core. The carrier may also lessen the acidity of the active ingredient. But for that a certain amount of the carrier is required.

In order that the amount of the carrier keeps within reasonable bounds, according to the present invention preferably a buffer substance can be used in the core. The mass of the buffer substance used is preferably lower than the mass of the carriers. In this case a mass ratio of carriers in the core to buffer substances in the core of preferably at least 3:1, further preferably at least 4:1 and exceptionally preferably at least 4.5:1 is advantageous, and it was possible to achieve both, a sufficient compensation of the hygroscopy and a sufficient lessening of the acidity, together with good processability of the core. The core preferably contains at least 1 % by weight of buffer substance, preferably at least 8 % by weight. Preferably, the core contains at most 26 % by weight of buffer substance, further preferably at most 16 % by weight. The proportion of buffer substance should not exceed certain values, because this component may compromise the stability of the medicament form.

As a buffer substance organic acids are particularly suitable, wherein preferably they are low-molecular ones. “Low-molecular” organic acids are organic acids with a molar mass of lower than 300 g/mol. The buffer substance 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. Particularly preferable are alpha-hydroxyl carboxylic acids which due to the alpha-hydroxyl group show an optimum buffer effect. Preferably they are selected from lactic acid, tartaric acid, citric acid and mixtures thereof. Citric acid is exceptionally preferable, because it can be processed very easily and it does not significantly modify the release of the active ingredient from the core. This is a surprising fact, because citric acid in a lot of presentation forms results in an acceleration of the release, which would not be desired here.

The mass ratio of the active ingredient in the core to the buffer substance in the core is preferably at least 0.5:1, preferably at least 0.8:1, further preferably at least 0.9:1. The mass ratio is preferably at most 1.5:1, further preferably at most 1.2:1 and particularly preferably at most 1.1:1. When the amount of the buffer substance is too low, then it is possible that the acidity of the active ingredient cannot be buffered to a sufficient extent. When the amount of the buffer substance is too high, then in turn the acidity may increase in an unfavorable manner. According to the present invention, the core preferably contains at least 8 mg of buffer substance, preferably at least 15 mg and exceptionally preferably at least 20 mg. Preferably at most 48 mg and exceptionally preferably at most 30 mg of buffer substance are contained in the core.

The core may contain at least one further pharmaceutically acceptable adjuvant, such as for example fillers and/or binders. In addition, the core may contain disintegrating agents, which are in particular selected from alginic acid, calcium carboxymethyl cellulose, cross-linked carboxymethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl starch, cross-linked polyvinylpyrrolidone and mixtures thereof. The addition of such a disintegrating agent prevents that the proportion of the active ingredient in the core is only released in sections of the intestine which are too deep. Due to the reduced resorption area this would result in a considerably worse resorption of the proportion of the active ingredient. It has been shown that an addition of cross-linked polyvinylpyrrolidone is particularly suitable.

Preferably, the disintegrating agent amounts to a weight proportion of the core of at least 1 % by weight, further preferably at least 2 % by weight, for effecting a sufficient stimulation of the disintegration. The maximum content of disintegrating agent is preferably 8 % by weight, preferably at most 6.5 % by weight. When the proportions of the disintegrating agent are too high, then this results in a release of the active ingredient which is too fast. In an alternative the core is preferably free of such disintegrating agents, because with the special core composition

according to the present invention surprisingly most often already a sufficiently quick disintegration is guaranteed.

According to the conditions of the production the core may comprise at least one granulating agent. Preferably, the amount of the granulating agent in the core amounts to at least 0.1 % by weight, further preferably at least 0.25 % by weight, still further preferably at least 0.5 % by weight and still further preferably at least 0.75 % by weight. The core contains a maximum of preferably 5 % by weight, further preferably a maximum of 2.5 % by weight of granulating agent. Granulating agents which are preferred in the core are mentioned below.

According to the conditions of the production the core preferably contains at least one lubricant, preferably in a mass proportion of at most 10 % by weight, preferably at most 8 % by weight, based on the total mass of the core. Preferably, at least 0.5 % by weight, further preferably at least 1 % by weight of lubricant are contained in the core. Lubricants which are preferred in the core are mentioned below.

Thus, in one embodiment the core contains:

a. an active ingredient; and
b. optionally at least one carrier (preferably with a mass proportion of 50 % by weight to 90 % by weight) which in particular has the purpose "to carry" the active ingredient, to lessen the hygroscopy and acidity thereof and also to guarantee a certain retardation; and
c. optionally at least one buffer substance (preferably with a mass proportion of 1 % by weight to 26 % by weight), in particular for lessening the acidity of the active ingredient; and
d. optionally a disintegrating agent (preferred mass proportion of 1 % by weight to 8 % by weight) for accelerating the disintegration of the core; and
e. optionally according to the conditions of the production at least one granulating agent (preferred mass proportion of 0.1 % by weight to 5 % by weight); and
f. optionally according to the conditions of the production at least one lubricant (preferred mass proportion of 0.5 % by weight to 10 % by weight); and
g. optionally further adjuvants, such as for example fillers and/or binders.

On the surface of the core is disposed an intermediate layer. It has been shown that such a layer is advantageous for providing a time interval between the release of the active ingredient from

the core and the shell. Preferably, an additional purpose of the intermediate layer is the bonding of the core and the shell to one another. Without the intermediate layer most often no medicament form with sufficient breaking strength and storability could be achieved.

Furthermore it has been shown that fewer adjuvants in the core are required, when the intermediate layer exclusively or in addition controls the release of the active ingredient from the core. So the size of the core can be reduced and an adequate size of the whole medicament form is guaranteed which is necessary for a good compliance of the patient. It has also been shown that it is in particularly difficult to exclusively control the release of the active ingredient by the core, when the active ingredient is an active ingredient with high solubility. So often it was not possible to sufficiently temporally separate the release of the active ingredient from the core from the release of the active ingredient from the shell by the exclusive use of a retardation matrix. Thus the release could not be maintained sufficiently long. Only with the intermediate layer according to the present invention it was possible to sufficiently temporally separate the release of the active ingredient from the core and that from the shell.

The intermediate layer is preferably designed to be gastric juice-resistant. "Gastric juice-resistant" preferably means that the intermediate layer does not dissolve in the pH range of the stomach, thus preferably does not dissolve in 0.1 N HCl at 36°C to 38°C within 120 minutes. This means preferably that the core on which surface the intermediate layer is disposed does not disintegrate in 0.1 N HCl at 36 to 38°C within 120 minutes. The measurement of the disintegration is conducted with common disintegration apparatuses, preferably with the stirrer blade apparatus.

Thus the release from the core at the earliest starts with the entry into the milieu of the small intestine by dissolving, disintegrating, cracking or other modification of the intermediate layer, preferably by the dissolution of the intermediate layer, when a certain pH value is reached. So the intermediate layer preferably is dissolved, when a certain pH value in the aqueous milieu of the gastrointestinal tract is reached. According to the present invention the different possible processes are described by the term "dissolving". The dissolution of the intermediate layer preferably starts at a pH value of at least 5, further preferably at a pH value of at least 6 and exceptionally preferably at a pH value of at least 6.5. It is exceptionally preferable, when the dissolution of the intermediate layer starts at a pH value of at least 7.0 and still more preferably at a pH value of at least 7.2. A dissolution at pH values which are too low would result in a too early release of the active ingredient in the second phase even in the stomach or in upper

sections of the duodenum. Depending on the active ingredient, this involves the risk of plasma levels which are too high. The intermediate layer should preferably be dissolved at the latest at a pH value of 7.65, preferably at the latest at pH 7.5. When the intermediate layer is dissolved only at pH values which are too high, then a sufficient resorption of the active ingredient can no longer be guaranteed.

The intermediate layer preferably comprises at least one pharmaceutically acceptable adjuvant, in particular a film-forming component which preferably guarantees the gastric juice-resistance. Optionally, also an active ingredient may be contained in the intermediate layer.

It has been shown that suitable film-forming components are natural and synthetic polymers having free acid functions. Preferably, these acid functions in salt form are well soluble. Preferably, each polymer comprises at least 0.1 free acid functions per monomer entity, further preferably at least 0.3 free acid units per monomer entity. Such polymers are suitable for being dissolved in the basic pH range of the intestine, but not in the acidic pH range of the stomach. Preferably, such free acid functions are carboxyl groups, since these are most often sufficiently well soluble in salt form.

Preferred film-forming components are cellulose derivatives, methacrylic acid polymers, polyvinyl derivatives and mixtures thereof.

Cellulose derivatives are preferably celluloses which are esterified with organic acids. The organic acids may be aliphatic or aromatic. Preferably, these organic acids comprise at most 10 carbon atoms, further preferably at most 8 carbon atoms. But preferably they comprise at least 2 carbon atoms. The cellulose derivative is particularly preferably selected from cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate and mixtures thereof.

