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Delayed-release preparations of quinolone antibiotics and processes for their preparation

The present invention relates to solid, orally administrable matrix preparations of quinolone antibiotics having delayed release and to a process for their preparation.

Active compounds from the quinolones class have been employed for a long time as broad-spectrum antibiotics, and numerous administration forms are obtainable on the market, such as tablets, infusion solutions, eye drops etc.

For many medicaments - as also for the quinolones class - formulations are desirable which after administration once daily guarantee a controlled, long-lasting and uniform release of the active compound. In this way, the desired active compound concentration in the plasma (below: "plasma level") and the therapeutic action can be maintained over a relatively long period without large variations. Formulations which release the active compound in this manner over a relatively long period are designated as delayed-release or controlled-release (CR) preparations.

It is very difficult, however, to develop orally administrable quinolone preparations which, in spite of administration only once daily, guarantee an adequately high antibiotic action; the patient must therefore take at least two doses daily. It is desirable, however, to reduce the frequency of taking of such quinolone antibiotics to once daily.

For the production of preparations having controlled release of active compound, in principle various techniques are known. Thus it is often desired to leave the preparation for a relatively long period in the stomach in order to make possible the rapid and complete absorption of the active compound to be delayed in the absorption window (i.e. in the section of the gastrointestinal tract in which absorption takes place). The residence time in the stomach, however, depends strongly on the nature and nutritive value of the food in the stomach (S.S. Davis in G. Hardy et al., Drug Delivery to the Gastrointestinal Tract, Ellis Holwood Ltd., Chichester, England 1989). In order to prolong the residence time in the stomach, various attempts have been investigated which either

a) increase the density of the preparation (EP-A 265 061),



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b) use special additives such as ammonium myristate which, as is known, slow the further transport of preparations in the gastrointestinal tract (R. Gröning; G. Heung, Int. J. Pharm. 56, 111 (1989)),

c) employ preparations swelling in the stomach (balloon tablets) (Agyilirah et al., Int. J. Pharm. 75, 241 (1991)),

d) employ preparations having a large spatial expansion (EP-A 235 718) or

e) employ bioadhesive preparations which preferably should adhere to the mucous membranes of the gastrointestinal tract (R. Khosla, S.S. Davis, J. Pharm. Pharmacol. 39, 47 (1987)).

Another delayed-release technique makes use of a matrix of hydrophilic polymers and, if appropriate, pharmaceutical excipients in which the active compound is embedded. In an aqueous environment, the polymer swells to give a gel, which then either slowly erodes (together with the poorly soluble active compound) or diffuses through the (readily soluble) active compound. The polymer can by hydrophilic, hydrophobic or mixed hydrophilic/hydrophobic. At present, matrix tablets are very popular, since they are comparatively inexpensive and highly tolerable and can be produced in conventional equipment.

Another method consists in the use of buffered or pH-sensitive coatings which allow controlled release in certain sections of the gastrointestinal tract.

A technically complicated method consists in the use of osmotic systems (OROS) which function according to the following principle: water penetrates slowly into the tablet through a water-permeable membrane and leads to swelling of a water-swellable ingredient there; the pressure resulting due to the increase in volume drives the active compound out of the tablets through an opening intended for this purpose.

All these techniques have disadvantages, in particular expensive and complicated production methods, inter- and intraindividual variability or dependence of the desired action on the posture.

In the production of delayed-release preparations, care also has to be taken in each case of where the absorption of the active compound can take place: the smaller the

absorption window, the more difficult the production of delayed-release preparations turns out to be. Quinolones such as ciprofloxacin, for example, are mainly absorbed in the upper part of the small intestine (duodenum); absorption in the lower part of the small intestine and in the large intestine is significantly lower (S. Harder et al., Br. J. Clin. Pharmacol. 30, 35-39, (1990)). Therefore the active compound must be released in order to achieve maximum bioavailability before the preparation leaves this absorption window. Moreover, the strong influence of the pH of the surrounding medium on the solubility of quinolone active compounds has to be taken into account; it decreases with increasing pH.

