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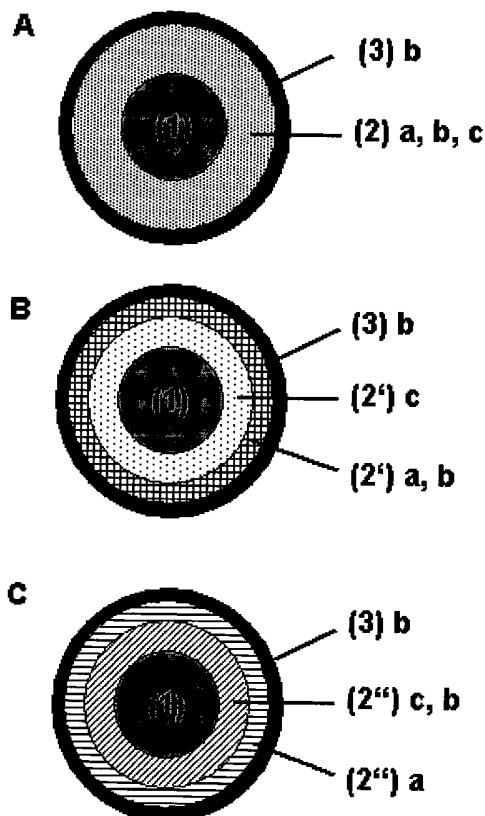
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(54) Title: PHARMACEUTICAL PREPARATION FOR SUSTAINED RELEASE OF A PHARMACEUTICALLY ACTIVE INGREDIENT



(57) Abstract: Pharmaceutical preparation for sustained release of a pharmaceutically active ingredient A pharmaceutical preparation for sustained release of a pharmaceutically active ingredient(s), which preparation comprises particles having an inner core (1) and a first coating (2) provided thereon, wherein said coating (2) contains a mixture of: (a) between 50% and 95% by weight of a copolymer of ethyl acrylate, methylmethacrylate and trimethylamminoethyl methacrylate chloride in a molar ratio of the three acrylates of 1 : 1.8-2.2 : 0.08-0.12, preferably of 1:2:0.1, (b) between 2% and 30% by weight of a copolymer of ethylacrylate and methacrylic acid in a molar ratio of 1: 0.8-1.2, preferably of 1:1, and (c) between 1 % and 40% by weight of the pharmaceutically active ingredient.



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PHARMACEUTICAL PREPARATION FOR SUSTAINED RELEASE OF A PHARMACEUTICALLY ACTIVE INGREDIENT

5 **Field of the invention**

The present invention relates to a pharmaceutical preparation for sustained release of a pharmaceutically active ingredient.

10 **Technical background**

For many applications it is desirable to use an oral preparation with modified release characteristics, to control the timing of release, the location of drug release in the gastro-intestinal tract or the temporal
15 release profile of a drug.

One of the most common modified release preparations is such wherein the active ingredient or the pharmaceutical product is provided with a coating of enteric, i.e. gastric juice-resistant material, which is insoluble
20 in the acid environment of the stomach (ca. pH 1 to 3), but dissolves in the weakly acidic to weakly alkaline region of the duodenum (pH > 5.5). This type of preparation allows to control the location of release dependent on pH of the gastro-intestinal tract, and also results in a delayed release (i.e. delayed by the time spent in an acid environment).
25 Such particles are e.g. used to protect the gastric lining from certain compounds, or to protect acid-instable active ingredients from the harsh gastric environment, that would result in their immediate inactivation.

This type of modified release preparation can further be developed to exhibit an equivalent pH-optimum for release that corresponds to the pH
30 normally encountered in particular sections of the intestinal tract. Thus, a more differentiated control of the location of release of the pharmaceutically active ingredient can be achieved.

35 Many such modified release preparations comprise multi-layered particles, wherein the active ingredient is usually located close to the centre, optionally on or in a neutral particle, which then is coated with a

- 2 -

material of desired solubility in a defined portion of the intestine. A further layer may consist of an enteric coating, i.e. gastric juice-resistant material. This type of preparation is exemplified in EP 0 720 473 that describes budesonide particles with a controlled release profile, which
5 comprise from the inside to the outside: (a) a neutral particle, (b) an active substance layer comprising micronized budesonide and one or more water-soluble auxiliary agents, (c) a first lacquer layer comprising lacquers which are insoluble in gastric juice and soluble or insoluble in intestinal juice, and (d) a second lacquer layer consisting of lacquers
10 insoluble in gastric and intestinal juices.

Other preparations primarily result in a temporally protracted liberation of the active ingredient from the galenic preparation, so-called sustained release preparations. This can be a necessity, for example, for active
15 ingredients that exhibit a short plasma half-life, but need to act over a prolonged time to achieve the pharmaceutical effect. Sustained release preparations can help to avoid repetitive dosing, which is prone to human error and uncomfortable for the patient.

20 Such sustained release preparations can comprise, for example, a sponge-like polymeric matrix in which the active compound is incorporated. Diffusion, mechanical and chemical erosion of the matrix in the course of gastro-intestinal passage results in the liberation of the active ingredient from the matrix over a prolonged period.

25 Alternatively, sustained release can be achieved by composite preparations that comprise particles (also called pellets, particles, grains, microtablets or granules) with different polymer coatings. The coatings on the different particles differ in their solubility. The solubility of the
30 coating layers can be adjusted to the local pH value of the digestive tract, as outlined above. Thus, in the finished medicament (for example, hard gelatine capsules) a mixture of laminated particle is present which releases the active ingredient in different portions of the digestive tract. Such a preparation results in the control of both the location and timing
35 of release of the active ingredient.

- 3 -

- Also, release characteristics can be modified by protecting the active ingredient by a coating layer of a certain thickness and a defined pH-dependent solubility. When the thick layer is slowly degraded in the intestinal environment, degradation is not even at the entire surface of the particle. Thus, at some places clefts or pores may form that allow initial liberation of active ingredient. As the coating layer is further degraded, an increasing amount of the active ingredient layer is exposed and can dissolve.
- 10 In particular for highly active drugs, a slow and tightly controlled release must be achieved, to prevent temporal "spikes" of plasma levels to occur. The sustained release preparations wherein the active ingredient layer is covered by a layer of a polymer of a certain solubility may not achieve the desired level of reproducibility and control of release.
- 15 Obviously, for many active ingredients the control of both the location within the gastrointestinal tract and the timing of release is beneficial. Preparations exist that combine layers with delayed-release characteristics, e.g. by employing polymers with a pH-dependent solubility with layers that provide sustained-release characteristics e.g. by using water insoluble polymer matrixes with a defined permeability for the active ingredient.
- 20 Frequently, different Eudragit[®] polymers are used for the different coating layers outlined above. Eudragit[®] L100 is a copolymer of methacrylic acid and methylmethacrylate combined in a certain ratio and is insoluble in an acidic environment, for example in the stomach, and therewith forms a largely impermeable protective layer well-know like the enteric coating. Eudragit[®] L100-55 is a copolymer of methacrylic acid and ethylacrylate, whereby the ratio of the monomers is chosen in such a manner that it is insoluble at a pH inferior to 5.5, but is soluble at a pH above this.
- 25 30 35 Another type of polymers widely used are exemplified by Eudragit[®]RS (low permeability) or Eudragit[®]RL (high permeability). These polymers are water-insoluble, and independently of pH form membranes of

- 4 -

differing permeability. The mixing ratio of RS/RL and the layer thickness defines the permeability characteristics of the resulting preparation.

5 Furthermore, mixtures of polymers with pH dependent solubility, such as Eudragit®L and polymers that form water-insoluble diffusion barriers, such as Eudragit®RL or RS are known in the art.

10 Preparations with coating layers comprising mixtures of insoluble polymers and such with pH dependent solubility are exemplified by EP 0 377 517. It describes a sustained release pharmaceutical preparation which comprises a core particle with a theophylline compound embedded therein and a coating thereon including (i) a polymeric matrix, which is substantially insoluble independent of pH, (ii) an enteric polymer whose solubility is pH dependent, and (iii) an at least partially water
15 soluble component.

A different kind of mixed layer is disclosed in US 5,175,003. It describes a galenic preparation comprising particles with a mixed layer of a polymer with pH dependent solubility, an active pharmaceutical
20 ingredient and hydroxyethyl cellulose, or hydroxypropyl cellulose, or shellac, or mixtures thereof.

A mixture of the active ingredient with a certain kind of polymer is also known in the art. EP 1 060 743 discloses a dosage form of cisapride for
25 sustained release. This dosage form comprises a layer wherein a single type of an enteric polymer with pH dependent solubility, such as e.g. Eudragit®L and cisapride are mixed.

30 The insoluble or partially soluble polymers used in the prior art are rather expensive and their thickness cannot be reduced beyond a certain limit to ensure a sustained release after passing the stomach. Furthermore, the degree of sustained release achievable by coating layers of a certain thickness is inadequate for some applications. Furthermore, the degree of pH-dependent solubility is inadequate for some applications.

35 Thus, it is desirable to provide a galenic preparation that has well defined delayed- and sustained-release characteristics, an improved sustained-

- 5 -

release profile (i.e. slower liberation of active ingredients), an improved pH-dependent solubility and at the same time a minimized use of expensive excipients such as the Eudragit® polymers.