Preferred polyvinyl derivatives are polyvinyl derivatives which are esterified with organic acids. The latter may be of aliphatic or aromatic nature and preferably comprise at least 2 carbon atoms, but preferably at most 10 carbon atoms. Preferably, the polyvinyl derivative is esterified with both, aliphatic and also aromatic residues. A particularly preferable polyvinyl derivative is polyvinylacetate phthalate.

Under the methacrylic acid polymers those have been shown to be suitable which are composed of methacrylic acid monomers with free carboxyl groups and monomers with esterified carboxyl group. The monomers with esterified carboxyl group are preferably selected from

methacrylic acid monomers and acrylic acid monomers. The monomers with esterified carboxyl group are preferably esterified aliphatically, preferably with organic groups. These organic groups preferably comprise at least 1 carbon atom, but preferably at most 5 carbon atoms, further preferably at most 4 carbon atoms. Monomers with esterified carboxyl group preferably are selected from methylmethacrylate monomers, ethylacrylate monomers and methylacrylate monomers.

Preferred methacrylic acid polymers are polymethacrylic acid/polymethylmethacrylate copolymers, polymethacrylic acid/polyethylacrylate copolymers, polymethacrylic acid/polymethylacrylate/polymethylmethacrylate copolymers and mixtures thereof. In this case the molar ratio of monomers with esterified carboxyl groups to methacrylic acid monomers with free carboxyl group is preferably at least 0.5:1, particularly preferably at least 0.9:1. The molar ratio is preferably at most 12:1, further preferably at most 10:1 and exceptionally preferably at most 2.5:1. Exceptionally preferable methacrylic acid polymers are polymethacrylic acid/polymethylmethacrylate copolymers. Particularly preferably, the film-forming component comprises at least one methacrylic acid polymer.

Particularly preferred film-forming components 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. Exceptionally preferred are Eudragit® L, Eudragit® S and mixtures thereof, in particular Eudragit® L 100, Eudragit® S 100 and mixtures thereof. Eudragit® L 100 conforms with poly(methacrylic acid-co-methylmethacrylate) 1:1 (CAS 25086-15-1). Eudragit® S 100 conforms with poly(methacrylic acid-co-methylmethacrylate) 1:2 (CAS 25086-15-1). Eudragit® L 100-55 conforms with poly(methacrylic acid-co-ethylacrylate) 1:1 (CAS 25212-88-8). Eudragit® L 30 D-55 conforms with poly(methacrylic acid-co-ethylacrylate) 1:1 (CAS 25212-88-8). Eudragit® L 12,5 conforms with poly(methacrylic acid-co-methylmethacrylate) 1:1 (CAS 25086-15-1). Eudragit® S 12,5 conforms with poly(methacrylic acid-co-methylmethacrylate) 1:2 (CAS 25086-15-1). Eudragit® FS 30 D conforms with poly(methylacrylate-co-methylmethacrylate-co-methacrylic acid) 7:3:1 (CAS 26936-24-3). In further preferable embodiments methacrylic acid polymers are used which are polyethylacrylate/polymethylmethacrylate copolymers. Particularly preferable is Eudragit® NE 30 D. Eudragit® NE 30 D conforms with poly(ethylacrylate-co-methylmethacrylate) 2:1 (CAS 9010-88-2).

The film-forming component is exceptionally preferably a methacrylic acid polymer, exceptionally preferably the film-forming component is at least a polymethacrylic acid/polymethylmethacrylate copolymer. In a special embodiment exclusively methacrylic acid polymers are used as film-forming components. Exceptionally preferably here a mixture of different methacrylic acid polymers is used. Through the high solubility of the polymer in the milieu of the intestine a targeted release of the active ingredient in the second phase, preferably from the core in the small intestine can be guaranteed. Furthermore, these film-forming components can be processed cheaply and can be applied onto the surface of the core in a quick and easy manner. By mixing different methacrylic acid polymers the pH value at which the dissolution of the intermediate layer should take place can be adjusted in a targeted manner. Exceptionally preferably is a mixture of Eudragit® S 100 and Eudragit® L 100. The mass ratio of Eudragit® S 100 to Eudragit® L 100 in this case is preferably at least 1.5:1, preferably at least 2.5:1, still more preferably at least 3:1. Preferably, the mass ratio is at most 10:1, preferably at most 7.5:1 and still more preferably at most 5:1. In alternative embodiments the film-forming component is Eudragit® S 100 or Eudragit® L 100.

In an alternative a natural polymer may be used as a film-forming component, wherein shellac is preferred.

The proportion of the film-forming component in the intermediate layer is preferably at least 20 % by weight, preferably at least 35 % by weight and exceptionally preferably at least 40 % by weight and further preferably at least 45 % by weight. A content of the film-forming component which is too low may result in dissolution of the intermediate layer already in the stomach. But the content of the film-forming component in the intermediate layer is preferably at most 75 % by weight, further preferably at most 70 % by weight and still further preferably at most 65 % by weight. A content which is too high results in a very brittle intermediate layer without sufficient binding effect.

The weight of the intermediate layer is preferably at least 4 mg, further preferably at least 5 mg and particularly preferably more than 5 mg. A weight of the intermediate layer of at least 8 mg is exceptionally preferable and still more preferably are at least 10 mg. When the weight of the intermediate layer is too low, then the mechanic stability of the core may be reduced. The weight of the intermediate layer is preferably not higher than 55 mg, further preferably at most 50 mg and still more preferably at most 35 mg. Exceptionally preferably, the weight of the intermediate layer is not higher than 28 mg. When the weight is too high, thus the amount of the

intermediate layer is too high, then there is the risk that the release of the active ingredient from the core is compromised. There is also the risk that the medicament form in total becomes too large and too heavy and thus worse swallowable. It has been shown that a weight of the intermediate layer of 12 to 25 mg is particularly suitable.

The intermediate layer is suitable for bonding the core and the shell to one another. The effect of bonding of the intermediate layer is preferably achieved by the addition of at least one plasticizer. According to the present invention, they are liquids at room temperature and normal pressure. Particularly suitable are plasticizers which are hygroscopic. Particularly preferable are polyalcohols with at least two hydroxyl groups. These polyalcohols preferably contain at least 2 carbon atoms, preferably at most 10 carbon atoms. The hydroxyl groups may be present in free form. Also all or a part of the hydroxyl groups may be present in esterified form, preferably with organic acids. Preferably, these organic acids are aliphatic acids, wherein they further preferably comprise at least 2 carbon atoms, preferably at most 24 carbon atoms, most preferably at most 22 carbon atoms.

Exceptionally preferable plasticizers are selected from glycerol, propylene glycol, glycerol triacetate, castor oil, acetylated fatty acid glycerides and mixtures thereof. According to the present invention it has also been shown that polyethers of polyalcohols are suitable, wherein the polyalcohol entities preferably comprise at least 2 carbon atoms and preferably at most 10 carbon atoms. Preferable polyethers are polyethylene glycols, preferably having a mean molar mass of up to 600 g/mol. By addition of such plasticizers a good bonding effect of the intermediate layer could be achieved. Furthermore, these plasticizers are useful for guaranteeing the mechanic stability also over longer periods of time.

The proportion of the plasticizer in the intermediate layer is preferably at least 1 % by weight, preferably at least 5 % by weight, for achieving a good bonding effect. Preferably, the proportion of the plasticizer in the intermediate layer is at least 8 % by weight and further preferably at least 12 % by weight. Preferably, a maximum of 30 % by weight, further preferably a maximum of 25 % by weight and still further preferably a maximum of 20 % by weight of a plasticizer are contained in the intermediate layer. When the content of the plasticizer is too high, then a sufficient strength of the intermediate layer and also a sufficient gastric juice-resistance cannot longer be guaranteed.

The intermediate layer may contain at least one further pharmaceutically acceptable adjuvant which can simplify the processing and the application of the layer and/or is suitable for

adjusting the consistency thereof. In particular, normal fillers, pore-formers and/or further plasticizers may be contained. Further plasticizers may be esters of organic acids, wherein these organic acids preferably comprise at least 2 carbon atoms and preferably at most 10 carbon atoms. Preferred are citric acid and phthalic acid. Such plasticizers are for example tributyl citrate, triethyl citrate, diethyl phthalate, dibutyl phthalate.

For facilitating the application of the intermediate layer, the intermediate layer preferably contains fillers which are preferably selected from talcum, titanium dioxide, magnesium stearate, colorants, glycerol monostearate, lactose, microcrystalline cellulose, polyvinylpyrrolidone and mixtures thereof. Preferably, the filler is talcum. Particularly preferably, the filler is suitable for perforating the intermediate layer so that there is an additional possibility for controlling the release of the active ingredient in the core. But the mass proportion of the filler has to be restricted to preferably at most 40 % by weight, further preferably at most 35 % by weight, in particular in the case, when the intermediate layer should have a bonding effect. The filler may reduce the bonding effect of the intermediate layer. The minimum content of the filler preferably amounts to at least 5 % by weight, further preferably at least 15 % by weight.