The object of the invention was therefore to make available delayed-release preparations of quinolone antibiotics which guarantee an adequate therapeutic action on administration once daily.

The invention therefore relates to an orally administrable antibiotic matrix preparation comprising quinolone active compound, characterized in that it releases 80% of the active compound both in 0.1 N hydrochloric acid and in acetate buffer at pH 4.5 in the USP XXIV paddle test at 50 revolutions per minute/37°C in the course of 1 to 4 hours. In order to prevent floating up of the tablet during the test, it can be placed in a wire cage, as is described, for example, in the Japanese Pharmacopoeia.

The term "quinolone active compound" in the context of the present invention denotes the class consisting of the substances having a quinolone parent structure which can be used as antiinfectives, in particular the quinolonecarboxylic acids. Preferred quinolone active compounds include ciprofloxacin, olamufloxacin, clinafloxacin, trovafloxacin, cadrofloxacin, alatrofloxacin mesylate, gatifloxacin, rufloxacin, sparfloxacin, levofloxacin, irloxacin, grepafloxacin, moxifloxacin, prulifloxacin, pazufloxacin, gemifloxacin, sitafloxacin, tosulfloxacin, amifloxacin, lomefloxacin, R-lomefloxacin and nitrosoxacin-A. The most preferred quinolone active compound is ciprofloxacin and its hydrates.

The term "quinolone active compound" in the context of the present invention also includes quinolone derivatives which only release the active compound in the body ('prodrugs'), e.g. esters of a quinolonecarboxylic acid.

According to a preferred embodiment, the preparation according to the invention contains as active compound a combination, preferably a mixture, of two different

quinolone derivatives. An example of such an embodiment according to the invention would be a preparation which as active compound contains a mixture of two different quinolone salts.

A preferred embodiment relates to preparations which as active compound contains the mixture of a free quinolone base and its salt. Mixtures of ciprofloxacin hydrochloride and ciprofloxacin betaine are particularly preferred.

Ciprofloxacin hydrochloride is highly soluble, for example, at low pH values; the solubility is significantly decreased, however, at the pH of the intestinal tract (≥ 6.5). However, it has turned out that mixtures of ciprofloxacin hydrochloride and free ciprofloxacin base (betaine) in a weight ratio of 1:20 to 20:1, in particular 1:10 to 10:1, are released from the preparation largely independently of pH (in the pH range from 1 to 4.5). An equivalent effect can also be achieved by using mixtures of other derivatives, e.g. salts, bases or prodrugs of the active compound. Mixtures of stereoisomers in the context of the invention do not come, however, under the term "combination of two different quinolone derivatives", but rather mixtures of hydrate and anhydrate.

A particular embodiment of the preparations according to the invention relates to matrix tablets. Preferred matrix tablets contain a delayed-release part (CR part) and a rapid-release part (IR part). Suitable release-delaying polymers for the matrix are water-swellable polymers, e.g. polysaccharides such as starches and starch derivatives (maize, wheat, rice and potato starch, carboxymethyl starches, sodium starch glycolates), cellulose ethers such as alkylcelluloses, hydroxyalkylcelluloses, carboxyalkylcelluloses and their alkali metal salts (methyl-, hydroxymethyl-, hydroxyethyl-, hydroxypropyl- and sodium carboxymethylcelluloses, crosslinked carboxymethylcelluloses), dextrins, dextran, pectins, polyoses, gum arabic, tragacanth, carrageenan, galactommanans such as guar gum, algin, alginic acid and alginates, polypeptides and proteins such as gelatin and casein, furthermore chitin derivatives such as chitosan, fully synthetic polymers such as (meth)acrylic acid copolymers (methyl methacrylate, hydroxymethyl methacrylate copolymers, polyvinyl alcohol, uncrosslinked polyvinylpyrrolidone and vinylpyrrolidone copolymers, and mixtures of the compounds mentioned. Since the water-swellable polymers form gels in the presence of water, they can also be called "gel-forming polymers".