5 Summary of the invention

The present invention provides a solution to these problems, by providing a pharmaceutical preparation for sustained release of a pharmaceutically active ingredient, which preparation comprises particles
10 having an inner core (1) and a first coating (2) provided thereon, wherein said coating (2) contains a mixture of:

(a) between 50% and 95% by weight of a copolymer, preferably 60 to 80 percent by weight of ethyl acrylate, methylmethacrylate and
15 trimethylammonioethyl methacrylate chloride in a molar ratio of the three acrylates of 1 : 1.8–2.2 : 0.08–0.12, preferably 1:2:0.1, (Eudragit ® RS) and

(b) between 2% and 30% by weight, preferably 5 to 20 percent by
20 weight of a copolymer of ethyl acrylate and methacrylic acid in a molar ratio of 1: 0.8–1.2, preferably of 1:1, (Eudragit ® L 100-55) and

(c) between 1% and 40% by weight, preferably 5 to 15 percent by
25 weight of the pharmaceutically active ingredient; wherein the percent values of components (a), (b) and (c) relate to coating (2) only;

and optionally, a second coating (3) thereon, which comprises an enteric coating. Said second coating (3) is particularly preferable in cases where
30 acid-sensitive active ingredients are used, or such that have the potential to irritate the gastric mucosa. Furthermore, said second coating (3) is preferably employed to minimize in-vivo variability of drug delivery, as gastric delivery of the drug is avoided.

Surprisingly, when using a pharmaceutical preparation according to the
35 invention, comprising a mixed layer of components (a), (b) and (c) on an inner core, a more prolonged release profile can be obtained as compared to prior art preparations.

- 6 -

Moreover, the present preparation shows a surprisingly high and reliable sensitivity to varying pH conditions. This means that the sustained release can be adjusted very accurately to broader pH ranges than it was possible for prior art preparations. Thus it is possible to precisely modify the delivery of the drug in accordance with pH conditions encountered in the gastrointestinal tract having a physiological pH-range of approximately 1.5 to 8.

10 A particular advantage of the present invention resides in the surprising finding that a lower amount of insoluble or partially soluble polymers can be used compared to the sustained release preparations of the prior art which however still has a comparable sustained release profile as prior art preparations.

15 An additional advantage of the present invention is the fact that the production process of the pharmaceutical preparation contains fewer steps, and thus is shorter, easier to perform, and therefore economically preferable. This advantage is due to the use of only one mixed active ingredient / polymer layer where prior art uses two separate layers of active ingredient and polymer (irrespective of further layers that may be present).

Brief description of the drawings

25 Figure 1: a schematic cross section of particles according to the invention (A) and different prior art particles (B) and (C). The prior art particles are made of the same basic components in the same amounts as (A), namely insoluble copolymer (a) and copolymer (b) with pH dependent solubility (e.g. Eudragit ® RS and Eudragit ® L 100-55, respectively) and a pharmaceutically active ingredient (c), but comprising layers with different compositions of said components.

35 Figure 2: Release profiles (% dissolution over time) of particles and reference particles at pH=6. a) 0.4 mg Tamsulosin particles according to Example 1 and Reference Example 1, b) 0.4 mg Diltiazem particles according to Example 2 and Reference Example 2, c) 1 mg Diltiazem

- 7 -

particles of Example 3 and Reference Example 3, d) 0.6 mg Tamsulosin particles of Example 4 and Reference Example 4, and e) 0.6 mg Tamsulosin particles according to Example 5 and Reference Example 5.

5 Figure 3: Release profiles (% dissolution over time) of 0.4 mg Tamsulosin particles according to Example 1 and Reference Example 1 at two different ambient pH values (pH=6.0 and 6.8).

10 Figure 4: Release profiles (% dissolution over time) of 0.4 mg Diltiazem particles according to (a) Example 2 and (b) Reference Example 6 at three different ambient pH values.

15 Figure 5: Release profiles (% dissolution over time) of Tamsulosin particles according to Example 6 at four different ambient pH values (pH=5.5, 6.0, 6.8, and 7.2).

20 Figure 6: Release profiles (% dissolution over time) of three different batches A, B and C of particles according to Example 9 containing 0.4 mg Tamsulosin and different amounts of copolymers (a) and (b) in layer (2) at ambient pH=6.8.

25 Figure 7: Release profiles (% dissolution over time) of two different batches of Tamsulosin particles according to Example 6 and Example 10 at two different ambient pH values ((a) pH= 6.0 and (b) pH =6.8).

Figure 8: Release profiles (% dissolution over time) of Tamsulosin particles according to Example 6 at two different paddle stirring speeds.

Detailed description of the invention

30

“Sustained release” as used in the invention refers to any temporally protracted release of an active ingredient from a galenic preparation. This means that by physical or chemical measures related to the active ingredient and / or further excipients, fillers, coatings or other elements of the galenic preparation, a more protracted release is achieved than in
35 the absence of said physical or chemical measures.

- 8 -

- A "particle" as used in the invention refers to any kind of particles that can form part of or constitute a galenic preparation. Such particles comprise, but are not limited to pellets, granules, powder, grains, seed elements, tablets, capsules. They can consist of a homogenous material, or comprise distinguishable layers or components. Particles may also be composite particles comprising smaller particles. Such composite particles may be tablets or capsules, but are not limited to such. Composite particles may comprise one or several types of smaller particles, wherein each type may consist of different layers and substances. Composite particles may comprise smaller particles that comprise an enteric coating. Alternatively, an enteric coating may be applied to the whole composite particle, rather than to the smaller particles comprised therein.
- A "physiologically acceptable excipient" as used in the invention refers to any excipient used in pharmaceutical preparations for oral application generally known in the art. Such excipients are exemplified, but not limited to talcum, sucrose, corn starch, starch hydrolysates, sugar, lactose, micro crystalline cellulose, manitol, dextrose, triethyl citrate, methacrylic acid polymers, cellulose derivatives, plasticizers, lubricants and/or release agents, and optionally coloured pigments and/or a silicone antifoam agents.
- A "Pharmaceutically active ingredient" as used in the invention relates to any active ingredient that is suitable for oral administration, or can be made suitable for oral administration by providing a suitable galenic preparation. Such active ingredients comprise, but are not limited to Amlodipine, Budesonide, Candesartan, Cisapride, Diclofenac, Diltiazem, Donepezil, Fentanyl, Glimepiride, Mebeverine, Memantine, Nicardipine, Olanzapine, Omeprazole, Ondansetron, Oxybitinin, Pramipexol, Ramipril, Risperidone, Rivastigmin, Tamsulosin, Theophylline, Tibolone, Tolterodine, Topiramate, or Trandolapril.
- Other active ingredients that can be administered orally include for example, acidic compounds such as acetylsalicylic acid and Diclofenac (o-(2,6-dichloroanilino) phenyl) acetic acid). As these substances exhibit

- 9 -

side-effects which irritate or damage the mucosa of the stomach with longer use, they are often incorporated in modified-release preparations.

Also, modified-release preparations are used to protect acid-unstable
5 active ingredients from the harsh gastric environment, that would result in their immediate inactivation. Among such acid-sensitive compounds are e.g. the benzimidazole derivatives employed as a H⁺/K⁺-ATPase inhibitor for ulcer treatment, Omeprazole (5-methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridyl)methyl)-sulfinyl)-1H-benzimidazole), Lansoprazole (2-
10 (((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl)-sulfinyl)-1H-benzimidazole) and Pantoprazole (5-difluoromethoxy-2-((3,4-dimethoxy-2-pyridyl)methyl)-sulfinyl)-1H-benzimidazole) which function as potent inhibitors in the secretion of gastric acid. Omeprazole has proven itself in the therapy of duodenal ulcer, gastric ulcer, reflux esophagitis and
15 Zollinger-Ellison syndrome. Parenteral and solid peroral medicaments are employed in this connection. Omeprazole, for example, has a half-life of less than ten minutes in aqueous solution at pH values under 4. Therefore, solid peroral medicines (tablets, pellets, granulates) of Omeprazole and derivatives must be completely protected against
20 gastric juice during passage through the stomach.

Further typical active ingredients for modified release preparations, and in particular sustained release preparations, are such that have a short plasma half life. Then, sustained release preparations may reduce
25 dosing frequency.

Particles according to the invention may comprise one or more active ingredient(s), wherein said active ingredients may be comprised in one or more of the particle layers.

30 The present invention provides a pharmaceutical preparation for sustained release of a pharmaceutically active ingredient, which comprises particles with layers made of different components. Such particles may contain an inner core, made of physiologically acceptable excipients, preferred examples include, but are not limited to, sucrose,
35 corn starch, hydrolysates of starch, sugar, lactose, micro crystalline cellulose, mannitol, or dextrose. Such an inner core is also called inert

- 10 -

core. Alternatively, the particles may contain an inner core comprising a pharmaceutically active ingredient. Such a core is also called active core.

5 The size of the inner core is not limiting for the invention, as long as it is suitable for the desired pharmaceutical preparation. A person skilled in the art is familiar with the size and type of inner cores used for composite particles in pharmaceutical preparations. The diameter of the inert core may vary from approximately 0.1 to 2 mm. In a preferred embodiment, the inner core has a diameter in the range of 0.4 to 0.8 mm, most
10 preferably of 0.5 mm. This core seed may be of such a diameter to provide a final particle having a diameter of approximately 0.3 to 2.5 mm. The core seeds may vary from approximately 5 to 95% by weight, preferably 50 to 90% by weight based on the total weight of the finished particles. For the purpose of reference, said core element in the following
15 is also referred to by the numerical (1).