The mass ratio of core to intermediate layer should preferably be at least 2:1, further preferably at least 3:1, still further preferably at least 6.5:1 and exceptionally preferably at least 7.5:1. Thus, the intermediate layer in relation to the core should not have a mass proportion which is too high, in particular in the case, when the intermediate layer does not contain any active ingredient. So it is guaranteed that also the total weight and thus the dimensions of the medicament form are suitable for oral intake. The mass ratio should preferably be at most 60:1, further preferably at most 45:1. In a preferred embodiment the mass ratio is at most 40:1 and still further preferably at most 30:1 as well as especially preferably at most 20:1. When the ratio becomes too high, then the thickness of the intermediate layer is no longer sufficient for the desired function.

The intermediate layer preferably covers at least 40 % of the total surface of the core. This is in particularly advantageous, when the core at the non-covered area is covered with another layer. Particularly preferably, at least 95 % of the total surface of the core are covered by the intermediate layer, further preferably at least 98 % and particularly preferably at least 99 %. In particularly preferable embodiments the core is completely covered by the intermediate layer. In a preferred embodiment the intermediate layer preferably has no pores. “Pores” means holes

in the intermediate layer, through which the active ingredient may be prematurely released from the core.

Thus, in one embodiment the intermediate layer contains:

a. an active ingredient,
b. optionally a film-forming component (preferred mass proportion of 20 to 75 % by weight), in particular for guaranteeing a gastric juice-resistance of the intermediate layer, and
c. optionally a plasticizer (preferred mass proportion of 1 to 30 % by weight) which preferably is hygroscopic, in particular for guaranteeing a good bonding effect of the intermediate layer; and
d. optionally a filler, in particular talcum, in a preferred mass proportion of 5 % by weight to 40 % by weight; and
e. optionally further pharmaceutically acceptable adjuvants, such as for example further fillers, pore-formers and/or further plasticizers.

The shell contains active ingredient, thus contains at least the active ingredient. Besides the active ingredient preferably at least one pharmaceutically acceptable adjuvant is contained.

The mass ratio of shell to core is preferably at least 0.5:1, further preferably at least 1.1:1, more preferably at least 1.8:1, further preferably at least 2:1 and particularly preferably at least 2.2:1. This enables a sufficient processability of the shell. The mass ratio is preferably at most 10:1, preferably at most 5:1, preferably at most 4.5:1 and further preferably at most 4:1. When the mass ratios are too high, then a size of the medicament form which is suitable for intake cannot longer be guaranteed. Preferably, the shell in comparison to the core contains a higher proportion of pharmaceutically acceptable adjuvants, for guaranteeing a certain volume of the shell and also for embedding the active ingredient and so sufficiently shielding it from influences from outside, for example from humidity and in particular also from light. The mass ratio of the adjuvants in the shell to the proportion of the adjuvants in the core is preferably at least 1.8:1, further preferably even at least 2.5:1.

In particular, it has also been shown that the use of at least one carrier as an adjuvant in the shell is advantageous. Preferably, the carrier in the shell is hygroscopic. Normally it would be expected that this would compromise the stability of the medicament form, since the shell preferably does not comprise a further coating and insofar the constituents of the shell are not

shielded from humidity and light. The mass ratio of the carrier in the shell to the active ingredient in the shell is preferably at least 7.5:1, preferably at least 10:1, further preferably at least 14:1, and in exceptionally preferable embodiments it is at least 15:1. Then, the active ingredient is preferably distributed and matrix-likely embedded in the relatively higher proportion of the carrier in the shell so that a further up-take of water from the environment can considerably be reduced. However, the mass ratio is preferably at most 50:1, further preferably at most 35:1, for guaranteeing a suitable size of the medicament form. Further preferably, the mass ratio is at most 30:1 and still further preferably at most 28:1.

Suitable carriers in the shell may be of inorganic or organic kind. Preferable carriers in the shell are selected from natural and synthetic polymers. Preferably, they are natural or modified polysaccharides, preferably consisting of two or more equal or different monosaccharide entities. Such substances can be obtained cheaply and can be easily processed. It has been shown that polysaccharides containing glucose units are particularly advantageous. Preferably, the carrier is a disaccharide, particularly preferably this is selected from lactose, sucrose and mixtures thereof.

In an alternative this carrier in the shell may be a polysaccharide with more than 10 monosaccharide entities which in contact with water is preferably swellable. Particularly preferably, here starch including starch derivatives, cellulose including cellulose derivatives or mixtures thereof are used. Powdered cellulose such as microcrystalline cellulose is exceptionally preferable. Also starch in native or pre-gelatinized form, in particular corn starch can be used. Such carriers are still more capable of taking up water from the proportion of the active ingredient. But it has been shown that the breaking strength of the tablet with increasing storage time may decrease, when in the case of the use of certain active ingredients exclusively only such polysaccharides are used as carriers in the shell.

Therefore, in a particularly preferable embodiment at least two carriers are contained in the shell, wherein exceptionally preferably in this case they are at least one disaccharide and at least one polysaccharide with more than 10 monosaccharide entities which in contact with water is preferably swellable. With this combination an optimum breaking strength and an optimal stability were achieved. Also the proportion of the active ingredient is optimally fixed, preferably on the carrier mixture. Exceptionally preferably, the shell contains at least three carriers. The mass ratio of polysaccharides with more than 10 monosaccharide entities to

disaccharides is preferably at least 1.1:1, preferably at least 1.25:1 and exceptionally preferably at least 1.3:1.

Also inorganic carriers, preferably having hygroscopic properties can be used in the shell. Inorganic carriers may also be contained in the shell in addition to the above mentioned carriers.

Preferably, the shell contains salts of the above mentioned organic or inorganic substances in a proportion of at most 5 % by weight, preferably at most 2 % by weight and exceptionally preferably in a proportion of at most 1 % by weight. When salts of the above mentioned organic substances or salts of inorganic substances are used in the shell according to the present invention, then this may result in reaction of the active ingredient in the shell with these substances, by what the stability of the active ingredient in the shell can negatively be influenced. In this case in particular salts comprise alkali and alkaline earth metal salts of such substances. It is particularly preferable, when the shell is free of salts of the above mentioned organic or inorganic substances, i.e. salts of such substances, in particular comprising calcium phosphate, sodium salts of celluloses and magnesium stearate, are only contained as impurities in a proportion of preferably at most 0.5 % by weight, preferably at most 0.1 % by weight of the total mass of the shell. However, salts of such substances may be contained in an optional coating of the shell.

It is particularly preferable, when at least two carriers are contained in the shell, and exceptionally preferable are three carriers. Preferably, the total proportion of the carriers with respect to the total mass of the shell is at least 70 % by weight, preferably at least 77.5 % by weight and exceptionally preferably at least 80 % by weight, for sufficiently compensating the hygroscopy of the active ingredient in the shell and for guaranteeing a good processability of the shell at the same time. Preferably, the shell contains at most 97 % by weight of carrier, further preferably at most 95 % by weight. When the amounts of carrier are too high, then this complicates the processability of the shell.

Preferably, the shell contains a buffer substance. As buffer substances organic acids are particularly suitable, wherein preferably they are low-molecular ones. “Low-molecular” organic acids are organic acids with a molar mass of lower than 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. Particularly preferable are alpha-hydroxyl carboxylic acids which due to the alpha-hydroxyl group show an optimum

buffer effect. Preferably they are selected from lactic acid, tartaric acid, citric acid and mixtures thereof. Citric acid is exceptionally preferable, because it can be processed very easily and it does not significantly modify the release of the active ingredient from the shell. This is a surprising fact, because citric acid in a lot of presentation forms results in an acceleration of the release, which would not be desired 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 further preferably at least 0.9:1. The mass ratio is preferably at most 1.5:1, further preferably at most 1.2:1 and particularly preferably at most 1.1:1. When the amount of the buffer substance is too low, then it is possible that the acidity of the active ingredient in the shell cannot be buffered to a sufficient extent. When the amount of the buffer substance is too high, then in turn the acidity increases in an unfavorable manner. Preferably, the shell contains at least 0.5 % by weight, further preferably at least 1 % by weight and still further preferably at least 2.5 % by weight of buffer substance. Preferably, the shell contains at most 15 % by weight, further preferably at most 10 % by weight and still further preferably at most 8 % by weight of buffer substance.

Surprisingly it has been found that citric acid as a buffer substance is also particularly suitable for the shell. So a sufficient lessening of the acidity could be achieved, without any recognizable acceleration of the release of the proportion of the active ingredient from the shell. Normally it would be expected that the buffer substance accelerates the release of the active ingredient. According to the present invention, the shell preferably contains at least 8 mg of buffer substance, preferably at least 15 mg and exceptionally preferably at least 20 mg. Preferably, in the shell are contained at most 48 mg and exceptionally preferably at most 30 mg of buffer substance.

