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(54) Title: ACTIVE SUBSTANCE CONTROLLED RELEASE DEVICES AND PROCESS FOR PRODUCING THE SAME

(57) Abrégé/Abstract:
A process for the production of devices for the controlled release of active substances, consisting of an active substance-containing matrix and an erodible mass of solids at least partially covering the matrix, with the thickness of the erodible mass across its extension being determined by thickness gradients, and the active substance-containing matrix itself being produced with thickness gradients which determine the thickness gradients of the erodible mass, is characterized in that in a first step the active substance-containing matrix is formed in the form of pressed articles having thickness gradients, and in a second step It is transferred onto a laminated tablet-compressing machine where it is compressed with the erodible mass.

ABSTRACT

A process for the production of devices for the controlled release of active substances, consisting of an active substance-containing matrix and an erodible mass of solids at least partially covering the matrix, with the thickness of the erodible mass across its extension being determined by thickness gradients, and the active substance-containing matrix itself being produced with thickness gradients which determine the thickness gradients of the erodible mass, is characterized in that in a first step the active substance-containing matrix is formed in the form of pressed articles having thickness gradients, and in a second step it is transferred onto a laminated tablet-compressing machine where it is compressed with the erodible mass.

Active Substance Controlled Release Devices and Process for Producing the Same

SPECIFICATION

The present invention relates to a process for the production of devices for the controlled release of active substances in liquid media; the devices have an active substance-containing matrix and an erodible mass of solids covering the matrix at least partially, the thickness of the mass being determined by gradients.

Devices of this kind serve to release active substances in liquid media, e.g. body fluids, in a controlled manner, i.e. with a given velocity profile. An important field of application of these devices is the peroral administration of drugs. Here the frequent objective is to administer active substances having a short biological half-life in such a manner that even plasma concentrations are maintained connected with a low taking frequency.

In these devices the velocity profile of the active substance release is particularly influenced by the thickness gradients of the erodible mass of solids which covers the active substance-containing matrix at least partially first. In the course of the release a progressive erosion of this mass of solids takes place, causing the contact surface between the active substance-containing matrix and the liquid medium, in which the device is present, to enlarge as a function of its thickness gradients. Through this effect, provided that the thickness gradients have been chosen adequately, a relatively constant release rate – as is frequently desired in sustained-release drugs – can be maintained, for example.

Owing to the novel constructional conception there is no prior art description of possibilities to manufacture devices of this kind. In particular, the problem of combining masses for the formation of an active substance-containing matrix with an erodible mass of solids in a manner by which thickness gradients are formed in the erodible solids mass is not solved in the art. Accordingly, it is the object of the present invention to provide a process for the production of the devices, which offers a solution for this problem and is efficient.

According to the present invention this object is achieved by (a) combining the erodible mass with the active substance-containing matrix after formation of the same or (b) combining and forming the active substance-containing matrix and the erodible mass in one process step.

In this connection, there are several process technological methods which can contribute to the solution of this problem. For instance, tableting which is frequently preferred in pharmaceutical process technology can realize solution (a). To this effect, an active substance-containing pressed article representing the active substance-containing matrix is formed first. Preferably, the shape of this pressed piece is already adjusted to the desired thickness gradients of the erodible solids mass. This is possible in that the pressed article itself contains thickness gradients which tend to be complementary to the thickness gradients of the erodible mass of solids. These pressed articles are transferred to laminated tablet-compressing machines where they are compressed with the erodible mass. The use of mantle-core presses is particularly advantageous for this purpose since, provided that they are constructed accordingly, they are able to transfer the prefabricated pressed pieces automatically and continuously into the die bores in which the second compression cycle takes place.

In particular for large scale manufacture, producing devices of the above-mentioned type according to the process described herein by means of tableting is very economical. However, in case the active substance or other required components of the device cannot be tabletted, as is the case with liquid substances or solid substances having a low melting point, or if tableting is to be omitted for other reasons, forming of the active substance-containing matrix and/or of the erodible mass of solids may be effected by means of an alternative method. When thermoplastic starting materials are used, processes utilizing the thermoplasticity and forming the materials by melting, casting, injecting or extruding are suitable.

According to the present invention it will be preferred in many cases to conduct the process continuously and to form the active substance-containing matrix in the form of a web, tape or rope-shaped body first. Into this material depressions or thickness gradients may be made by stamping or rolling - optionally when still in hot condition. During the subsequent combination with the erodable mass of solids these depressions or thickness gradients substantially influence the thickness gradients of the solids mass. Devices of the above-mentioned type may subsequently be separated by cutting or punching.

Even if the starting materials do not exhibit distinct thermoplastic properties, a similar process is possible according to the present invention. In this case, shaping may also be effected by using a liquid phase, i.e., by processing a solution, a gel, a suspension, or a paste. For instance, supporting films may be coated with solutions and suspensions and web-shaped bodies may be produced by subsequent drying. These are to be finished in correspondence to the bodies formed by thermoplastic shaping. Also, it

is possible to premix powdery materials up to a pasty condition, to obtain the active substance-containing matrix therefrom by extrusion and to conduct further processing as described above.

A process according to the present invention for the production of devices of the above-mentioned type may also include the combination of different process steps. For instance, it may be advantageous to manufacture the active substance-containing matrix by one or several consecutive coating processes first, to emboss depressions by means of stamps and then inject the erodible mass in molten condition into these depressions.

It may be necessary to apply one or several adhesion promoters on the contact surface between the individual components of the device prior to joining the active substance-containing matrix with the erodible mass. The application of the adhesive adjuvants is preferably effected by applying a solution of these substances by means of a coating, spraying or dipping processes.

As an alternative to the above-mentioned embodiments of the process, the active substance-containing matrix and the erodible mass of solids may be formed simultaneously and the combination may be carried out in one process step. This manner of production is in particular suitable when the active substance-containing matrix and the erodible mass of solids may be manufactured by similar processes and under similar process conditions. If, for instance, all components of the device to be manufactured may be produced through thermoplastic shaping at the same or a similar temperature, coextrusion of the components is a preferred process.

Irrespective of the embodiment of the production method, all options described also apply when devices for the controlled release

of active substances are to be manufactured which have more than one active substance-containing matrix and an erodable mass of solids covering these matrices at least partially.

PATENT CLAIMS

1. A process for the production of a device for the controlled release of active substances, consisting of an active substance-containing matrix and an erodible mass of solids at least partially covering the matrix, with the thickness of the erodible mass across its extension being determined by thickness gradients, and the active substance-containing matrix itself being produced with thickness gradients which determine the thickness gradients of the erodible mass, said process comprising the steps of:

   a) pressing the active substance containing matrix into the form of pressed articles having thickness gradients; and
   b) transferring the pressed article to a laminated tablet-compressing machine where it is compressed with the erodible mass.

2. The process according to claim 1, characterized in that the device for the controlled release of active substances is produced with more than one active substance-containing matrix.

3. The process according to any one of claims 1 or 2, characterized in that prior to combination of active substance-containing matrix and erodible mass, a solution of an adhesion promoting auxiliary is applied on the contact surface between the two components.