On the inner core (1) is applied a mixed layer formed by at least one active ingredient mixed with copolymers, and / or excipients and / or fillers (2) that according to the invention comprises:

20 - 50% and 95% by weight of a copolymer of ethyl acrylate, methylmethacrylate and trimethylamminoethyl methacrylate chloride in a molar ratio of the three acrylates of 1 : 1.8–2.2 : 0.08–0.12, preferably of 1:2:0.1, also referred to as component (a) in the following,

25 - between 2% and 30% by weight of a copolymer of ethylacrylate and methacrylic acid in a molar ratio of 1: 0.8–1.2, preferably of 1:1, also referred to as component(b) in the following, and

30 - between 1% and 40% by weight of the pharmaceutically active ingredient, also referred to as pharmaceutical ingredient(s) (c) in the following, and

35 - plastifiers / lubricants / excipients, also referred to as component (d) in the following.

In a preferred embodiment, layer (2) comprises:

- 11 -

5 - component (a) with 60 - 90% by weight of a copolymer of ethyl
acrylate, methylmethacrylate and trimethylamminoethyl methacrylate
chloride in a molar ratio of the three acrylates of 1 : 1.8–2.2 : 0.08-0.12,
preferably of 1:2:0.1,

10 - component (b) with 5% - 20% by weight of a copolymer of
ethylacrylate and methacrylic acid in a molar ratio of 1: 0.8-1.2,
preferably of 1:1, and

15 - pharmaceutical ingredient(s) (c) with 5% - 15% by weight of the
pharmaceutically active ingredient(s), and

20 - component (d) with plastifiers / lubricants / excipients.

In an especially preferred embodiment of the invention the layer (2)
consists of:

25 - component (a) with 50 – 85% by weight of a copolymer of ethyl
acrylate, methylmethacrylate and trimethylamminoethyl methacrylate
chloride in a molar ratio of the three acrylates of 1 : 1.8–2.2 : 0.08-0.12,
preferably of 1:2:0.1,

30 - component (b) with 10 - 30% by weight of a copolymer of
ethylacrylate and methacrylic acid in a molar ratio of 1: 0.8-1.2,
preferably of 1:1,

35 - pharmaceutical ingredient(s) (c) with 5 – 40% by weight of the
pharmaceutically active ingredient(s), and

40 - component (d) with plastifiers / lubricants / excipients.

45 In another preferred embodiment, further layers with or without
pharmaceutically active compounds may be present. In a particularly
preferred embodiment, such further layer is an enteric coating. In another
preferred embodiment, such further layer is a lacquer layer.

- 12 -

Pharmaceutical preparations comprising the components (a), (b) and pharmaceutical ingredient(s) (c) are well known in the art. However, it is not known to mix all three components in a single layer. The art teaches mixtures of components (a) and (b) as a separate layer applied on top of
5 a layer comprising pharmaceutical ingredient(s) (c), or teaches a layer comprising a mixture of component (b) and pharmaceutical ingredient(s) (c), with a separate further layer comprising component (a).

10 Surprisingly, the mixture of all three elements, components (a), (b) and pharmaceutical ingredient(s) (c) results in improved characteristics of the pharmaceutical preparation with respect to sustained release, pH-sensitivity and amount of substances needed for a desired release profile.

15 When comparing release characteristics of particles according to the invention with prior art particles containing the same amounts of the individual components, but wherein pharmaceutical ingredient(s) (c) forms a separate layer that is coated by a layer comprising components (a) and (b), particles of the present invention exhibit improved release
20 characteristics. This means that the active compound is more slowly released, i.e. release is more sustained from particles according to the invention. This finding is unexpected, as in the prior art particles the mixed layer comprising components (a) and (b) covering the separate layer of the pharmaceutical ingredient(s) (c) must first be eroded at least
25 partially before pharmaceutical ingredient(s) (c) can be liberated. In contrast, one would assume, that in the present invention pharmaceutical ingredient(s) (c) can be liberated as soon as the mixed layer starts to erode or is exposed to the surrounding liquids. Unexpectedly this is not the case.

30 A further advantage of a pharmaceutical composition according to the invention is that where prior art uses two separate layers (e.g. pharmaceutical ingredient(s) (c) in one layer and components (a) and (b) in a separate layer; or pharmaceutical ingredient(s) (c), and component
35 (b) in one layer and component (a) in a separate layer), the invention uses only one layer (components (a) and (b) and pharmaceutical ingredient(s) (c), all mixed in one single layer). In the first case, each layer

- 13 -

is applied consecutively in the course of production, and is therefore associated with processing time and additional handling requirements. Thus, reduction of the absolute number of layers required to obtain a desired release profile results in shorter and less complex production processes which are associated with economic benefits.

Furthermore, the composition according to the present invention exhibits a surprising effect regarding the pH-sensitivity of release of the active compound. This can be observed for particles containing all components of the different layers in the same total amount in a pellet, but the composition of individual layers is different. Thus, where particles according to the invention have one mixed layer of all three elements (components (a), (b) and active ingredient (c)), state of the art pellets have two separate layers made of different mixtures of these three elements (see also Figure 1A (particles of the invention), B and C (particles included in the state of the art)).

In particles included in the state of the art, the liberation of the active ingredient is sensible to small variations of ambient pH that result in different release profiles of the active ingredient over time. That means e.g. less active ingredient is released at an ambient pH=6 as at ambient pH=6.8. Such differences in the amount of active ingredient released can be observed at different time-points, thus resulting in different release profiles over time.

Surprisingly, in particles according to the invention this sensitivity of active ingredient release to small pH changes was more pronounced as compared to prior art particles. That means, the active ingredient release was more strongly affected over a longer period of time as compared to the prior art pellets. Thus, at time-points where prior art particles exhibited no difference in active ingredient liberation at different pH values (e.g. at 300 min after start of the dissolution at pH = 6 and pH= 6.8), particles according to the invention still showed a different release of active ingredient at the same two pH values. Also, the degree to which release was affected at such pH values was more pronounced for particles of the invention, as compared to prior art particles. This means, that the release profiles at different pH values were more different for the

- 14 -

particles of the invention. In other words, e.g. the difference of active ingredient released at a certain pH value at a given time-point was bigger than the difference observed at the same pH values and time-point for state of the art particles.

5

Moreover, the pH sensitivity of prior art particles is restricted to a narrower pH range. This means, pH-dependent differences in release profiles can e.g. only be observed for an ambient pH in the range of 6 to 6.8, but not below or above that value. Thus, the release profiles at e.g. pH=6.8 or 7.2 are indiscernible for the particles included in the prior art. In contrast, particles of the invention results in a different release profile over a wider range of pH values. In other words, the release profiles at an ambient pH of e.g. 7.2 is still different to one at e.g. pH=6.8.

Also, the pH sensitivity of the particles according to the invention is evenly graded over a wide pH range, e.g. from pH= 5.5 and pH= 7.2. This means, that the difference between release profiles at different ambient pH values like, e.g. 5.5 and 6.0 is similar to the difference in release profiles obtained to values of pH like, e.g. 6.8 and 7.2. In other words, the differences in the amount of active ingredient released at any given time-point for differing ambient pH values are similar (e.g. between pH 5.5 and 6.0 or between pH 6.8 and 7.2).

Such a reliable and predictable response to different pH values is a prerequisite for precise control of the timing and the location of drug release in the gastrointestinal tract.

Another advantage of particles according to the invention is that lower amounts of components (a) and (b) can be used to obtain a specific release profile. Thus, using in particles of the invention the same amounts of components (a) and (b) that in particles included in the prior art, a more sustained, or slower release can be achieved with particles of the invention. On the opposite, when the amount of components (a) and (b) are reduced, the particles of the present invention results in a release profile comparable to that of a prior art particle with higher amounts of components (a) and (b).

- 15 -

Also, layer (2) may be covered with one or more further layers. In a preferred embodiment said further layer is an enteric coating, also referred to by the numerical (3) in the following. "Enteric coating" in this context means that the coating prevents or diminishes liberation of the active ingredient(s) from the particle, and / or prevents or diminishes access of substances found in the gastro-intestinal tract to the active ingredient(s). Preferably, enteric coatings are engineered to fulfil these functions at certain ambient pH values, and stop to have their barrier function at other pH values typical for certain sections of the gastrointestinal tract. A preferred example of an enteric coating is resistant to gastric juices. Enteric coatings may preferably comprise substances such as a methacrylic acid polymers, cellulose derivatives, plasticizers, lubricants and/or release agents, and optionally coloured pigments and/or a silicone antifoam agents.

The particles of the present invention may be further processed to obtain typical pharmaceutical forms for oral administration. Preferred examples are capsules, tablets or granules. A multitude of pharmaceutical forms is well known in the art that are available to the skilled person and fulfil the specific requirements of a certain drug or a certain application.

The present invention also relates to a process for producing a pharmaceutical preparation for sustained release comprising a mixed layer (2) according to the invention. In this production process, components (a) and (b) and pharmaceutical ingredient(s) (c) are dissolved, partially dissolved, dispersed or suspended in appropriate solvents to finally form one single, homogenous mixture. Such solvents comprise water and organic solvents, such as ethanol, methanol, or acetone. Other organic solvents, including halogenated organic solvents, may also be suitable. Mixtures of solvents may also be used. The person skilled in the art readily knows what solvents are suitable for certain active ingredients and substances comprised in layer (2) of the invention.