The shell may contain at least one further pharmaceutically acceptable adjuvant, such as for example fillers and binders. However preferably, no disintegrating agent is contained in the shell, because such an agent may result in a release of the active ingredient from the shell which is too fast.

According to the conditions of the production the shell may comprise at least one granulating agent. Preferably, the amount of the granulating agent in the shell amounts to at least 0.02 % by weight, further preferably at least 0.1 % by weight. Preferably, the shell contains a maximum of 2.5 % by weight of granulating agent. Granulating agents which are preferred in the shell are mentioned below.

According to the conditions of the production the shell preferably contains at least one lubricant, preferably in a mass proportion of at most 5 % by weight, further preferably at most 4.5 % by weight. Preferably, at least 0.25 % by weight, further preferably at least 0.5 % by weight of lubricant are contained in the shell. Lubricants which are preferred in the shell are mentioned below.

The shell preferably covers at least 40 % of the total surface of the intermediate layer on the side which is the opposite side of the intermediate layer from the core. A part of the surface may then completely remain uncovered, for example for reducing the size of the medicament form, or when the surface should be covered by another layer. It is particularly preferable, when at least 95 % of the total surface are covered by the shell, further preferably at least 98 % and particularly preferably at least 99 %. In a preferable embodiment the intermediate layer is completely covered by the shell.

Preferably, the shell itself does not contain a further coating, wherein in particular there is no coating on the shell which retards or prolongs the release of the active ingredient. So preferably no film is applied on the shell. In an alternative embodiment however a quickly disintegrating coating which preferably quickly disintegrates in the aqueous milieu of the stomach may be advantageous on the shell. This preferably contains water-soluble polymers as film-forming components such as cellulose derivatives, polyvinylpyrrolidone, polyvidone acetate. Cellulose derivatives are preferably selected from methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and mixtures thereof. In an alternative the shell may be coated with a sugar-containing sugar-coat syrup.

Thus, in one embodiment the shell contains:

a. an active ingredient; and
b. optionally at least one carrier (preferably with a mass proportion of 70 % by weight to 97 % by weight) which in particular has the purpose “to carry” and to embed the active ingredient, to lessen the hygroscopy and acidity thereof and also to guarantee a certain retardation; and
c. optionally at least one buffer substance (preferably with a mass proportion of 0.5 % by weight to 15 % by weight), in particular for lessening the acidity of the active ingredient; and
d. optionally according to the conditions of the production at least one granulating agent (preferred range of the amount thereof is 0.02 % by weight to 2.5 % by weight); and

e. optionally according to the conditions of the production at least one lubricant (preferred range of the amount thereof is 0.25 % by weight to 5 % by weight); and
f. optionally further adjuvants, such as for example fillers and binders.

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

a) producing the core,
b) producing the intermediate layer,
c) producing the shell.

Often directly compressing of the active ingredient, preferably together with adjuvants, is difficult due to the typically present hygroscopy of the active ingredient. Compression of granulates results in a compressed material with good strength and especially low abrasion. Furthermore, the provision of the mixture to be compressed as granules normally only guarantees a sufficient adhesion and flowability. Thus, the production of the core preferably comprises the production of active ingredient granules from the active ingredient and preferably the adjuvants which are preferred for the core. However, the direct production of the active ingredient granules was considerably complicated by the hygroscopy of the active ingredient. In particular, it was difficult to obtain sufficiently dry and stable active ingredient granules with the common granulation methods. Often the obtained active ingredient granules were too wet, so that this resulted in insufficient strength, fluctuations of the dose and capping of the core, for example during compressing.

Surprisingly it has been found that a combined granulation is advantageous. According to the present invention this granulation at first comprises the production of pre-granules which according to the present invention are free of active ingredient. The pre-granules preferably comprise the carrier of the core and the buffer substance of the core as well as optionally further adjuvants. Subsequently, from the pre-granules the active ingredient granules are prepared.

It has been shown that this preferred combined granulation in total is more gentle for the active ingredient. Surprisingly also hard and stable cores without any appreciable fluctuations of the dose could be produced. Here without any appreciable fluctuations of the dose means that the content of the active ingredient in the core, measured in 5 cores, is preferably at least 93 %, preferably at least 95 % and preferably at most 108 %, further preferably at most 107 % of the theoretical amount of active ingredient per core. This is a surprising fact, since combined

granulation is generally connected with the risk of an unequal distribution of the active ingredient and an increased tendency to demixing and thus normally is avoided.

It has been shown that wet granulation is advantageous for the production of the pre-granules, wherein the production of adhesive granules is particularly preferable. So the production of the pre-granules preferably comprises the step of mixing the carrier and preferably the buffer substance with a granulation solution. Surprisingly, with such a method stable pre-granules with low residual moisture can be obtained. Since typically the carrier is hygroscopic, normally it should be expected that a low residual moisture of the adhesive granules can only be achieved with an enormous effort at high drying temperatures, which again is costly.

Preferably, the granulation solution comprises an aqueous solution of a granulating agent. A granulating agent is a substance with adhesive and gelatinizing properties. Preferably, these agents are synthetic and/or natural polymers. Preferably, the granulating agent is selected from starches, polyvinylpyrrolidone, gelatine, cellulose ethers and mixtures thereof. It is exceptionally preferable to use polyvinylpyrrolidone, because with the use of hygroscopic active ingredients it was possible to achieve an especially good adhesive effect. But preferably, the polyvinylpyrrolidone has to be selected such that the mean molar mass does not become higher than 40.000 g/mol. Molecular weights which are too high are connected with a high viscosity of the granulation solution so that the granulation procedure is considerably complicated. In particular, Povidon K25 is suitable.

The production of the pre-granules preferably comprises a drying step. In this step drying methods such as spray drying, fluidized bed drying, vacuum drying and/or lyophilization can be used. Here it is preferable to use fluidized bed drying, preferably with a temperature of the inlet air of at most 75°C, further preferably at most 65°C. The residual moisture of the pre-granules is preferably adjusted to a value of lower than 8 % by weight, further preferably lower than 5 % by weight. When the residual moisture of the pre-granules is too high, then this results in a core strength which is insufficient. Furthermore, fluctuations of the dose can be observed.

The production of the active ingredient granules preferably comprises the mixing of the pre-granules with an active ingredient solution. So the active ingredient is bonded to the pre-granules. Preferably, the active ingredient solution comprises the active ingredient and a solvent. Preferably, the solvent is an alcohol, particularly preferably an aliphatic alcohol. Preferably, the aliphatic alcohol is selected from methanol, ethanol, n-propanol, *iso*-propanol and mixtures thereof. Here, methanol shows good solubility at a low boiling point and is thus

particularly preferable. But the use of methanol is also connected with the disadvantage that possible residues have to be removed nearly completely due to the toxicity thereof.

The method for the production of the active ingredient granules preferably comprises a drying step. It has been shown that in particular the fluidized bed drying is particularly advantageous, because with fluidized bed drying it was possible to achieve quick drying. So according to the present invention it was possible to completely remove the solvent from the active ingredient granules. According to the present invention, completely removing the solvent means a content of residual solvent of lower than 5,000 ppm (m/m), further preferably of at most 3,000 ppm (m/m), exceptionally preferably the content of residual solvent is lower than 3,000 ppm (m/m), based on the total mass of the dried active ingredient granules.

According to the present invention, preferably the production of the core comprises the compression of the active ingredient granules. The compression may for example be conducted in a rotary pelleting machine, eccentric press or other tableting facility. But here the core may adhere and cap at the punch. Preferably, therefore the active ingredient granules are mixed with at least one lubricant, for obtaining a compressible core mixture. It has been shown that this procedure is advantageous, and hard cores with good disintegration can be obtained. This is a surprising fact, because a tendency to demixing would be expected, when the highly compact active ingredient granules are mixed with the lubricant. The addition of the lubricant already in the step of the preparation of the pre-granules and/or the active ingredient granules may result in granules with lower hardness and worse compressibility. Therefore preferably the addition of the lubricant is conducted only after the production of the active ingredient granules.

It has been shown that in particular fatty acid derivatives are advantageous lubricants. According to the present invention, fatty acid derivatives 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, further preferably at least 12 carbon atoms. On the other hand, the use of talcum as lubricant in the method according to the present invention may often result in a sub-optimal lubrication effect. Particularly advantageous is the use of fats which are liquid at room temperature and thus allow an easy processing. In this case particularly preferable is cottonseed oil. When such fats are used, then cores with optimum breaking strength without any tendency to capping are obtained.

The lubricant is used in such an amount that a mass proportion of at most 10 % by weight, preferably at most 8 % by weight, based on the total mass of the mixture consisting of active

ingredient granules and lubricant, thus the core mixture, is not exceeded. When the amounts of lubricant are too high, then this lowers the wettability of the core, and thus the disintegration of the core may be negatively influenced. For achieving a sufficient lubrication effect, preferably at least 0.5 % by weight, preferably at least 1 % by weight of lubricant, based on the total mass of the core mixture, should be used, which are then also correspondingly contained in the core.