Highly viscous polymers are often used for delayed-release preparations. In the present invention, it has been found, however, that low-viscosity polymers positively effect the release behaviour of the preparations. In principle, all hydrophilic polymers of low viscosity can be used for the purpose of delaying release. The term "low-viscosity" in the context of the present invention means an (apparent) viscosity of 5 to 400 mPa·s (cP), preferably of at most 75 cP, in particular of at most 50 cP, measured using a rotary viscometer as a 2% strength by weight aqueous solution at 20°C.

Hydroxypropylmethylcellulose (HPMC) is particularly preferred. HPMC of USP XXIV Specification 2910, i.e. having a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight, e.g. Metolose® 60 SH (Shinetsu, Japan) is especially preferred. The desired degree of delay of the preparation can be adjusted by choice of viscosity and amount of HPMC.

Preferred HPMC has a viscosity of 5 to 400 cP, preferably of at most 75 cP, in particular of at most 50 cP (in each case measured using a rotary viscometer as a 2% strength by weight aqueous solution at 20°C).

The content of the hydrophilic polymer, preferably of the HPMC, can vary within wide limits. Preferably, however, 1 part by weight of hydrophilic polymer per 2 to 20, preferably per 5 to 15, parts by weight of active compound is employed.

In order to guarantee the release of the active compound from the dose form even in the small intestine and to keep the pH of the external layer and the environment of the preparation in the acidic range and thereby to prevent as largely as possible the risk of the precipitation of the active compound in the higher pH of the intestinal fluid, an organic acid can be incorporated into the preparation (if present, preferably in the delayed-release part); in this way, the active compound is prepared in a form which is more accessible for absorption. For this purpose, preferred organic acids have 2 to 10 C atoms and 1 to 4 carboxyl groups, for example acetic acid, malonic acid, succinic acid, fumaric acid, tartaric acid and citric acid.

Besides active compound, hydrophilic release-delaying polymer and, if appropriate, organic acid, the preparations according to the invention can also contain disintegrants, e.g. crosslinked polyvinylpyrrolidone such as ®Kollidon CL, glidants, e.g. colloidal silica such as ®Aerosil, hydrogenated vegetable oils, stearic acid, talc or

mixtures thereof, lubricants, e.g. magnesium stearate, and also, if appropriate, other excipients. Both glidants and lubricants are preferably incorporated into the granules before the tabletting phase.

The tablets can then be coated in order, if appropriate, to mask a bitter taste of the active compound, to protect the active compound from the effect of light and/or in order to make the tablets aesthetically more pleasing. The coating can be carried out, for example, by spraying on an aqueous suspension of: film formers, e.g. HPMC, plasticizers, e.g. polyethylene glycol, and light-scattering and light-absorbing pigments, e.g. titanium dioxide. To dry off the water, hot air can be directed at the tablet bed during the coating.

Delayed-release preparations can be prepared using the components described. Besides the delayed-release part (CR part), a rapid-release part (IR part) can also be employed in order to obtain a rapid influx and a higher plasma level. Rapid-release (IR) preparations are understood in the context of the present invention as meaning those which release the active compound according to USP XXIV paddle method as rapidly as desired, preferably within 3 minutes to less than 60 minutes. The rapid release can be controlled within certain limits by variation of the composition, e.g. by variation of the disintegrant content, or by the production parameters. Rapid-release parts of the preparation according to the invention do not unconditionally have to contain two different quinolone derivatives.

It is thus possible to produce combination preparations which in a single-unit dose form contain preparations having different release profiles: thus preparations having a different release profile can be used in order to control the plasma level exactly timewise. "Combination preparations" within the meaning of the invention are understood as meaning not only single-unit dose forms ('fixed combinations') and combination packs, which separately of one another each contain a preparation having a different release profile (kit of parts), but also IR or CR parts which are administered simultaneously or at different times, provided they are employed for the treatment or prophylaxis of the same disease.

The present invention thus also relates to a combination preparation which has a rapid-release part and a delayed-release part, e.g. in the form of a two-layer tablet.