The mixture of solvents and substances is then applied to a core particle as a coating layer. Said core particle can be an inert core. The core particle may comprise multiple layers of different composition. Methods

- 16 -

of applying the mixture to particles are well known in the art, and include, but are not limited to, spraying in a Wurster insert of a Glatt apparatus.

5 Optionally, the production process according to the invention may also comprise adding other coatings onto layer (2). Such coatings may comprise enteric coatings, coatings comprising active substances, or other coatings known for galenic preparations, either alone or in combination.

10 In the following the invention is described in more detail by reference to examples as described below.

Examples

15 In the following examples, multilayered particles according to the invention (Examples 1 to 6, see Figure 1A) and state of the art particles (Reference Examples 1 to 6, see Figure 1 B and C) are compared with respect to their release profiles at different ambient pH values.

20 All particles according to the invention and the reference examples comprise an inner core (1) with a diameter in the range of 0.5 and 0.7 mm, and containing between 60% and 90% by weight sugar and between 10% and 40% by weight corn starch.

25 Particles according to the invention comprise a first coating (2), wherein said coating (2) contains a mixture of:

30 - component (a): between 50% and 95% by weight of a copolymer, preferably between 60% and 80% by weight of ethyl acrylate, methylmethacrylate and trimethylammonioethyl methacrylate chloride in a molar ratio of the three acrylates of 1 : 1.8–2.2 : 0.08-0.12, preferably of 1:2:0.1, (Eudragit ® RS), and

35 - component (b): between 2% and 30% by weight, preferably between 5% and 20% by weight of a copolymer of ethyl acrylate and methacrylic acid in a molar ratio of 1: 0.8-1.2, preferably of 1:1, (Eudragit ® L 100-55), and

- 17 -

- pharmaceutical ingredient(s) (c): between 1% and 40% by weight, preferably between 5% and 15% by weight of the pharmaceutically active ingredient(s), and

5

- excipients (d). In a preferred embodiment, an enteric coating (3) is also applied.

10

Reference particles in reference examples 1-5 contain mixed layers (2'), which in total contain the same quantities of the components of layer (2) of the invention. However, layers (2') comprise two separate layers containing the active ingredient(s) (c), and a layer with the modified release agents (components (a) and (b)). Optionally a gastric-juice resistant enteric coating layer (3) is also included (see Figure 1B). In reference example 6, particles present an inert core (1), and the layers (2'') which again contains the same quantities of the same ingredients as layer (2) of the invention, but are divided into a layer comprising the active ingredient(s) (c) and a modified release agent with pH-dependent solubility, component (b), and a layer with pH-independent modified release agent, component (a). Optionally an enteric coating layer (3) may be present (see Figure 1C).

15

20

25

The proportions of components (a) and (b) and pharmaceutical ingredient(s) (c) in layer (2) of Examples 1-6 and the corresponding layers in Reference Examples 1-6 are summarized in Table 1.

EXAMPLE 1: 0.4 mg Tamsulosin hydrochloride particles with enteric coating

30

Layer (2), (components (a) and (b) and pharmaceutical ingredient(s) (c)):

35

1.4 g of Tamsulosin HCl, 19 g of Eudragit ® RS (Rohm Pharma, Germany), 2 g of Eudragit ® L 100-55 (Rohm Pharma, Germany) and 2 g of triethyl citrate were dissolved in a mixture of 400 ml ethanol (96%) and 200 ml acetone. 53 g of talcum was dispersed as a process adjuvant. 650 g of inert core particles were charged in a Wurster Insert of a Glatt apparatus equipped with a 1.2 mm spray nozzle. The inlet air

- 18 -

temperature was maintained at 40°C. The particles were coated with the mixed solution.

Layer (3), component (b):

5

An enteric coating layer was prepared by dispersing 200 g of Eudragit ® L-30D 55 (Rohm Pharma, Germany), 5 g of triethyl citrate and 58 g of talcum in water, to obtain a dispersion of the solid content of 24.6%. The enteric coating was applied in the Wurster equipment equipped with a

10

Upon completion, the particles were dried in an oven at 40°C for 24 hours.

15 In terms of weight, the finished particles were composed of an inert core of 180 mg, a layer (2) of 22 mg, and a layer (3) of 39 mg, with a final particle weight of 241 mg. All finished particles of the following examples had a similar composition.

20 **REFERENCE EXAMPLE 1:** 0.4 mg Tamsulosin hydrochloride particles with enteric coating

Layer (2'), pharmaceutical ingredient(s) (c):

25 1.4 g of Tamsulosin HCl and 21 g of polyvinyl pyrrolidone (PVP) were completely dissolved in 400 g of ethanol (96%). 35 g of talcum was dispersed as an adjuvant in the process. This suspension was applied to 650 g of core particles charged in a Wurster Insert of a Glatt apparatus, equipped with a 1.2 mm spray nozzle. The inlet air temperature was

30

Layer (2'), (components (a) and (b)):

35 19 g of Eudragit ® RS (Rohm Pharma, Germany), 2 g of Eudragit ® L 100-55 (Rohm Pharma, Germany) and 2 g of triethyl citrate were dissolved in a mixture of 400 ml ethanol (96%) and 200 ml acetone. 18 g of talcum was dispersed as an adjuvant in the process. This suspension

- 19 -

was applied to the previous particles charged in a Wurster Insert of a Glatt apparatus, equipped with a 1.2 mm spray nozzle. The inlet air temperature was maintained at 40°C.

5 Layer (3), component (b):

An enteric coating layer was prepared and applied as in Example 1.

The finished particles were dried in an oven at 40°C for 24 hours.

10

EXAMPLE 2: 0.4 mg Diltiazem hydrochloride particles with enteric coating

Layer (2), (components (a) and (b) and pharmaceutical ingredient(s) (c)):

15

This layer was prepared and applied to the inert core particles as in Example 1, but instead of Tamsulosin HCl, 1.4 g of Diltiazem HCl was used as an active ingredient(s).

20 Layer (3), component (b):

An enteric coating was applied as in Example 1. The finished particles were dried in an oven as in Example 1.

25 **REFERENCE EXAMPLE 2:** 0.4 mg Diltiazem hydrochloride particles with enteric coating

A reference particle was prepared as in Reference Example 1, unless that the active ingredient was 1.4 g of Diltiazem HCl, instead of the same amount of Tamsulosin.

30

EXAMPLE 3: 1 mg Diltiazem hydrochloride particles with enteric coating

Layer (2), ((a)(b) pharmaceutical ingredient (c)):

35

3.5 g of Diltiazem HCl, 19 g of Eudragit ® RS (Rohm Pharma, Germany), 2 g of Eudragit ® L 100-55 (Rohm Pharma, Germany) and 2 g of triethyl

- 20 -

citrate were dissolved in a mixture of 400 ml ethanol (96%) and 200 ml acetone. 53 g of talcum was dispersed as an adjuvant in the process. 650 g of inert core particles were charged in a Wurster Insert of a Glatt apparatus equipped with a 1.2 mm spray nozzle. The inlet air
5 temperature was maintained at 40°C. The particles were coated with the mixed solution.

Layer (3), component (b):

10 The enteric coating layer was prepared by dispersing 150 g of Eudragit ® L-30D 55 (Rohm Pharma, Germany), 4 g of triethyl citrate and 58 g of talcum in water to obtain a 24,6% solid content dispersion. The enteric coating was applied in the Wurster equipment equipped with a 0.8 mm spray nozzle.

15 Upon completion, the particles were dried in an oven of 40°C for 24 hours.

20 **REFERENCE EXAMPLE 3:** 1 mg Diltiazem hydrochloride particles with enteric coating

Layer (2'), pharmaceutical ingredient (c):

25 3.5 g of Diltiazem HCl and 3.5 g of PVP were completely dissolved in 400 g ethanol (96%). 35 g of talcum was dispersed as an adjuvant in the process. This suspension was applied to 650 g of inert core particles charged in a Wurster Insert of a Glatt apparatus, equipped with a 1.2 mm spray nozzle. The inlet air temperature was maintained at 40°C.

30 Layer (2'), (components (a) and (b)):

35 19 g Eudragit ® RS (Rohm Pharma, Germany), 2 g Eudragit ® L 100-55 (Rohm Pharma, Germany) and 2 g triethyl citrate were dissolved in a mixture of 400 ml ethanol (96%) and 200 ml acetone. 18 g of talcum was dispersed as an adjuvant in the process. This suspension was applied to the previous particles charged in a Wurster Insert of a Glatt apparatus,

- 21 -

equipped with a 1.2 mm spray nozzle. The inlet air temperature was maintained at 40°C.

Layer (3), component (b):

5

An enteric coating layer was prepared and applied as in the layer (3) of Example 3, and the finished particles were dried as in Example 3.