The obtained core preferably has a weight of at most 500 mg, preferably at most 350 mg, further preferably at most 250 mg. The diameter of the core is preferably at most 12 mm, further preferably at most 10 mm and particularly preferably at most 9 mm. When the cores are too large, then the further processing is complicated, and most often medicament forms are obtained which can be swallowed only with difficulties.

The production of the intermediate layer preferably comprises the dissolution of the film-forming component in a solvent. The production of the intermediate layer also preferably comprises the addition of optional further adjuvants, in particular of the plasticizer. The result is an intermediate layer mixture.

The solvent for the dissolution of the film-forming component is preferably an aliphatic alcohol, selected from methanol, ethanol, n-propanol, *iso*-propanol and mixtures thereof. Most preferable is *iso*-propanol. The intermediate layer mixture is applied onto the surface of the core. For that methods such as for example kettle methods in sugar-coating kettles, drum boilers, GS coating machines, as well as dip tube methods or fluidized bed methods can be used. It is particularly preferable to use GC coaters, because with them a faster and more equal coating of the core is possible than in the case of for example a common sugar-coating kettle. Here, the application of the intermediate layer mixture is preferably conducted at a temperature of the inlet air of at most 75°C, further preferably at most 60°C. When the temperatures are too high, then this may result in the decomposition of the active ingredient in the core and optionally in the intermediate layer.

The production of the shell preferably comprises the production of active ingredient granules. Preferably, these granules are prepared in the same manner as the active ingredient granules for the core. Since direct compression of the active ingredient granules is only possible with difficulties and for guaranteeing a suitable volume of the shell, preferably the active ingredient granules are mixed with at least one pharmaceutically acceptable adjuvant so that a shell mixture is obtained. Preferably, the at least one adjuvant is a carrier in the shell.

Here it has been shown that a mass proportion of the active ingredient granules in the shell of preferably at least 10 % by weight, preferably at least 20 % by weight is advantageous. Preferably, the mass proportion of the granules is at most 49 % by weight, preferably at most 42 % by weight.

Normally, with such a procedure actually a strong tendency to demixing would be expected between the relatively high proportion of the adjuvant and the compact active ingredient granules, which results in bad disintegration. Surprisingly it has been found that exactly with this procedure a stable shell with good disintegrating properties can be obtained.

The production of the medicament form according to the present invention preferably comprises the application of the shell mixture onto the intermediate layer. The term "application" according to the present invention comprises different methods, preferably pressing the shell onto the intermediate layer, preferably using common tablet-compressing machines. For avoiding capping, thus the detachment of single pressed layers and so the adhesion at the punches, at least one lubricant is preferably added to the shell mixture.

Preferred lubricants are the same which have already been mentioned for the use in the production of the core. But it has been shown that already very low proportions of lubricants are sufficient for good compressibility of the shell mixture and that surprisingly an increase of the amount quickly has a negative influence onto the wettability and the disintegration of the shell. Therefore the amount of the lubricant in the shell should preferably be restricted to 5 % by weight, preferably 4.5 % by weight. It has been shown that advantageous lubricants are in particular fats which at room temperature and normal pressure are liquid and thus can be processed very easily. It is exceptionally preferable to use cottonseed oil.

The pressing of the shell onto the intermediate layer is preferably conducted such that the shell mixture is placed in the press. When the core with the intermediate layer should be placed at about the center of the medicament form to be produced, then preferably at least 40 % by weight, further preferably at least 45 % by weight of the shell mixture is given into the die. But preferably at most 65 % by weight, further preferably at most 60 % by weight of the shell mixture are given into the die. Subsequently, the core with the intermediate layer is inserted and the form is filled with the remaining proportion of the shell mixture. Subsequently pressing power is applied.

When the shell is pressed onto the intermediate layer, then preferably a force of pressure of at most 35 kN, further preferably at most 30 kN and particularly preferably at most 28 kN is applied. When the used forces of pressure are too high, then often medicament forms which are too hard are obtained, which is connected with a worse release of the active ingredient. Also pressing with pressing powers which are too high, in particular in the case of a concave or biplanar form of the core, may result in deformation of the core. So the intermediate layer may crack and the active principle may be destroyed. Pressing powers which are too high may also result in fragmentation of the compressed material. But preferably the force of pressure should be higher than 7.5 kN, further preferably 8 kN. When the used forces of pressure are too low, then it can be observed that the strength of the medicament form is insufficient.

Preferably, the breaking strength of the medicament form should be at least 60 N, further preferably at least 100 N and exceptionally preferably at least 120 N. But the breaking strength should preferably not exceed 350 N, preferably 300 N. It is exceptionally preferable, when the breaking strength of the medicament form is between 140 N and 280 N, still more preferably between 170 and 270 N. When the breaking strengths are too high, then it can be measured that the disintegration is worse. The breaking strength of a tablet can be determined according to common methods under standard conditions with hardness testers with the application of a diametrically acting force, normally a sharp or conical specimen. According to the present invention the breaking strength was determined with an Erweka TBH-30 hardness tester.

The diameter of the core is preferably at least 3 mm, further preferably at least 4 mm. When the diameter of the core is too low, then the handling and the processability may be complicated. Preferably, the diameter of the core is at most 16 mm, further preferably at most 15 mm and particularly preferably at most 14 mm. When the diameter of the core is too high, then the swallowability of the obtained medicament form may be compromised. The term “diameter” means the diameter of the core at its broadest site each.

The layer thickness of the shell is preferably at least 0.7 mm, further preferably at least 0.8 mm. When the layer thicknesses of the shell are too low, then the handling of the medicament form according to the present invention and its production are complicated. Preferably, the layer thickness of the shell is at most 5 mm, preferably at most 3 mm. When the layer thicknesses of the shell are too high, then the medicament form may become too large and the swallowability may be compromised. Layer thickness in this case is the thickness of the shell at its broadest site each.

The total diameter of the medicament form depends on the ingredients which are used respectively, in particular the active ingredients in the core and the shell. Also the diameter of the core is an important feature which influences the total diameter of the medicament form. Preferably, the total diameter of the medicament form is at most 20 mm, further preferably at most 18 mm, exceptionally preferably at most 16 mm. When the diameters are too high, then the swallowability may be compromised. The term "total diameter" relates to the diameter of the medicament form at its broadest site each. It has been shown that a diameter of the medicament form of between 8 mm and 14 mm, in particular between 11 mm and 13 mm is advantageous.

Preferably, the medicament form has a mass of at most 1100 mg, preferably at most 950 mg and most preferably at most 850 mg, so that it can be taken in very easily. But the medicament form according to the present invention preferably has a minimum weight of 115 mg, further preferably 225 mg, so that the handling of the medicament form also for elder persons is no problem. Particularly preferable was a weight of the medicament form of between 700 mg and 800 mg.

Also in the case of exposure to air the medicament form according to the present invention has preferably a residual moisture, thus an absolute proportion of water of at most 15 % by weight, preferably at most 13 % by weight. It is exceptionally preferable, when the absolute proportion of water is at most 5 % by weight. Preferably, this proportion is determined by drying at 105°C until constant weight is reached, in a drying oven or by means of an infrared dryer, the infrared dryer being preferred.

The medicament forms of the invention have the advantage of particularly good storage stability, which means that the criteria for storage stability of the ICH are at least fulfilled and are preferably exceeded, i.e. the medicament forms according to the present invention show better values than necessary. Storage stability preferably means that during a storage at certain storage conditions and for a certain storage time which can be deduced from the ICH directive Q3B (R2) (Impurities in New Drug Products) a sufficiently high content of drug of preferably more than 90 %, based on the original amount of the active ingredient, is available, and that degradation products which may endanger the patients do not exceed a certain maximum value. These maximum values can be deduced from the ICH directive Q3B (R2).

