The invention relates to a method for the production of carrier pellets for pharmaceutical active substances. Likewise, the invention relates to such carrier pellets and also to pharmaceutical formulations containing these. The carrier pellets according to the invention are used for transporting and releasing pharmaceutical active substances, in particular in the human body.
CARRIER PELLETS, METHOD FOR PRODUCTION THEREOF AND USE THEREOF


[0002] The invention relates to a method for the production of earlier pellets for pharmaceutical active substances. Likewise, the invention relates to such carrier pellets and also to pharmaceutical formulations containing these. The earlier pellets according to the invention are used for transporting and releasing pharmaceutical active substances, in particular in the human body.

[0003] Pharmaceutical administration forms which can be applied in particular orally are intended to be formulated suitably for the respective application in order to effect release of the pharmaceutical active substances at the connect time and without disturbing side-effects. Thus active substances which can be administered for example orally are intended to be released as far as possible such that an unpleasant, e.g. bitter, taste in the mouth is avoided since this can lead to reactions of repulsion in particular in children. On the other hand, the active substances must be released in the stomach or intestine as completely as possible and in a rapidly absorbable form if a systemic treatment is sought.

[0004] In the case of oral administration of drugs, the active substance is released in the gastrointestinal tract and a part of the active substance is absorbed. By controlling the release of the active substance, the degree of absorption and the effective duration can be influenced. Correspondingly, various proposals have been made for controlling release of the active substance by suitable galenic formulations of the active substance.

[0005] One approach resides in providing administration forms with coatings, release of the active substance being able to be influenced as a function of the solubility or permeability of the coatings. Such coatings can be applied for example on tablets or capsules. In this case, a disadvantage exists however in that a faulty or damaged coating can lead to the fact that the release of the total active substance dose is not controlled in the desired manner.

[0006] There are possible, as an alternative, multiparticulate administration forms in which the total quantity of the active substance is apportioned to a larger number of smaller units, such as pellets. If the individual pellets are provided with coatings, then, in the case of a faulty coating in one pellet, only a correspondingly small proportion of the total active substance dose is not subjected to the desired release.

[0007] A further advantage of such administration forms based on pellets resides in the fact that sufficiently small pellets pass into the intestine from the stomach relatively rapidly after ingestion. On the other hand, tablets, as long as they do not disintegrate, can also remain in the stomach for a fairly long time, the time in addition being very variable.

[0008] Known administration forms with controlled release are hence not entirely satisfactory. In addition, the problem exists that desired (prescribed) release profiles generally cannot be set. Furthermore, the production of administr-
Preferably water or organic solvents are used as solvents or emulsifiers. As organic solvents, particularly preferred are ethyl alcohol, isopropanol, n-propanol or mixtures thereof.

The quantity ratio of pH regulator to binder in the liquid formulation is preferably in the range of 50:50 to 99:1. A preferred liquid formulation has 30 to 80% by weight of the at least one pH regulator, 0.5 to 5% by weight of the at least one binder and 15 to 69.5% by weight of the at least one solvent.

The spray granulation can be effected both in a fluidised bed unit and in a spouted bed unit. The temperature in these units is thereby preferably in the range of 5 to 100°C. The drying gas flow entering the coating unit has, at the entrance into the unit, preferably a temperature in the range of 5 to 120°C. There are possible as drying gas, its particular conditioned air, nitrogen or inert gases, e.g. noble gases.

If the spray granulation is effected in a fluidised bed unit, the drying gas is supplied via a sieve plate. At the same time, the liquid formulation is introduced into the unit by nozzles disposed above the sieve plate.

If the spray granulation is effected in a spouted bed unit, then the drying gas is supplied through longitudinal gaps situated on the bottom. The liquid formulation is introduced via at least one nozzle disposed between the longitudinal gaps.

Preferably, introduction of the liquid formulation is effected through the nozzle from below to above.

According to the invention, likewise carrier pellets which contain at least one physiologically well-tolerated pH regulator are provided. These carrier pellets are produced according to the above-described method.

The carrier pellets preferably have a diameter in the range of 50 μm to 1.5 mm, in particular of 90 μm to 1.2 mm.

The carrier pellets are thereby preferably essentially spherical. The carrier pellets preferably have a sphericity of 0.8 to 1.0, in particular of 0.9 to 1.0.

The sphericity is thereby calculated according to the following formula:

\[
SPHT = \frac{4\pi A}{U^2}
\]

with \(A\) = surface area and \(U\) = circumference.