10 **EXAMPLE 4:** 0.6 mg Tamsulosin hydrochloride particles without enteric coating

Layer (2), (components (a) and (b) and pharmaceutical ingredient (c)):

15 1.8 g of Tamsulosin HCl, 16 g of Eudragit ® RS (Rohm Pharma, Germany), 5 g of Eudragit ® L 100-55 (Rohm Pharma, Germany) and 2 g triethyl citrate were dissolved in a mixture of 400 ml ethanol (96%) and 200 ml acetone. 53 g of talcum was dispersed as an adjuvant in the process. 540 g of inert core particles were charged in a Wurster Insert of a Glatt apparatus equipped with a 1.2 mm spray nozzle. The inlet air temperature was maintained at 40°C. The particles were coated with the mixed solution.

20 Upon completion, the particles were dried in the fluid bed at 40°C for 1 hour.

25

REFERENCE EXAMPLE 4: 0.6 mg Tamsulosin hydrochloride particles without enteric coating

Layer (2'), pharmaceutical ingredient (c):

30

1.8 g of Tamsulosin HCl and 25 g of PVP were completely dissolved in 450 g ethanol (96%). 35 g of talcum was dispersed as an adjuvant in the process. This suspension was applied to 650 g of inert core particles charged in a Wurster Insert of a Glatt apparatus, equipped with a 1.2 mm spray nozzle. The inlet air temperature was maintained at 40°C.

35

Layer (2'), (components (a) and (b)):

- 22 -

16 g of Eudragit ® RS (Rohm Pharma, Germany), 5 g of Eudragit ® L 100-55 (Rohm Pharma, Germany) and 2 g of triethyl citrate were dissolved in a mixture of 400 ml ethanol (96%) and 200 ml acetone. 18 g of talcum was dispersed as an adjuvant in the process. This suspension was applied to the previous particles charged in a Wurster Insert of a Glatt apparatus, equipped with a 1.2 mm spray nozzle. The inlet air temperature was maintained at 40°C.

10 The finished particles were dried as in Example 4.

EXAMPLE 5: 0.6 mg Tamsulosin hydrochloride particles with enteric coating

15 The particles of Example 4 were further coated with an enteric coating.

Layer (3), component (b):

20 An enteric coating layer was prepared by dispersing 120 g of Eudragit ® L-30D 55 (Rohm Pharma, Germany), 3.5 g triethyl citrate and 58 g of talcum in water to obtain a 24.6% solid content dispersion. The enteric coating was applied in the Wurster equipment on the particles obtained in Example 4. The inlet air temperature was maintained at 40°C and a 0.8 mm spray nozzle was used.

25 Upon completion, the particles were dried in an oven of 40°C for 24 hours.

30 **REFERENCE EXAMPLE 5:** 0.6 mg Tamsulosin hydrochloride particles with enteric coating

The particles of Reference Example 4 were further coated with an enteric coating as described in Example 5, and the finished particles were dried as in Example 5.

35 **EXAMPLE 6:** Large scale production of particles containing 0.4 mg Tamsulosin hydrochloride

- 23 -

Layer (2), (components (a) and (b) and pharmaceutical ingredient (c)):

40 g of Tamsulosin HCl, 620 g of Eudragit ® RS (Rohm Pharma,
5 Germany), 57 g of Eudragit ® L 100-55 (Rohm Pharma, Germany) and
68 g of triethyl citrate were dissolved in a mixture of 14.000 ml ethanol
(96%) and 7.000 ml acetone. Talcum was dispersed as an adjuvant in
the process. 18.000 g of inert core particles were charged in a Wurster
10 Insert of a Glatt apparatus (GPCG 15) equipped with a 1.2 mm spray
nozzle. The inlet air temperature was maintained at 40°C. The particles
were coated with the mixed solution.

Layer (3), component (b):

15 An enteric coating layer was prepared by dispersing 6.500 g of Eudragit
® L-30D 55 (Rohm Pharma, Germany), 200 g of triethyl citrate and
talcum in water, to obtain a 24.6% solid content dispersion. The enteric
coating was applied in the Wurster equipment equipped with a 0.8 mm
spray nozzle.

20 Upon completion, the particles were dried in an oven of 40°C for 24
hours.

REFERENCE EXAMPLE 6: Multilayered particles comprising only
25 Eudragit ® L in the active ingredient layer

Layer (2''), (pharmaceutical ingredient (c), component (b)):

This layer corresponds to layer 2 of Example 2, but Eudragit ® RS was
30 omitted. The auxiliary agents were adjusted accordingly.

1,4 g of Diltiazem HCl, 2 g of Eudragit ® L100-55, 0,2 g of triethyl citrate
were dissolved in a mixture of 50 ml of ethanol (96%) and 25 ml of
acetone. 5,5 g of talcum was dispersed as an adjuvant in the process.
35 650 g of inert core particles were charged in a Wurster Insert of a Glatt
apparatus equipped with a 1,2 mm spray nozzle. The inlet air

- 24 -

temperature was maintained at 40°C. The particles were coated with the mixed solution.

Layer (2''), component (a):

5

Eudragit ® RS was applied in a separate layer. 19 g of Eudragit ® RS100 and 1,9 g of triethyl citrate were dissolved in a mixture of 400 ml ethanol (96%) and 200 ml acetone. 47,5 g of talcum was dispersed as an adjuvant in the process. This suspension was applied to the previous particles charged in the Wurster Insert, equipped with a 1,2 mm spray nozzle. The inlet air temperature was maintained at 40°C.

10

Layer (3), component (b):

15

An enteric coating layer was prepared, applied and dried as in Example 1.

EXAMPLE 7: Dissolution experiments at pH=6

20

The finished particles of Examples 1-5 and corresponding Reference Examples 1-5 were subjected to dissolution experiments. Data are summarized in Table 2 and Figure 2. "In vitro" dissolution characteristics were determined by using an paddle stirrer of apparatus 2 in according to Eur. Pharm. This is a typical test used in preparing galenic preparations generally known to the skilled person. It allows to predict release characteristics of an active ingredient in the gastrointestinal tract. Paddle rotating speed was set to 50 rpm. The particles were dissolved in a 500 ml phosphate buffer (pH = 6). At regular intervals triplicate samples were drawn and analysed for the active ingredient(s) by HPLC.

25

30

Mean values are represented as percent of active ingredient(s) dissolved. The change of the percentage dissolution over time is also called dissolution profile.

These data indicate that the particles according to the invention (Examples 1-5) resulted in a more sustained release as compared to state of the art particles (Reference Examples 1-5), both in the presence (Examples 1 - 3, 5 and 6; and Reference Examples 1 - 3, 5 and 6) as in

35

absence (Example 4 and Reference Example 4) of an enteric coating layer.

EXAMPLE 8: Dissolution experiments at different pH values

5

A further technical effect of particles according to the invention is the responsiveness of their solubility characteristics to different ambient pH values. Therefore, in additional dissolution experiments following the experimental procedure set out in Example 7 (apart from ambient pH), it was assessed to what degree the dissolution characteristics of particles according to the invention are affected by the ambient pH. A comparison to prior art particles was performed.

10

Table 3 and Figure 3 show the comparison of dissolution behaviour of particles of Example 1 and Reference Example 1 at pH= 6.0 and pH= 6.8. The particles of Example 1 exhibited pH-dependent dissolution characteristics at all analysed time-points up to 300 min. In contrast, dissolution of the state of the art particles of Reference Example 1 was only influenced by the pH at the time-points 30 min and 60 min.

15

20

In Table 4 and Figure 4, the particles of Example 2 were compared to state of the art particles of Reference Example 6. Buffer solutions with three different pH values were used (6.0, 6.8 and 7.2).

25

As can readily be seen from Figure 4, particles of the invention exhibited a better pH responsiveness in terms of dissolution characteristics. This means, that different ambient pH values resulted in more different release profiles as compared to state of the art particles. At pH= 6.0 and 6.8, particles according to the invention exhibited different release profiles, in that more active ingredient was released at a higher pH. In contrast, differences in the release of the active ingredient from prior art particles at pH= 6.0 and pH= 6.8 was less pronounced. This means, the amounts of active ingredient released were more similar as compared to the amount of active ingredients released for particles of the invention at the time-points analysed. Furthermore, the differences in the release profiles at different pH values of state of the art particles was more irregular. This means, that e.g. at pH 6.0 and at pH 6.8, no difference in

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- 26 -

the amount released was demonstrated at the time-point 60 min, whereas in contrast there was a difference at time-points thereafter. On the other hand, particles according to the invention showed consistent differences in release of active ingredients at all time-points analysed.

5

Furthermore, prior art particles exhibited no or very little differences between the release of the active ingredient from particles at an ambient pH of 6.8 and 7.2. In contrast, particles of the invention showed clear-cut differences in the amount of active ingredient released at the pH values analysed (6.0, 6.8 and 7.2) at all time-points of the experiments (t= 0 min – 300 min).

10

This finding is also confirmed by the data of Table 5 and Figure 5. These data demonstrate that the pH dependency of release of active ingredient from particles of the invention is uniformly different for different pH values over a pH range of 5.5 to 7.2.

15

These results demonstrate that the dissolution behaviour of particles according to the invention is more sensitive to pH changes, this sensitivity is present over a wider range of ambient pH values, and the release profiles are more consistently and predictably affected by the pH that in the case of particles included in the prior art.