The medicament forms according to the present invention have shown a very good storage stability in a short-term stress study in common blisters (for example top foil aluminum foil, 20

µm strong and bottom foil PVC/PVDC foil, glassy) at 25°C and 60 % relative air humidity (corresponds to subtropical to Mediterranean climate), 30°C and 65 % relative air humidity (corresponds to hot and wet climate) as well as at 40°C and 75 % relative air humidity (corresponds to very hot and particularly wet climate). The medicament forms according to the present invention also after the storage at 25°C and 60 % relative air humidity, 30°C and 65 % relative air humidity or at 40°C and 75 % relative air humidity after 1 month preferably contain still between 95 % and 105 % of the theoretical amount of the active ingredient in the medicament form, thus fulfil the specification. Preferably, the amount of the active ingredient also after a storage for 1 month under one of the mentioned conditions (25°C and 60 % relative air humidity, 30 °C and 65 % relative air humidity or 40°C and 75 % relative air humidity) is between 96 % and 103 % and still more preferably between 97 % and 102 %, based on the amount of active ingredient in the not stored medicament form. The total mass of the stored medicament form differs from the mass of the not stored medicament form preferably by less than 5 %, still further preferably by less than 4 % and still more preferably by less than 2 %, when the storage of the medicament form is conducted for 1 month at 25°C and 60 % relative air humidity, 30°C and 65 % relative air humidity or 40°C and 75 % relative air humidity. This shows that an up-take of water from the environment can be avoided with the medicament form according to the present invention, normally comprising a hygroscopic active ingredient, also in the case of extreme humidity in the atmosphere of the environment. Also, after a storage time of 1 month in one of the given atmospheres, the diameter of the medicament form according to the present invention differs from the diameter of the not stored medicament form preferably by less than 4 %, further preferably by less than 3 % and still more preferably by less than 2 %. The medicament forms according to the present invention are preferably storage-stable over more than 6 months, preferably at least 12 months of storage time under standard conditions according to the international directives of the ICH.

The medicament forms according to the present invention are characterized by an excellent uniformity of the mass and uniformity of the content, which is guaranteed by the composition of the medicament forms and the production method. The tests are conducted according to the respective methods of the European Pharmacopoeia (Ph. Eur. 7). The medicament form preferably shows a uniformity of the mass in such a manner that the mass of 20 such medicament forms does preferably not differ by more than 5 %, differ further preferably by less than 5 %, still further preferably by less than 4 % from the mean value of the mass of the medicament form which is deduced from the mass of the 20 medicament forms. The

medicament form according to the present invention preferably shows a uniformity of the content in such a manner that the content of the active ingredient in 10 such medicament forms each is between 85 % and 115 %, preferably between 87 % and 113 % and ideally between 95 % and 105 %, based on the mean value of the content of the active ingredient in the 10 medicament forms.

With the medicament form according to the present invention and the production method according to the present invention it is thus possible to provide in particular hygroscopic active ingredients, thus active ingredients which can only be processed with difficulties, in such a manner that an intake several times a day is simulated. Here the first proportion of the active ingredient is immediately released in the first phase. Such a release is in particularly advantageous in the case of a short-term therapy, when the desired plasma level should be reached as quickly as possible and at the same time the effect should be prolonged by subsequent phases of release. Such a release system may also be advantageous in the case of a long-term therapy, in particular when in the case of long dosing intervals at the end of the interval the value falls below the minimum effect concentration. By the fast initial release of the active ingredient from the follow-up medicament form the plasma level is quickly increased and then in the required range again.

Here, the medicament form has a size which is suitable for oral intake. It is characterized by high mechanical stability also in the case of long storage. In particular hygroscopic active ingredients which are acidic and/or highly soluble profit from the design of the medicament form according to the present invention. So the daily dose of such active ingredients can in particular be reduced to a single daily intake which may have a positive influence onto the compliance of the patient and directly on the health expenditures.

The medicament form according to the present invention is in particularly suitable for the administration of the following active ingredients and/or their pharmaceutically acceptable salts: valproic acid, carbamazepine, tetracycline, lincomycin, clindamycin, erythromycin, rifampicin, metformin, atenolol, ranitidine, acetylsalicylic acid, diclofenac, omeprazole, methyldopa, minoxidil, betahistine, dexamethasone, prednisolone, piracetam, pravastatin and gemfibrozil.

Valproic acid and carbamazepine are in particularly used for the treatment of epilepsy. Tetracycline, lincomycin, clindamycin, erythromycin and rifampicin are suitable for the treatment of bacterial infection diseases. Metformin is used in the case of diabetes mellitus. The

active ingredient atenolol is used in the case of functional cardiovascular problems, arrhythmias, arterial hypertension and angina pectoris. Also methyldopa and minoxidil are suitable for the treatment of hypertension. The active ingredients ranitidine and omeprazole are in particularly used for the treatment of gastrointestinal ulcers, reflux esophagitis and Zollinger-Ellison syndrome. Acetylsalicylic acid and diclofenac are used against pain. Acetylsalicylic acid in low doses is also suitable for inhibiting the aggregation of thrombocytes in the case of angina pectoris or after acute cardiac infarction.

The active ingredient betahistine is used for the treatment of the Meniere symptom complex, the symptoms of which are dizziness, often in combination with nausea and/or vomiting, tinnitus and hearing loss. Dexamethasone as a corticosteroid is used in the case of autoimmune diseases, cerebral edema and asthma. Prednisolone as a corticosteroid is in particularly used in the case of adrenal cortex insufficiency. The active ingredient piracetam is in particularly suitable in the case of brain-related performance disorders. Gemfibrozil and pravastatin are normally used for the treatment of hypertriglyceridemia and hypercholesterolemia.

Therefore according to the present invention is also the use of the medicament form according to the present invention for the treatment of a patient suffering from a disease, selected from epilepsy, bacterial infection disease, diabetes mellitus, functional cardiovascular problems, arrhythmias, hypertension, angina pectoris, cardiac insufficiency, gastrointestinal ulcer, reflux esophagitis, Zollinger-Ellison syndrome, pains, dizziness, in particular in connection with the Meniere symptom complex, autoimmune disease, cerebral edema, asthma, adrenal cortex insufficiency, brain-related performance disorders, hypertriglyceridemia and hypercholesterolemia. Preferably here the medicament form is taken one time a day. According to the present invention the use of the medicament form for the treatment of dizziness in connection with the Meniere symptom complex is particularly preferable.

Also according to the present invention is a method for the treatment of a disease, selected from epilepsy, bacterial infection disease, diabetes mellitus, functional cardiovascular problems, arrhythmias, hypertension, angina pectoris, cardiac insufficiency, gastrointestinal ulcer, reflux esophagitis, Zollinger-Ellison syndrome, pains, dizziness in connection with the Meniere symptom complex, autoimmune disease, cerebral edema, asthma, brain-related performance disorders, hypertriglyceridemia and hypercholesterolemia, wherein the method comprises the administration of a medicament form according to the present invention. Preferably, this administration takes place one single time a day.

Examples

Example 1: Production of a medicament form according to the present invention

Element	Ingredient	Amount per medicament form (mg)	Function
Core	betahistine dihydrochloride	24	active ingredient
	lactose monohydrate (Granulac® 230)	53	carrier
	microcrystalline cellulose (Vivapur® 102)	30	carrier
	corn starch	53	carrier
	citric acid, anhydrous	24	buffer substance
	Povidon K25 (Plasdone® K25)	2	granulating agent
	hardened cottonseed oil (Lubritab®)	5	lubricant
	total mass	191	
Intermediate layer	Eudragit® S 100	6.67	film-forming component
	Eudragit® L 100	1.67	film-forming component
	triacetin	2.50	plasticizer
	talcum	4.17	filler
	total mass	15.01	
Shell	betahistine dihydrochloride	24	active ingredient
	lactose monohydrate (Granulac® 230)	53	carrier
	lactose monohydrate (Tablettose® 80)	128.5	carrier
	microcrystalline cellulose (Vivapur® 102)	230	carrier
	corn starch	53	carrier
	citric acid, anhydrous	24	buffer substance
	Povidon K25 (Plasdone® K25)	2	granulating agent
	pre-gelatinized corn starch (Starch 1500®)	30	carrier
	hardened cottonseed oil (Lubritab®)	5.5	lubricant
	total mass	550	
Medicament form	**mass**	**756.01**	

A medicament form according to the present invention in the form of a shell-core tablet was prepared. At first the core was prepared. For the production of the core pre-granules were prepared. For that the carriers lactose monohydrate, microcrystalline cellulose and corn starch and the buffer substance citric acid were intensively mixed in a mixing/granulating machine (Diosna P10). Subsequently, the mixture was granulated in the mixing machine Diosna P10 with a granulation solution. The granulation solution was prepared by dissolving the Povidon K25 in purified water so that the solution contained 16 % by weight of Povidon K25. Subsequently, the pre-granules were dried in a fluidized bed facility (GPCG-3) at 60°C to a residual moisture of < 5 %. Subsequently, the dried pre-granules were sieved (mesh size 1 mm).

From the pre-granules the active ingredient granules were prepared by the addition of a solution of betahistine dihydrochloride in methanol. Here the clear solution contained 28.5 % by weight of betahistine dihydrochloride. For that the pre-granules were placed in the mixing/granulating machine Diosna 10 and granulated with the active ingredient solution. The obtained active ingredient granules were dried in a fluidized bed facility (GPCG-3) to a content of residual methanol of < 3000 ppm. Subsequently, the dried active ingredient granules were sieved (mesh size 1 mm).

To the active ingredient granules subsequently hardened cottonseed oil was added and mixed in a mixing machine. The obtained core mixture was compressed with a rotary pelleting machine. Biconvex cores having a diameter of 8 mm were obtained. The obtained cores had a weight of 191 mg and a height of 3.85 mm.