The rapid-release part can contain quinolone active compound (e.g. ciprofloxacin hydrochloride and ciprofloxacin betaine), disintegrant (e.g. crosslinked polyvinylpyrrolidone such as Kollidon® CL), glidants (colloidal silica, e.g. Aerosil®) and lubricants (e.g. magnesium stearate) and, if appropriate, organic acid or other excipients. The delayed-release parts can contain active compound (ciprofloxacin hydrochloride and ciprofloxacin betaine), the release-delaying polymer (e.g. HPMC of low viscosity), organic acid (e.g. succinic acid), a glidant (e.g. colloidal silica) and a lubricant (e.g. magnesium stearate) and, if appropriate, further excipients. The starting materials for the rapid-release and the delayed-release part can be granulated before tabletting (e.g. using wet or dry granulation techniques). The granules can be mixed with glidants and lubricants, and the compressible (ready-to-compress) granules of the two layers can be tabletted (e.g. with the use of conventional two-layer tabletting machines) to give two-layer tablets. Some of the glidant could also be granulated.

Since the addition of an organic acid increases the release rate of the active compound, in particular of ciprofloxacin hydrochloride and betaine, it may also be recommended to admix organic acid to the IR part.

The delayed-release preparations according to the invention expediently contain 500 to 1 000 mg of active compound, calculated as betaine, per single-unit dose form. "Single-unit dose forms" are understood as meaning those preparations which are administered as an individual dose, e.g. tablets, coated tablets or capsules.

For the production of delayed-release preparations according to the invention having an IR and CR part, it is possible to use, for example, the following process: for the production of the IR part the active compound (preferably as a mixture of two derivatives) is mixed with disintegrant, in particular Kollidon CL, and granulated and mixed with glidant, in particular aerosol, and lubricant, in particular magnesium stearate, in order to obtain compactable (ready-to-compress) IR granules.
For the delayed-release part, the active compound (as a mixture of two derivatives) is mixed with acid, e.g. succinic acid, and gel-forming polymer, in particular HPMC, and granulated. These CR granules are mixed with glidant, in particular Aerosil®, and lubricant, in particular magnesium stearate, in order to obtain compressible (ready-to-compress) CR granules. The (ready-to-compress) CR granules and the IR granules are tabletted using a conventional two-layer tabletting machine to give a two-layer tablet. The tablet obtained can then be coated.

The following working examples are intended to explain the subject of the invention with the aid of two-layer tablets, but without restricting it thereto.

Examples

Example 1

Amount in mg	Substances employed
366.70	Ciprofloxacin hydrochloride
41.70	Ciprofloxacin betaine
46.700	Kollidon CL**
4.30	Aerosil 200***
4.70	Magnesium stearate
464.10	*Subtotal IR part*
302.70	Ciprofloxacin hydrochloride
464.30	Ciprofloxacin betaine
125.40	Succinic acid
103.10	Hydroxypropylmethylcellulose 50 cP*
5.20	Aerosil 200***
9.30	Magnesium stearate
1 010.00	*Subtotal CR part*
18.00	Hydroxypropylmethylcellulose 15 cP*
6.00	Titanium dioxide
6.00	Polyethylene glycol 400****
30.00	*Coating sub-total*
23 × 9.5 mm	Oblong tablet

* Viscosity, in each case measured as a 2% strength by weight aqueous solution at 20°C

** Crosslinked polyvinylpyrrolidone

*** Colloidal silica, specific surface area 200 m^2/g

**** The numerical information relates to the average molecular weight

Example 2

Amount in mg	Substances employed
183.40	Ciprofloxacin hydrochloride
20.90	Ciprofloxacin betaine
22.30	Kollidon CL
2.30	Magnesium stearate
1.10	Aerosil 200
230.00	*Subtotal IR part*
151.40	Ciprofloxacin hydrochloride
232.10	Ciprofloxacin betaine
64.00	Succinic acid
52.30	Hydroxypropylmethylcellulose 15 cP
7.60	Magnesium stearate
2.60	Aerosil 200
510.00	*Subtotal CR part*
12.00	Hydroxypropylmethylcellulose 15 cP
4.00	Polyethylene glycol 400
4.00	Titanium dioxide
20.00	*Coating sub-total*
19 × 8 mm	Oblong tablet