20

EXAMPLE 9: Influence of the quantity of components (a) and (b) in layer (2) on dissolution characteristics

25

In order to investigate the influence of the polymer quantity in layer (2) on dissolution characteristics, three batches (Batches A, B and C) of particles were produced that each comprised 0.4 mg Tamsulosin HCl as component (c), but differing amounts of components (a) and (b). The procedure of Example 1 was followed, but the amounts of components (a) and (b) were adjusted to result in the quantities of said components in layer (2) of the finished particles as depicted in Table 6. Thus, layer (2) of particles of Batch A contained a total of 8.42 mg of polymeric compounds (corresponding to 87.2% of polymer in relation to pharmaceutical ingredient and to the plastifier), layer (2) of Batch B contained the lower amount (5.31 mg) (85.1%) of polymer and layer (2) of Batch C contained

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- 27 -

a still slightly lower amount as compared to Batch B, namely 5.03 mg (84.8%) of polymer. The particles were subjected to dissolution experiments as described in Example 7, and the results are summarized in Table 6 and Figure 6.

5

As can readily be seen from these experiments, particles of Batch A, which contain the highest amount of polymers, show dissolution characteristics that result in the most retarded release profile as compared to Batches B and C, which contain less amount of polymers.

10 This means that the active ingredient is more slowly released from particles of Batch A. It can also be seen, that Batches B and C have release profiles that are similar to each other, wherein the profile of Batch C is only slightly more retarded than that of Batch B. This corresponds well to the amounts of polymers these Batches contain, in
15 that Batch B contains only slightly more polymers than Batch C.

These results clearly show that the relative amount of polymers in layer (2) affects of predictable and reproducible form on the release profile of a pharmaceutical ingredient from a particle according to the invention, and
20 that minor changes in polymer quantity allow fine tuning of drug release profiles.

EXAMPLE 10: Batch-to-batch reproducibility

25 In order to assess batch-to-batch reproducibility of dissolution characteristics, a second batch of particles was produced according to Example 6, and the dissolution characteristics of particles from the two batches at different pH values was compared. Table 7 and Figure 7 show a high degree of reproducibility of the release of the active
30 ingredient from the two batches of particles at pH = 6.0 and 6.8 over the entire time span analysed.

EXAMPLE 11: Influence of stirring speed on dissolution

35 In order to assess the influence of parameters other than ambient pH, particles according to Example 6 were dissolved at different stirring

- 28 -

speeds. Table 8 and Figure 8 demonstrate a slightly delayed release profile at 100 rpm as compared to 50 rpm.

5 The above data demonstrate that particles of the invention possess a more sustained release profile than prior art particles. Moreover, the relative amount of copolymers in the particles has a reproducible and predictable influence on release profiles. As a consequence, less amount of the copolymers (a) and (b) need to be used to achieve the same release profile over time as compared to state of the art particles.

10

Moreover, particles according to the invention show enhanced sensitivity to different pH values in their release profiles.

15

All these advantages allow fine-tuning of drug delivery from particles of the invention in accordance with the physiological conditions of the gastro-intestinal tract.

Table 1: Relative content (%) of components (a), (b) (c) and (d) in layer (2) of Examples 1-6 and the layers (2') and (2'') of the Reference Examples 1-6.

	Exam 1	Ref. Exam 1	Exam 2	Ref. Exam 2	Exam 3	Ref. Exam 3	Exam 4	Ref. Exam 4	Exam 5	Ref. Exam 5	Exam 6	Ref. Exam. 6
(a)	78	78	78	78	72	72	65	65	65	65	79	78
(b)	8	8	8	8	7.5	7.5	20	20	20	20	7	8
(c)	6	6	6	6	13	13	7	7	7	7	5	6
(d)	8	8	8	8	7.5	7.5	8	8	8	8	9	8

5 Table 2: Dissolution of particles of Examples 1-5 and the Reference Examples 1-5 at pH = 6.

Time (min)	Exam. 1	Ref. Exam. 1	Exam. 2	Ref. Exam. 2	Exam. 3	Ref. Exam. 3	Exam. 4	Ref. Exam. 4	Exam. 5	Ref. Exam. 5
0	0	0	0	0	0	0	0	0	0	0
30	29.1	32.9	14.0	46.2	22.6	67.7	8.6	2.6	9.0	1.9
60	43.0	69.9	25.9	68.6	65.8	86.7	12.1	13	12.2	7.0
120	68.1	96.9	32.3	80.5	89.6	96.6	18.8	37.7	16.9	31.5
180	79.5	102.3	38.9	84.8	92.4	100.2	23.6	63.3	21.9	60.1
240	87.4	104.9	46.6	86.4	98.1	100.8	27.5	78.3	25.2	79.3
300	92.1	105.8	48.8	86.8	99.0	101.4	31.4	84.4	29.2	89.8

Table 3: Dissolution behaviour of particles of Example 1 and the reference Example 1 at different pH-values.

Time (min)	Example 1		Reference Example 1	
	pH = 6	pH = 6.8	pH = 6	pH = 6.8
0	0	0	0	0
30	29.1	44.1	32.9	49.9
60	43.0	63.2	69.9	86.5
120	68.1	89.4	96.9	99.3
180	79.5	98.0	102.4	100.9
240	87.4	102.5	104.9	102.0
300	92.1	104.1	105.8	102.5

- 30 -

Table 4: Dissolution behaviour of particles of Example 2 and the Reference Example 6 at different pH-values.

Time (min)	Example 2			Reference Example 6		
	pH = 6	pH = 6.8	pH = 7.2	pH = 6	pH = 6.8	pH = 7.2
0	0	0	0	0	0	0
30				5.0	8.2	9.9
60	24.0	46.7	58.3	17.3	17.8	17.6
120	35.5	63.2	78.8	28.8	37.5	35.5
180	45.5	69.7	91.2	36.1	44.3	47.3
240	52.6	76.1	95.4	42.1	53.2	53.0
300	57.1	86.9	99.0	46.2	57.5	55.9

Table 5: Dissolution behaviour of particles of Example 6 at different pH-values.

5

Time (min)	Example 6			
	pH = 5.5	pH = 6	pH = 6.8	pH = 7.2
0	0	0	0	0
60	10.6	24.0	43.7	58.3
120	20.5	35.5	63.2	78.8
180	24.2	45.5	69.7	91.2
240	28.8	52.6	76.1	95.4
300	29.8	57.1	86.9	99.0

Table 6: Composition of layer (2) and dissolution characteristics of particles of Example 9 containing 0.4 mg of Tamsulosin and different amounts of polymeric components (a) and (b).

Composition of Layer (2) (mg)				Dissolution Characteristics (% Dissolved)			
Components	Batch A	Batch B	Batch C	Time (min)	Batch A	Batch B	Batch C
(c)	0.4	0.4	0.4	30	25.0	33.0	35.3
(a)	7.7	4.9	4.6	60	35.5	45.0	49.4
(b)	0.7	0.5	0.4	120	46.1	66.1	73.4
(d)	0.8	0.5	0.5	180	55.9	79.7	85.6
				240	62.5	88.1	91.4
				300	73.6	91.0	94.3

- 31 -

Table 7: Dissolution behaviour of different batches of particles (Example 6 and 9) at different pH-values.

	Example 6		Example 9	
Time (min)	pH = 6.0	pH = 6.8	pH = 6.0	pH = 6.8
0	0	0	0	0
60	24.0	43.7	21.1	41.7
120	35.5	63.2	43.0	57.0
180	45.5	69.7	49.4	72.4
240	52.6	76.1	55.4	88.6
300	57.1	86.9	61.6	89.4

5 Table 8: Dissolution behaviour of particles of Example 6 at different stirring speeds (rpm) at pH = 6.8

	Example 6	
Time (min)	50 rpm	100rpm
0	0	0
60	41.7	36.6
120	57.0	51.6
180	72.4	63.5
240	88.6	68.4
300	89.4	77.1

CLAIMS

1. A pharmaceutical preparation for sustained release of a
5 pharmaceutically active ingredient, which preparation comprises particles having an inner core (1) and a first coating (2) provided thereon, wherein said coating (2) contains a mixture of:
- (a) between 50% and 95% by weight of a copolymer of ethyl
10 acrylate, methylmethacrylate and trimethylamminoethyl methacrylate chloride in a molar ratio of the three acrylates of 1:1.8–2.2:0.08-0.12, preferably of 1:2:0.1,
- (b) between 2% and 30% by weight of a copolymer of ethylacrylate
15 and methacrylic acid in a molar ratio of 1: 0.8-1.2, preferably of 1:1,
- (c) between 1% and 40% by weight of at least one pharmaceutically active ingredient and optionally
- 20 (d) physiologically acceptable excipients;
- and optionally, at least one further coating (3) thereon.
2. The pharmaceutical preparation according to claim 1, wherein said
25 coating (2) contains a mixture of:
- (a) between 50% and 95% by weight of said copolymer of ethyl
acrylate, methylmethacrylate and trimethylamminoethyl
methacrylate chloride in a molar ratio of the three acrylates of
30 1:2:0.1,
- (b) between 2% and 30% by weight of said copolymer of ethylacrylate and methacrylic acid in a molar ratio of 1:1,
- 35 (c) between 1% and 40% by weight of at least one pharmaceutically active ingredient and optionally

- 33 -

(d) physiologically acceptable excipients.

3. The pharmaceutical preparation according to claim 1 or 2, wherein said coating (2) contains a mixture of:

5

(a) between 60% and 90% by weight of said copolymer of ethyl acrylate, methylmethacrylate and trimethylamminoethyl methacrylate chloride,

10

(b) between 5% and 20% by weight of said copolymer of ethylacrylate and methacrylic acid, and

(c) between 5% and 15% by weight of said pharmaceutically active ingredient(s).