Subsequently, the intermediate layer was prepared. For that the film-forming components Eudragit® S 100 and Eudragit® L 100 were dissolved in *iso*-propanol, wherein the content of the film-forming components in the solution was 5.9 % by weight. Into the solution the plasticizer triacetin as well as the adjuvant talcum were stirred in. Also water was added (6.67 ml). Subsequently, the intermediate layer mixture was applied onto the core so that it completely covered the core. The application of the intermediate layer mixture was conducted in a GS coating machine (GS-10) at a temperature of the inlet air of 50°C.

For the production of the shell the active ingredient granules were prepared analogously to the core so that 186 mg of active ingredient granules were available. These active ingredient granules were mixed with the carriers lactose monohydrate, microcrystalline cellulose and pre-gelatinized corn starch as well as the lubricant hardened cottonseed oil. This resulted in the

shell mixture. Thus the proportion of the active ingredient granules in the shell mixture was 33.8 % by weight.

In the last step the shell mixture was pressed onto the intermediate layer in a Syl-one press with tablet feeding system. For that 300 mg of the shell mixture were filled into a die (round, biconvex, diameter 12 mm, curvature radius 9.5 mm). Thereafter the core with the intermediate layer was centrically positioned. In a second filling step the residual proportion of the shell mixture was filled into the die. Subsequently, it was pressed with a force of pressure of 10 kN. The shell/core tablet showed a breaking strength of 140 N, measured with an Erweka TBH-30 hardness tester. In a further embodiment the same starting materials, amount ratios and production methods were used, wherein in the step of pressing the shell a force of pressure of 25 kN was applied, so that a shell/core tablet with a breaking strength of 280 N was obtained.

Example 2: Production of a medicament form according to the present invention

Element	**Ingredient**	**Amount per medicament form (mg)**	**Function**
Intermediate layer	Eudragit® S 100	8.874	film-forming component
	Eudragit® L 100	2.225	film-forming component
	triacetin	3.331	plasticizer
	talcum	5.556	filler
	total mass	**19.986**	

A shell-core tablet with a composition of the core and the shell like in example 1 was prepared.

However the composition of the intermediate layer was altered, wherein a higher weight of the intermediate layer was chosen. The chosen higher weight of the intermediate layer further contributed to an increase of the mechanical strength of the core. The chosen intermediate layer is dissolved at a pH value of 7.0 to 7.2. So the intermediate layer enables the release of the active ingredient proportion from the core into the middle section of the intestine.

The production of the core and the shell was conducted as described in example 1. The production of the intermediate layer comprised the dissolution of the film-forming components Eudragit® S 100 and Eudragit® L 100 in *iso*-propanol, wherein the content of the film-forming components in the solution was 5.9 % by weight. Into the solution the plasticizer triacetin as well as the adjuvant talcum were stirred in. Also water was added (8.86 ml). Subsequently, the intermediate layer mixture was applied onto the core so that it completely covered the core. The

application of the intermediate layer mixture was conducted in a GS coating machine (GS-10) at a temperature of the inlet air of 50°C.

Example 3: production of a medicament form according to the present invention

Element	Ingredient	Amount per medicament form (mg)	Function
Intermediate layer	Eudragit® S 100	11.099	film-forming component
	triacetin	3.331	plasticizer
	talcum	5.556	filler
	total mass	**19.986**	

A shell-core tablet with a composition of the core and the shell like in example 1 was prepared. However the composition of the intermediate layer was altered, wherein a higher weight of the intermediate layer was chosen, analogously to example 2. The chosen higher weight of the intermediate layer further contributed to an increase of the mechanical strength of the core. The chosen intermediate layer is dissolved at a pH value of 7.2 to 7.5. So the intermediate layer enables the release of the active ingredient proportion from the core into the lower section of the intestine.

The production of the core and the shell was conducted as described in example 1. The production of the intermediate layer comprised the dissolution of the film-forming component Eudragit® S 100 in *iso*-propanol, wherein the content of the film-forming component in the solution was 5.9 % by weight. Into the solution the plasticizer triacetin as well as the adjuvant talcum were stirred in. Also water was added (8.86 ml). Subsequently, the intermediate layer mixture was applied onto the core so that it completely covered the core. The application of the intermediate layer mixture was conducted in a GS coating machine (GS-10) at a temperature of the inlet air of 50°C.

Example 4:

In example 4 a test was made for the release of the active ingredient betahistine dihydrochloride from a core with intermediate layer having the composition according to example 1, however without shell. Thus the core with intermediate layer comprised 24 mg of betahistine dihydrochloride. The release was determined with a paddle apparatus. Figure 2 shows the respective results.

Example 5: Stability of the medicament form according to the present invention

A medicament form according to the present invention in the form of a shell-core tablet with a composition of the core and the shell as in example 1 was prepared. Blisters (top foil aluminum foil, 20 µm strong, bottom foil PVC/PVDC foil, glassy) comprising the medicament form were subjected to a stress test for 1 month, thus stored at 25°C/60 % relative air humidity, 30°C/65 % relative air humidity and 40°C/75 % relative air humidity. The medicament form after the storage showed the below listed parameters. It can be seen that the medicament form according to the present invention is also stable under extreme storage conditions and does not cap and/or swell despite the hygroscopic active ingredient. Also after a storage for 1 month at the extreme conditions the impurities according to the specification and/or the monograph pursuant to Ph. Eur. 7 were below the respectively defined limiting values and/or were not present in measurable amount.

Parameter	**Not stored medicament form**	**Storage for 1 month at 25°C/60 % relative air humidity**	**Storage for 1 month at 30°C/65 % relative air humidity**	**Storage for 1 month at 40°C/75 % relative air 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 theoretical amount of the active ingredient)	100.6	101.1	101.5	100.8

Description of the figures:

Figure 1 shows the course of the release of two medicament forms according to the present invention, prepared according to embodiment example 1, comprising 24 mg of betahistine dihydrochloride in the shell and 24 mg of betahistine dihydrochloride in the core. The shell was pressed onto the core with the intermediate layer with a force of pressure of 10 kN or 25 kN. Here a pH course which corresponds to the physiological conditions is mimicked. A release of 100 % means a release of 48 mg of betahistine dihydrochloride from the medicament form, thus 24 mg from the shell and 24 mg from the core. The medicament form according to the present

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invention releases betahistine dihydrochloride in a biphasic form, thus pulsed at first from the shell and starting at a pH value of 7.0 (after about 8.5 hours) after the dissolution of the gastric juice-resistant intermediate layer from the core. So an intake two times a day is simulated, thus the intake of two commercially available medicament forms without any particular release modification in an interval of 8 to 12 hours. With the special design of the medicament form an optimum release profile is achieved. It can be expected that this will also be confirmed in vivo.

Figure 2 shows the course of the release from the core with intermediate layer according to example 4. A release of 50 % means the release of 24 mg of betahistine dihydrochloride. It can be seen that only starting at a pH value of 7.0 the dissolution of the intermediate layer takes place and the proportion of the active ingredient is released from the core. Thus, the core with the intermediate layer is stable in the upper sections of the intestine, wherein the disintegration only starts at a pH value of 7.0, which corresponds to the intestine section ileum to colon and a residence time in the gastrointestinal tract without release of 7 to 12 hours.

The term “comprise” and variants of the term such as “comprises” or “comprising” are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

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Claims

1. A medicament form, comprising
   a. a core,
   b. a gastric juice-resistant intermediate layer being disposed on the surface of the core, and
   c. a shell being disposed on the opposite side of the intermediate layer from the core,
   wherein both the core and the shell contain a proportion of an active ingredient each, and wherein the medicament form releases the active ingredient in an at least biphasic form, wherein the first phase relates to the immediate release of the active ingredient after ingestion into the gastric juice, wherein the mass ratio of shell to core has a value of at least 0.5:1.

2. The medicament form according to claim 1, wherein the intermediate layer comprises a film-forming component.

3. The medicament form according to claim 1 or claim 2, wherein in total between 1 mg and 200 mg of the active ingredient are contained in the medicament form.

4. The medicament form according to any one of claims 1 to 3, wherein the core comprises at least one carrier.

5. The medicament form according to any one of claims 1 to 4, wherein the core comprises at least one buffer substance.

6. The medicament form according to any one of claims 1 to 5, wherein the proportion of the active ingredient in the core and in the shell each amounts to 40 % to 60 % of the total amount of the active ingredient in the medicament form.

7. The medicament form according to any one of claims 1 to 6, wherein the mass ratio of shell to core has a value of at least 1.8:1.

8. The medicament form according to any one of claims 1 to 7, wherein the mass ratio of core to intermediate layer has a value of at least 3:1.

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9. The medicament form according to any one of claims 1 to 8, wherein the mass ratio of core to intermediate layer has a value of at most 40:1.

10. The medicament form according to any one of claims 1 to 9, wherein the active ingredient is betahistine or a pharmaceutically acceptable salt of betahistine.

