

geously this coating should retain the acid being present in the core as long as the formation of the propiverine acid ionpair has completely finished. If the coating prematurely solubilises or if it leaks too much, the gastric fluid always being present in a large excess penetrates into the interior of the particles and neutralises the acid being present there. Thus, because of the low solubility of the propiverine in the pH range of the gastric fluid practically no active agent can be dissolved and diffuse from the particles. The acid being present in the interior of the particles lowers the pH value of the penetrating intestinal fluid, and then forms the corresponding ionpair. After that the solution of the propiverine acid ionpair being formed in the interior diffuses through the membrane into the intestine. Although unfavourable pH conditions are again dominating here, obviously over-saturation phenomena occur, ensuring a sufficient resorption of the per se hardly soluble active agent. Naturally the acid being present in the particles is furthermore reduced during the course of the release so that actually a strong decrease in the diffusing amount or in the release of propiverine should occur. In order to avoid the latter the retardation coating controlling the release rate should preferably be "partially soluble" in the gastric fluid. The term "partially soluble" has to be understood in the meaning of a certain permeability or as a diffusion resistance, respectively. Further, said retardation coating should additionally guarantee that in the interior of the particles acidic pH conditions are always predominating and optionally occurring pH deviations caused by food influences or by other influences are adjusted.

Even small deviations in the ratio of Eudragit® RS/Eudragit® RL/Eudragit® S lead to drastic changes of the release profiles. If the ratio of Eudragit® RS/Eudragit® RL/Eudragit® S of 2:1:2 purely found by chance is slightly changed to a ratio of 1.5:1:2.5 (Example 9) this reduction of the intestinal fluid insoluble component with low permeability (Eudragit® RS) and the increased portion of the intestinal fluid soluble material (Eudragit® S) leads to a faster release of the active agent or to a heavy diffusion of the acidic component, respectively.

This effect may be explained as follows: Since the gastric fluid insoluble, intestinal fluid soluble material of this coating is dissolved in the intestinal fluid after a certain residence time of the particles in the intestinal fluid, a too heavy release in the upper intestinal tract is effectively suppressed with a ratio of Eudragit® RS/Eudragit® L/Eudragit® S of 2:1:2, and the release of the active agent is completely shifted to the medium and lower intestinal tracts. Thus, said retardation coating reduces the particularly rapid resorption in the upper intestinal tract without reducing the total release of the active agent from the particles. This leads indisputably to a prolongation of the release of the active agent.

In order to obtain a gastric fluid resistance and not too high initial release values in the following or to further modify the release characteristics, respectively, it is common practice in the art to apply further retardation coating with gastric fluid insoluble and intestinal fluid soluble materials, for example Eudragit® L or Eudragit® S, respectively.

Furthermore the retardation coatings used according to the invention may contain typical adjuvants, like for example plasticisers, wetting agents and anti-adhesive agents. Examples for suitable pharmacologically secure plasticisers are glycerine triacetate, polyethyleneglycols and citric acid esters, like triethylcitrate. The application of retardation coatings onto the active agent containing particles may be done with methods known per se, for example in a rapidly rotating vessel or by spraying the lacquers in fluidised bed processes.

The subsequent drying of the pellets in order to remove the residual solvents originating from the suspension is known from the prior art.

The retarded particles obtained which may be in the form of retarded pellets, granules or compacted particles may be filled into capsules or sachets, preferably hard gelatine capsules, as desired. It is possible to blend particles having different delay levels and to optionally also add non-delayed particles of the active agent as a so-called starting dose. The retarded particles may, however, be compacted together with tableting adjuvants, like cellulose, lactose, magnesiumstearate and the like, into tablets. This is in particular possible with retarded particles having a diameter below 1 mm without substantially damaging the retardation coatings. Such a table decomposes in less than 1 minute and releases the propiverine retarding particles in their inventive form—like the hard gelatine capsule does.

A further preferred embodiment of so-called multiple-unit formulations are granules and compact particles containing one or more acidic substances apart from propiverine or one salt thereof which are not embedded in a retarding matrix, but which only include this mixture together with one or more controlled release coatings, and which are subsequently compacted into tablets.

These so-called spheroid tablet formulations are produced in that propiverine or one of the pharmaceutically acceptable salts thereof in the inventive molar ratio with one or several acidic substances is compacted under strong pressure together with spheronising agents, like for example lactose, microcrystalline cellulose, hydroxypropylcellulose, with lubricating agents, like for example magnesiumstearate, and with further adjuvants, like for example polyvinylpyrrolidone, in a microcrystalline form, for example with a particle size of less than 0.25 mm, and is then once again broken and screened to a particle size of, for example, 0.5-1.5 mm, the fine fraction is once again compacted and these technological steps are repeated as long as the total mixture of the granular particles have been transferred into the desired size.

Such granular particles may, however, also be produced by other methods, for example by extrusion/spheronisation, apart from the compacting method described.

In the following the granular particles are coated with generally known gastric fluid insoluble and intestinal fluid soluble and/or gastric fluid insoluble and intestinal fluid insoluble retarded agents, like for example Eudragit® NE, Eudragit® L etc. Generally known tableting adjuvants, like microcrystalline cellulose, crospovidone, polyvinylpyrrolidone, magnesiumstearate etc., are added, the total blend is thoroughly mixed and pressed into tablets. Furthermore the thus produced tablets can be coated with suitable coatings, which may be release modifying. Even in this case the retardation layers guarantee the formation of a propiverine acid ionpair and its controlled diffusion. Since the inventive formulations decompose in less than 5 minutes and thereby release hundreds of retarded propiverine acid particles the decomposition time does not have any influence on the release behaviour.

In contrast to the so-called multiple-unit formulations based on pellets or spheroid particles, retarded preparations of propiverine may also be produced in any other way, for example as single-unit formulation.

In particular suitable release characteristics may be achieved by matrix retardation, for example by means of a matrix tablet.

Preferably, however, also in this embodiment one of the already mentioned acidic substances is used and the acidic substance as well as the active agent is embedded in the