Example 3

Amount in mg	Substances employed
183.40	Ciprofloxacin hydrochloride
20.90	Ciprofloxacin betaine
22.30	Kollidon CL
2.30	Magnesium stearate
1.10	Aerosil 200
230.00	*Subtotal IR part*
151.40	Ciprofloxacin hydrochloride
232.10	Ciprofloxacin betaine
65.10	Succinic acid
73.00	Hydroxypropylmethylcellulose 15 cP
10.70	Magnesium stearate
2.70	Aerosil 200
535.00	*Subtotal CR part*
12.00	Hydroxypropylmethylcellulose 15 cP
4.00	Polyethylene glycol 3350
4.00	Titanium dioxide
20.00	*Coating sub-total*
19 × 8 mm	Oblong tablet

Example 4

Amount in mg	Substances employed
183.40	Ciprofloxacin hydrochloride
20.90	Ciprofloxacin betaine
22.30	Kollidon CL
2.30	Magnesium stearate
1.10	Aerosil 200
230.00	*Subtotal IR part*
151.40	Ciprofloxacin hydrochloride
232.10	Ciprofloxacin betaine
64.00	Succinic acid
72.00	Hydroxypropylmethylcellulose 50 cP
7.90	Magnesium stearate
2.60	Aerosil 200
530.00	*Subtotal CR part*
12.00	Hydroxypropylmethylcellulose 15 cP
4.00	Polyethylene glycol 400
4.00	Titanium dioxide
20.00	*Coating sub-total*
19 × 8 mm	Oblong tablet

Example 5

Amount in mg	Substances employed
262.00	Ciprofloxacin hydrochloride
29.80	Ciprofloxacin betaine
8.90	Succinic acid
42.20	Kollidon CL
1.80	Aerosil 200
5.30	Magnesium stearate
350.00	*Subtotal IR part*
116.40	Ciprofloxacin hydrochloride
178.50	Ciprofloxacin betaine
134.00	Succinic acid
87.80	Hydroxypropylmethylcellulose 15 cP
2.70	Aerosil 200
10.60	Magnesium stearate
530.00	*Subtotal CR part*
12.00	Hydroxypropylmethylcellulose 15 cP
4.00	Polyethylene glycol 400
4.00	Titanium dioxide
20.00	*Coating sub-total*
19 × 8 mm	Oblong tablet

Example 6

Amount in mg	Substances employed
183.40	Ciprofloxacin hydrochloride
20.90	Ciprofloxacin betaine
6.20	Succinic acid
24.70	Kollidon CL
1.20	Aerosil 200
3.60	Magnesium stearate
240.00	*Subtotal IR part*
151.40	Ciprofloxacin hydrochloride
232.10	Ciprofloxacin betaine
174.00	Succinic acid
95.70	Hydroxypropylmethylcellulose 15 cP
3.40	Aerosil 200
13.40	Magnesium stearate
670.00	*Subtotal CR part*
12.00	Hydroxypropylmethylcellulose 15 cP
4.00	Polyethylene glycol 400
4.00	Titanium dioxide
20.00	*Coating sub-total*
19 × 8 mm	Oblong tablet

Example 7

Amount in mg	Substances employed
366.70	Ciprofloxacin hydrochloride
41.70	Ciprofloxacin betaine
46.60	Kollidon CL
4.70	Magnesium stearate
2.30	Aerosil 200
462.00	*Subtotal IR part*
302.70	Ciprofloxacin hydrochloride
464.30	Ciprofloxacin betaine
125.30	Succinic acid
103.00	Hydroxypropylmethylcellulose 15 cP
20.50	Magnesium stearate
5.20	Aerosil 200
1 021.00	*Subtotal CR part*
18.00	Hydroxypropylmethylcellulose 15 cP
6.00	Polyethylene glycol 3350
6.00	Titanium dioxide
30.00	*Coating sub-total*
23 × 9.5 mm	Oblong tablet