11. The medicament form according to any one of claims 1 to 10, wherein the active ingredient is selected from betahistine dihydrochloride and betahistine dimesylate, and wherein between 2 mg and 55 mg, based on the base of the active ingredient, are contained in the medicament form.

12. The medicament form according to any one of claims 1 to 11, wherein the medicament form consists of the core, the intermediate layer and the shell.

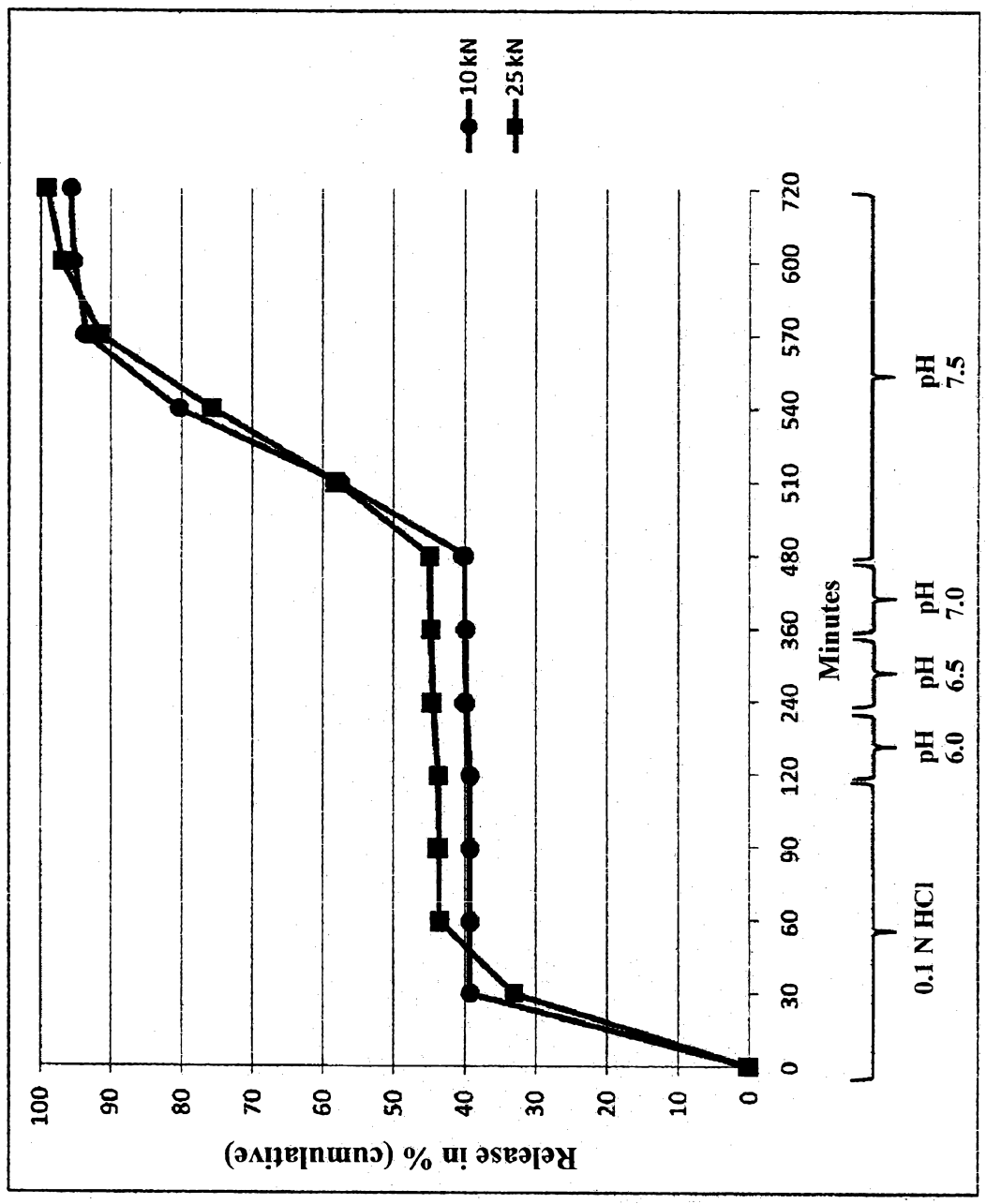
13. The medicament form according to any one of claims 1 to 12, wherein the medicament form is a shell-core tablet.

14. A method for the production of a medicament form according to any one of claims 1 to 13 with the steps
    a. preparing the core,
    b. preparing the intermediate layer,
    c. preparing the shell.

15. Use of the medicament form according to any one of claims 1 to 13 in a therapy method.

16. A method of treating a disease comprising administration of a medicament form according to any one of claims 1 to 13.

Dated: 23 December 2014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10
0
10 kN
25 kN
0
30
60
90
120
240
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570
600
720
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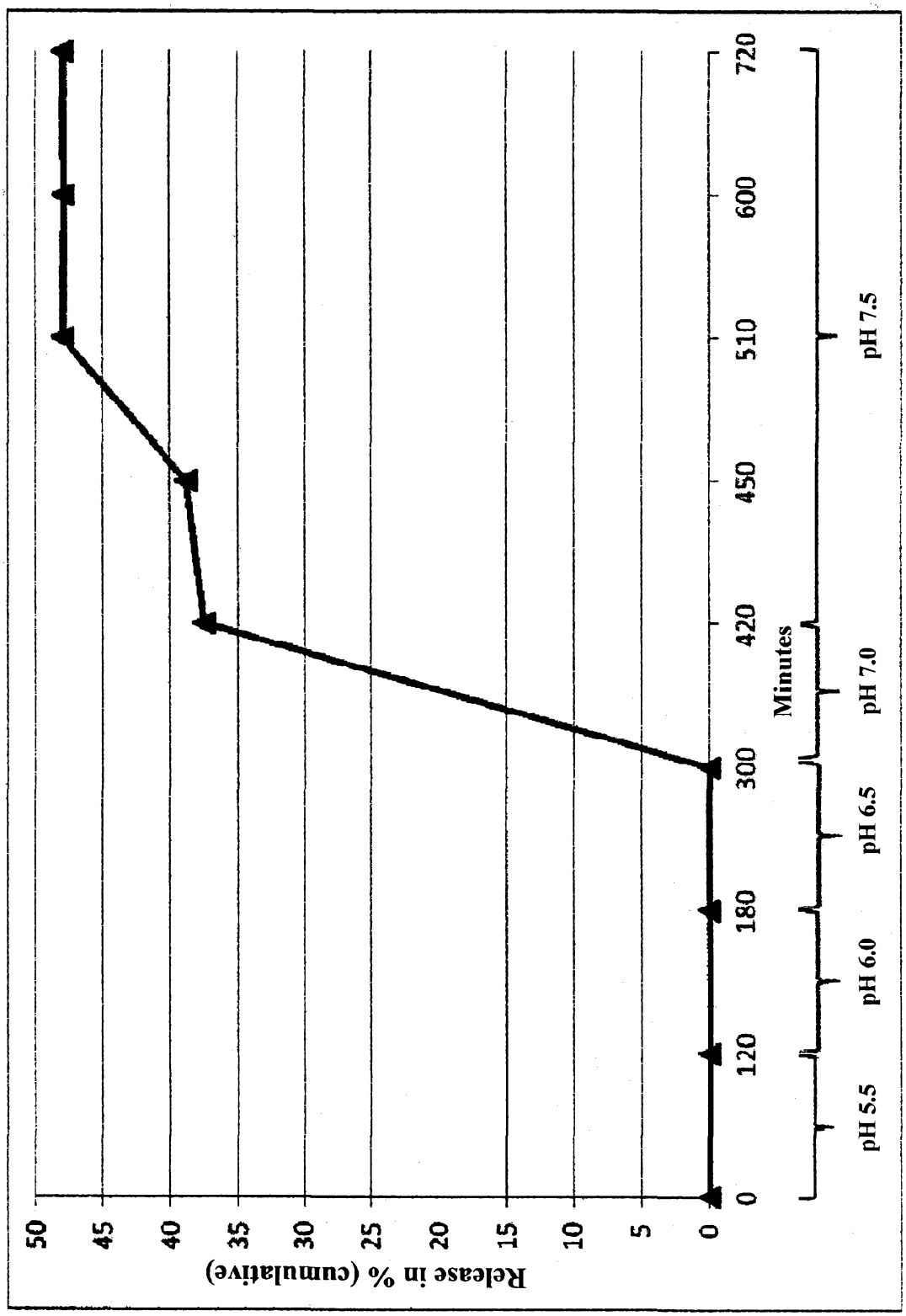
pH 6.5
pH 7.0
pH 7.5

Figure 1


Release in % (cumulative)
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120
180
300
420
450
510
600
720
Minutes
pH 5.5
pH 6.0
pH 6.5
pH 7.0
pH 7.5

Figure 2