15

4. The pharmaceutical preparation according to any one of claims 1 to 3, wherein the pharmaceutically active ingredient(s) is selected from at least one of Amlodipine, Budesonide, Candesartan, Cisapride, Diclofenac, Diltiazem, Donepezil, Fentanyl, Glimepiride, Mebeverine, Memantine, Nicardipine, Olanzapine, Omeprazole, Ondansetron, Oxybitinin, Pramipexol, Ramipril, Risperidone, Rivastigmin, Tamsulosin, Theophylline, Tibolone, Tolterodine, Topiramate, Trandolapril.

20

- 25 5. The pharmaceutical preparation according to any one of claims 1 to 4, wherein the inner core (1) contains a physiologically acceptable excipient.

30

6. The pharmaceutical preparation according to claim 5, wherein the physiologically acceptable excipient is at least one selected from sucrose, glucose and starch.

35

7. The pharmaceutical preparation according to any one of claims 1 to 6, wherein the inner core (1) has a diameter in between 0.1 and 2.0 mm, preferably in between 0.4 and 0.8 mm, especially of 0.5 mm.

- 34 -

8. The pharmaceutical preparation according to any one of claims 1 to 7, wherein said further coating (3) is at least one selected from enteric coatings and lacquer coatings.
- 5 9. The pharmaceutical preparation according to claim 8, wherein said enteric coating is gastric juice resistant.
- 10 10. The pharmaceutical preparation according to claims 8 or 9, wherein the enteric coating contains at least one component selected from methacrylic acid polymer, cellulose derivatives, plasticizers, lubricants, release agents, coloured pigments or a silicone antifoam.
- 15 11. The pharmaceutical preparation according to any one of claims 1 to 10, prepared in form of capsules, tablets or granules.
- 20 12. A process for producing a pharmaceutical preparation for sustained release according to any one of claims 1 to 7, wherein the components (a), (b) and (c) are dissolved in a mixture of solvents and applied on the inner core (1).
- 25 13. A process for producing a pharmaceutical preparation for sustained release according to any one of claims 8 to 11 by use of the process according to claim 12, wherein at least one further coating (3) is provided on the first coating (2).