Comparative Example A

Amount in mg	**Substances employed**
357.00	Ciprofloxacin betaine
58.00	Kollidon CL
6.00	Magnesium stearate
4.00	Aerosil 200
425.00	*Subtotal IR part*
833.00	Ciprofloxacin betaine
108.00	Succinic acid
108.00	Hydroxypropylmethylcellulose 50 cP
16.00	Magnesium stearate
10.00	Aerosil 200
1 075.00	*Subtotal CR part*
18.00	Hydroxypropylmethylcellulose 15 cP
6.00	Polyethylene glycol 400
6.00	Titanium dioxide
30.00	*Coating sub-total*
23 × 9.5 mm	Oblong tablet

Comparative Example B

Amount in mg	Substances employed
357.00	Ciprofloxacin betaine
58.00	Kollidon CL
6.00	Magnesium stearate
4.00	Aerosil 200
425.00	*Subtotal IR part*
833.00	Ciprofloxacin betaine
108.00	Succinic acid
108.00	Hydroxypropylmethylcellulose 3 cP
16.00	Magnesium stearate
10.00	Aerosil 200
1 075.00	*Subtotal CR part*
18.00	Hydroxypropylmethylcellulose 15 cP
6.00	Polyethylene glycol 400
6.00	Titanium dioxide
30.00	*Coating sub-total*
23 × 9.5 mm	Oblong tablet

In 0.1N HCl solution or acetate buffer at pH 4.5, the preparations according to the invention of Examples 1 to 7 show largely pH-independent release in conventional release apparatuses (USP paddle test), while the preparations of Comparative Examples A and B show strong pH dependence.

Patent Claims

1. Orally administrable antibiotic matrix preparation comprising quinolone active compound, characterized in that it releases 80% of the active compound both in 0.1 N hydrochloric acid and in acetate buffer at pH 4.5 in the USP XXIV paddle test at 50 revolutions per minute/37°C in the course of 1 to 4 hours.

2. Orally administrable preparation comprising a quinolone antibiotic, characterized in that it contains a mixture of

   a) gel-forming polymer of a viscosity of 5 to 400 cP, measured as a 2% strength by weight aqueous solution at 20°C, and

   b) a mixture of at least two derivatives of the quinolone antibiotic.

3. Orally administrable preparation comprising a quinolone antibiotic, characterized in that it contains a mixture of

   a) water-swellable polymer and

   b) a mixture of at least two derivatives of the quinolone antibiotic.

4. Preparation according to Claims 1 to 3, characterized in that it contains, as a mixture of two derivatives of the quinolone antibiotic, a mixture of a salt with the free base.

5. Preparation according to Claims 1 to 4, characterized in that it contains, as a mixture of two derivatives of the quinolone antibiotic, a mixture of two salts.

6. Preparation according to Claims 1 to 5, characterized in that the quinolone antibiotic is ciprofloxacin.

7. Preparation according to Claims 1 to 6, characterized in that the two derivatives are ciprofloxacin hydrochloride and ciprofloxacin betaine.

8. Preparation according to Claims 1 to 7, characterized in that the gel-forming polymer is hydroxypropylmethylcellulose of a viscosity of at most 75 cP, measured as a 2% strength by weight aqueous solution at 20°C.

9. Preparation according to Claims 1 to 8, characterized in that the hydroxypropylmethylcellulose has a viscosity of at most 50 cP, measured as a 2% strength by weight aqueous solution at 20°C.

10. Preparation according to Claims 1 to 9, characterized in that the preparation is a combination preparation comprising a rapid-release (IR) part and a delayed release (CR) part.

11. Preparation according to Claims 1 to 10, characterized in that it contains 2 to 20 parts by weight of active compound mixture per part by weight of hydroxypropylmethylcellulose.

12. Process for the production of a preparation according to Claims 1 to 11, according to which
one part of the active compound is mixed with disintegrant, granulated and mixed with glidant and lubricant (IR part), and
another part of the active compound is mixed with acid and hydroxypropylmethylcellulose, granulated and mixed with glidant and lubricant (CR part),
and IR part and CR part are tabletted to give combination tablets and the resulting tablets are coated.