The sphericity can be implemented with devices for particle size- and particle shape analysis with dynamic image analysis. A device suitable for this purpose is for example the CAMSIZER by Retsch Technology.

Furthermore, it is preferred that the ratio of width to length of the carrier pellets is in the range of 0.8 to 1.0, in particular of 0.9 to 1.0. The ratio of width to length is thereby calculated according to the following formula:

\[
h/l = \frac{\min(x_C)}{\max(x_C)}
\]

with \(x_C\) = Feret diameter and \(x_C\) = maximum width of the particle.

Also the width-length ratio can be determined for example with the mentioned CAMSIZER.

Preferably, the carrier pellets according to the invention concern dense carrier pellets, which implies a weight reduction relative to extrusion pellets.

The carrier pellets have essentially the same particle size, i.e. a narrow scatter range with respect to the particle size is present.

The carrier pellets preferably contain at least one physiologically well-tolerated binder. This binder is thereby preferably selected from the group comprising methyl celluloses, hydroxymethyl celluloses, hydroxypropylmethyl celluloses, alginites, pectins, polyvinylpyrrolidones, xanthuranes and also other hydrocolloids and also mixtures thereof.

According to the invention, likewise a pharmaceutical formulation is provided, containing the above-described carrier pellets and at least one active substance.

The carrier pellets according to the invention are used as carrier structure for pharmaceutically effective components.

**EXAMPLE 1**

Production of Dicarboxylic Acid Pellets by Means of D/L Malic Acid

1.1 Production of the Spray Solution

The spray solution comprises purified water, methyl cellulose and malic acid. A 4% binder solution is produced from the purified water and methyl cellulose. This is temperature-controlled at 70°C. Thereafter, the addition of malic acid is effected with constant agitation until a complete solution is present (proportion of purified water corresponds to proportion of malic acid).

1.2 Particle Formation

The temperature-controlled spray solution is sprayed into the spouted bed apparatus (ProCell) in the bottom spray method. A constant particle formation is effected by atomising the solids solution in the main airflow. The latter comprises two partial flows which are produced through gap openings, leading along through the process chamber. The particle construction takes place by evaporation of the solvent water, malic acid and methyl cellulose remain in the airflow dried as particles. By means of the defined flow profile of the apparatus, the particles in the upper process chamber separate from the central airflow and flow laterally, caused by gravity and the suction effect of the main airflow, back towards the process gas inlet. There, they are entrained again with the main airflow and coated continuously with solids from the spray solution. The process air is conditioned.

During the continuous introduction of the solids mixture via atomisation, the removal of acidic pellets is effected at the same time. The malic acid pellets are fractionated for the desired particle size.

Undersize particles and prepared oversize particles can thereby be returned to the process. The end product is a homogeneous virtually spherical malic acid particle with a uniform surface structure.

1. A carrier pellet for carrying a pharmaceutically active substance, the carrier pellet comprising at least one physiologically well-tolerated pH regulator, wherein the carrier pellets are produced by the method comprising:

   a) producing a liquid formulation by dissolving, dispersing, or a combination of dissolving and dispersing at least one physiologically well-tolerated pH regulator in at least one solvent or emulsifier;
b) introducing the liquid formulation into a fluidized-bed or spouted-bed unit using at least one nozzle;
c) forming essentially spherical carrier pellets by spray granulation in the unit wherein the solvent is evaporated by a drying gas flow; and
d) discharging the carrier pellets from the unit.
2. The carrier pellet according to claim 1; wherein the carrier pellet has a diameter in the range of 50 μm to 1.5 mm.
3. The carrier pellet according to claim 1; wherein the carrier pellet is essentially spherical.
4. The carrier pellet according to claim 3; wherein the carrier pellet has a sphericity of 0.8 to 1.0.
5. The carrier pellet according to claim 1; wherein the carrier pellet has a width-length ratio of 0.8 to 1.0.
6. The carrier pellet according to claim 1; wherein the carrier pellet is a dense carrier pellet.
7. A combination of carrier pellets comprising:
at two of the carrier pellets according claim 1; wherein at least two of the carrier pellets in the combination have essentially the same size.
8. A pharmaceutical formulation comprising:
one or more carrier pellets according to claim 1; and at least one pharmaceutically active substance.
9. A method of releasing a pharmaceutically active substance, the method comprising:
introducing one or more pharmaceutical formulations according to claim 8 into physiological surroundings, wherein the one or more carrier pellets releases the pharmaceutically active substance into the physiological surroundings.
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