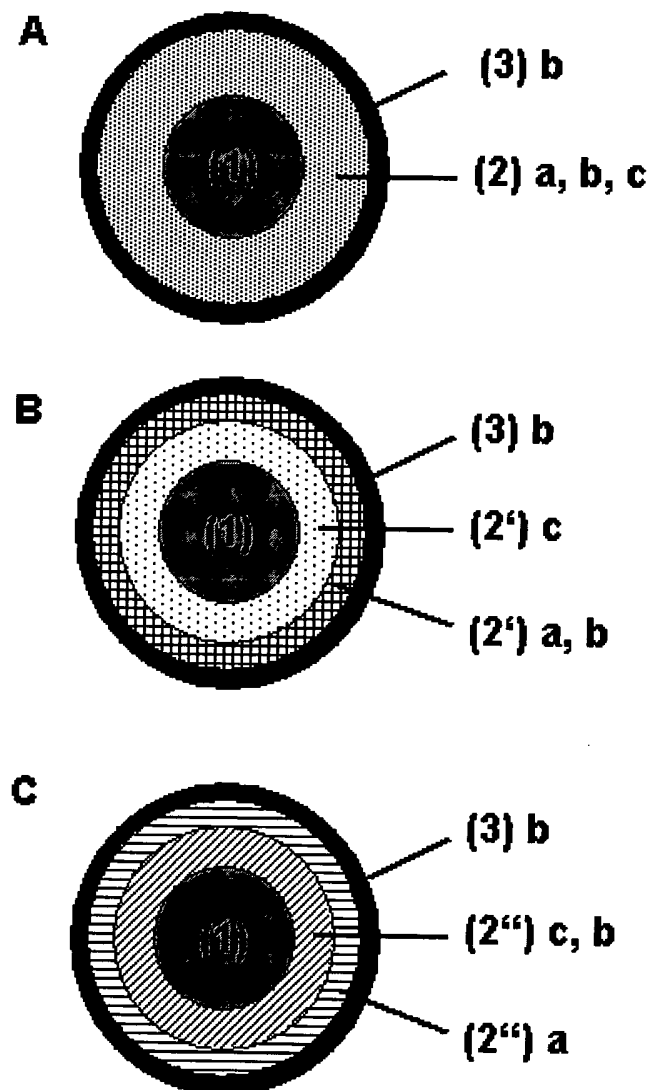


Figure 1/8

2 / 8

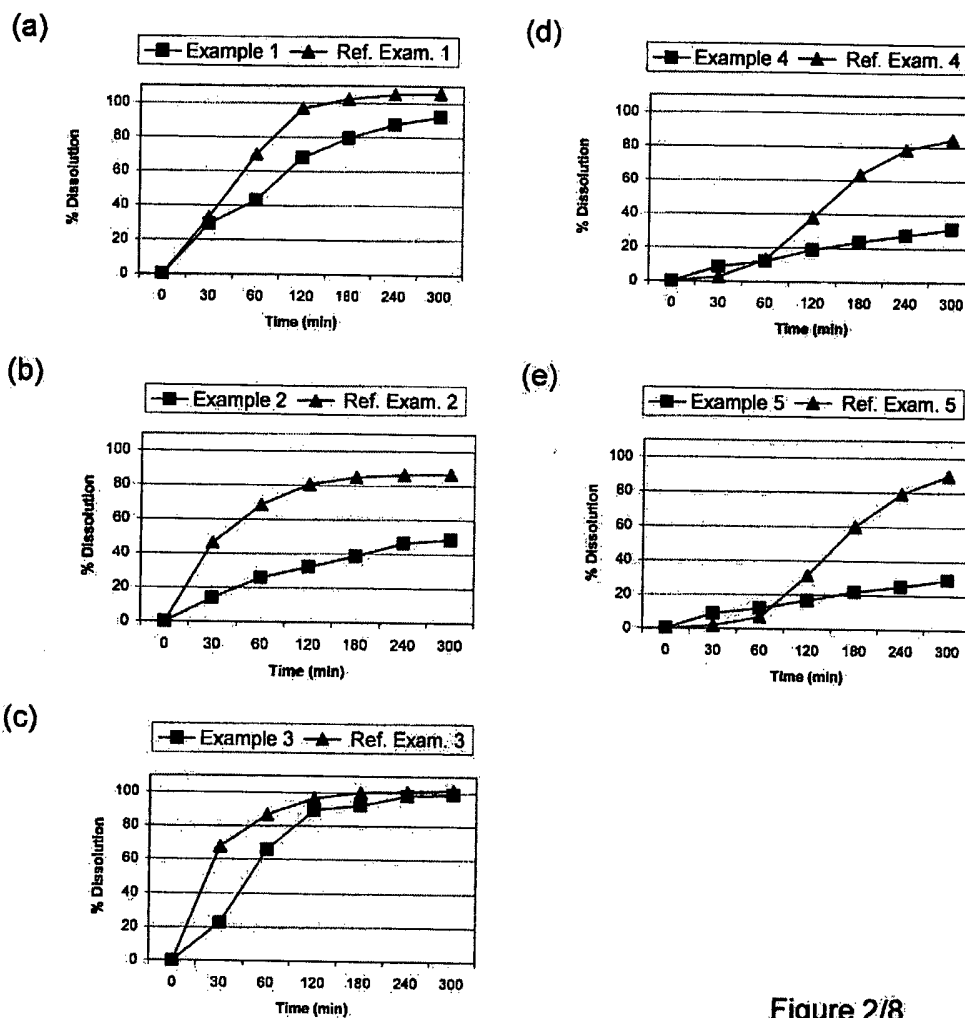


Figure 2/8

3 / 8

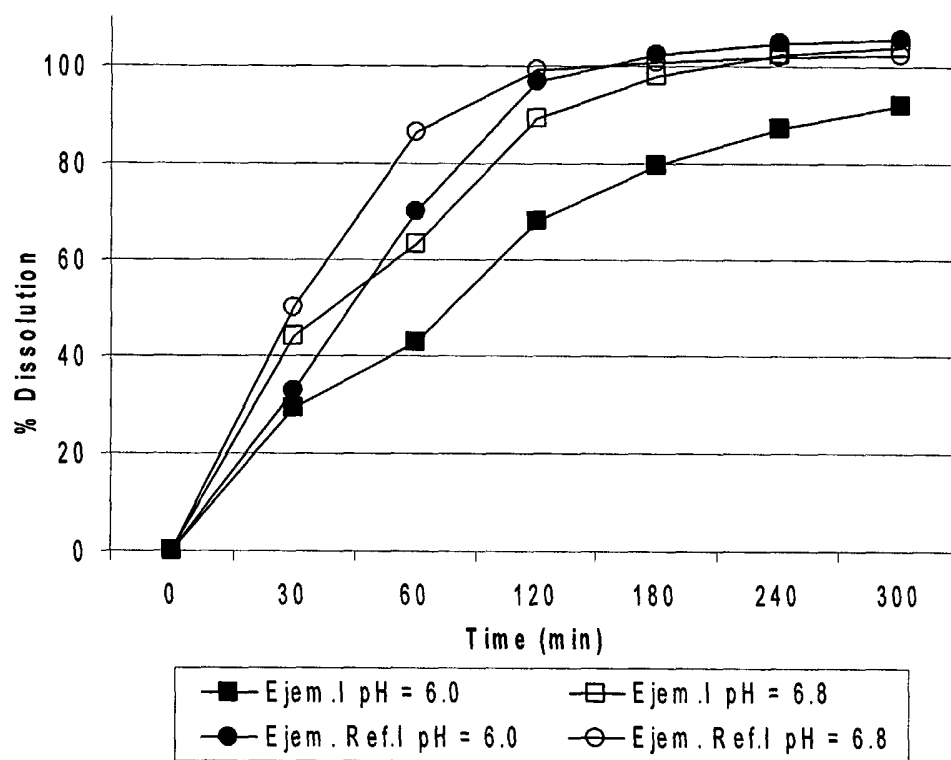
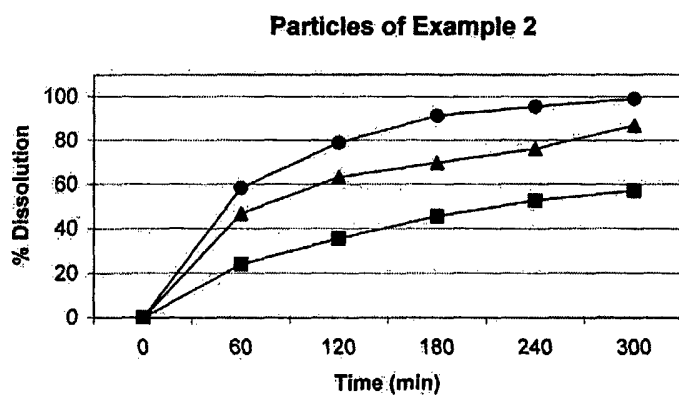


Figure 3 / 8

4 / 8

(a)



(b)

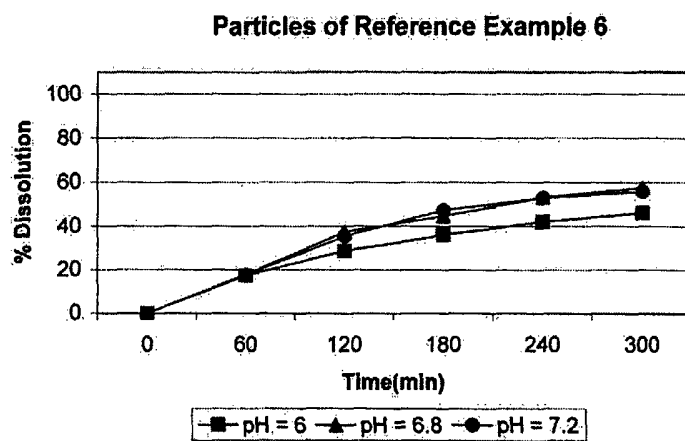


Figure 4/8

5 / 8

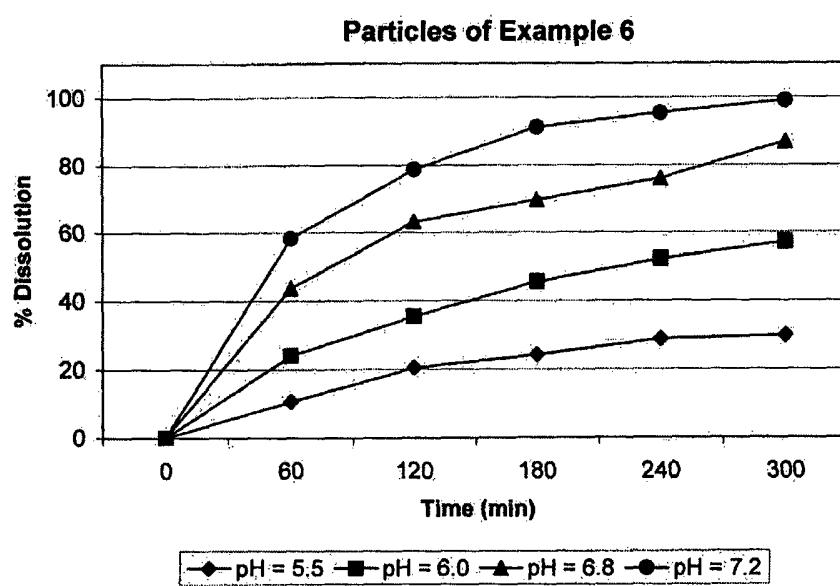


Figure 5/8

6 / 8

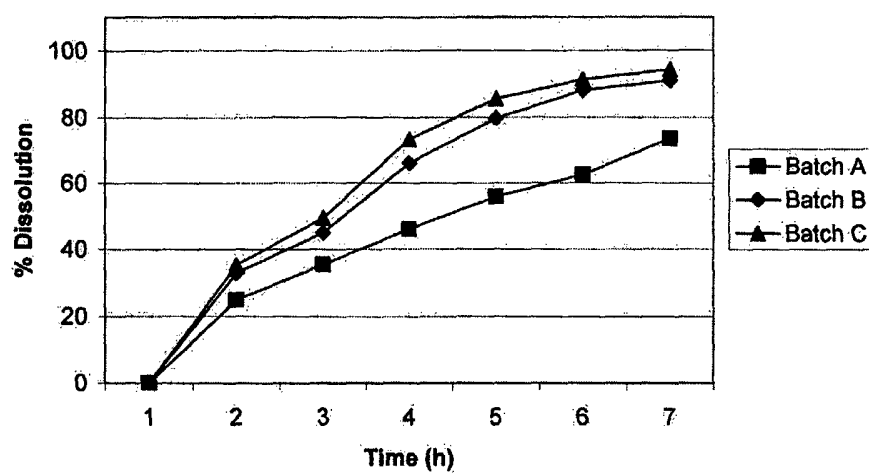


Figure 6/8

7 / 8

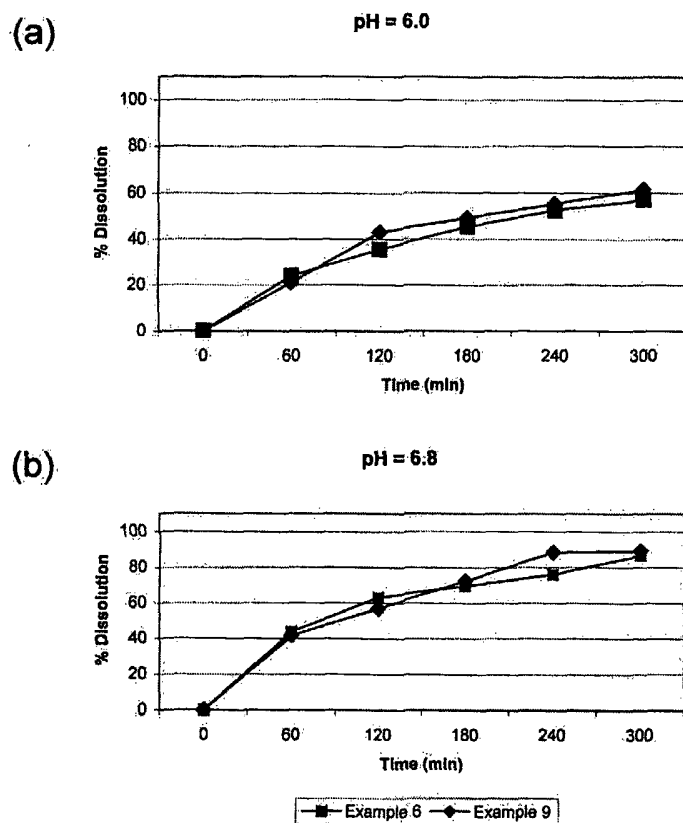


Figure 7/8

8 / 8

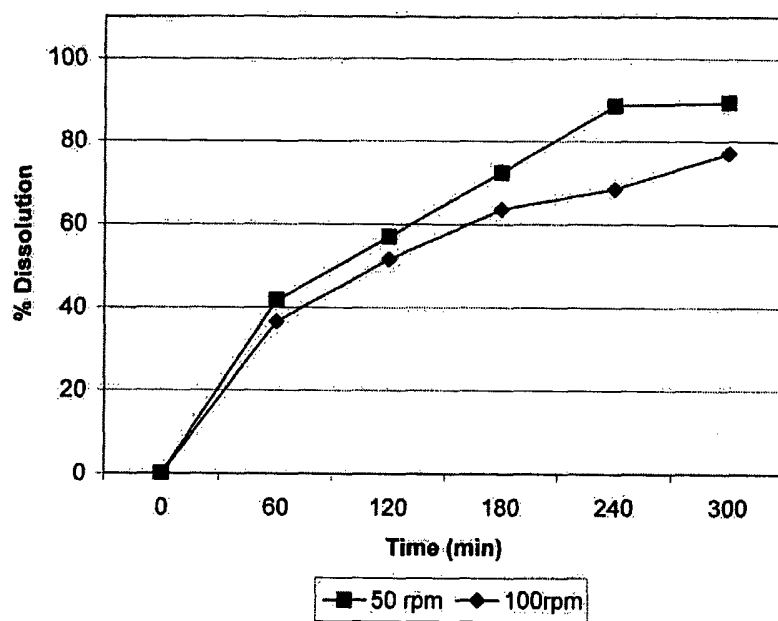


Figure 8/8