

PATENT SPECIFICATION

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(54) PREPARATIONS HAVING CONTROLLED RELEASE OF AN ACTIVE COMPONENT

(71) We, AB HASLE, a Swedish Body Corporate of, Fack, S-431 20 Molndal 1, Sweden, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a preparation comprising one or more active components, which may be released in a surrounding medium at a controlled rate during a predetermined period of time.

The present invention is concerned with making a preparation which can provide a constant concentration of an active agent, during a predetermined period of time, in a medium by releasing the agent into the medium, from one or more bodies comprising the agent, at a controlled rate.

The properties of the present invention make it useful especially for preparation of therapeutic preparations intended for oral or local administration. The invention may however be employed to obtain constant release of other active agents, such as pesticides and fertilizers to the surrounding environment.

The most common preparations for drugs are tablets and capsules. This is due to the fact that these preparations are convenient to the patient and that the handling and administration is simple and may be carried out by the patient himself. From ordinary tablets the drug is rapidly released. Such rapid release often leads to an initially highly elevated concentration in the plasma. Drugs which are eliminated relatively rapidly must therefore be administered frequently to avoid reaching concentrations which produce side effects.

In many cases the pharmacological effect of a drug is correlated to a certain concentration thereof in the organism, usually the concentration in blood plasma. Due to this, optimal treatment usually implies that a certain concentration in blood plasma must be maintained, at which

concentration the agent exerts its desired effect without giving side effects. Maintenance of an adequate concentration of a drug in the organism requires that the amount of drug supplied corresponds to the amount eliminated from the organism. To fulfil this simple principle one must have access to a preparation which releases the drug at a constant amount per time unit. In certain cases it may be desirable to obtain a release rate which increases during a period of time.

In the commercially available depot preparations attempts have been made in many different ways to sustain the release of the drug. In this way it is possible to achieve a more even plasma profile, but as the release rate in these known depot preparations decreases with time, a constant level in plasma may never be achieved, which is desirable with many drugs. The depot preparations, which have only one type of release profile are, in many instances, not sufficiently flexible to provide an optimal form of treatment.

From German Offenlegungsschrift 1 767 765 it is known to prepare multi-layer tablets having different concentration of an active substance in the different layers. The procedure disclosed for preparation of said tablets is repeated pressing to increased diameter in tableting machine. That procedure is however very complicated and in reality not useful in rational production of pharmaceuticals. Said procedure further does not make possible preparation of small bodies, such as granules, having decreasing concentration of an active substance. In addition, it is not possible to obtain a continuous concentration gradient in bodies prepared according to the procedure thus known, as a discontinuous layering takes place and the concentration within each layer is constant. Problems and drawbacks with the prior art technique have now surprisingly been substantially overcome through the present invention,

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whereby preparations giving controlled release of an active substance are provided.

The present invention provides a controlled release pharmaceutical or agricultural chemical preparations having a core and an outer layer and containing at least one active component and at least one release-controlling inactive component, which, on disintegration, releases at least one active component at a controlled rate, in which preparation the core comprises active and/or inactive material and the outer layer around the core comprises at least one active component and at least one inactive release-controlling substance and has a concentration of said active component which decreases in a direction outwards from the core, the outer layer having been applied to the core in a coating operation uninterrupted by other process steps. There is thus a negative concentration gradient in the direction outwards in the outer layer of the bodies thus prepared.

A further aspect of the present invention provides a process for producing the preparation of the invention wherein a particle comprising active and/or inactive material is provided with an outer layer having a decreasing concentration of said active component in a direction outwards from the particle, by coating it, in a coating operation uninterrupted by other process steps, with a composition comprising at least one said active component and at least one inactive release-controlling substance, to form a body in which the particle forms a core.

According to a preferred embodiment of the invention the coating operation is carried out by spraying the composition onto the particles. Suitably the concentration is decreased by adding to the composition more of an inactive release controlling substance.

The coating operation must not be interrupted by other processes such as repeated pressings between coatings as in the prior art process discussed above. In that sense it must be a continuous operation but, as is clear from the following description, the outer layer may be applied either continuously or batchwise to achieve the desired result.

The preparations according to the present invention, may release the active component to a surrounding medium at a controlled rate. This rate may be continuously decreasing, continuously increasing or constant during a certain period of time depending on other factors affecting the release.

The active component may, in the case of the pharmaceutical preparations, be a drug (i.e. a therapeutically active component) or in the case of the agricultural preparations

be a pesticide, a herbicide, a growth promoting component for a plant, (i.e. a fertiliser) or an agent having some other effect.

The pharmaceutically active compounds that may employed in preparations according to the present invention are substantially all those which may be used for oral or local administration. Suitably the preparations are in the form of tablets, capsules or granules. In the case of capsules, these will contain a plurality of the preparations of the invention in the form of granules. Other dosage units containing a plurality of such granules are also possible, for example, tablets may be composed of such granules. The invention is especially applicable to compounds which are used in long term therapy, such as psychopharmacological agents, blood-fat reducing compounds, compounds active on heart and blood vessels anti-parkinson-active compounds, digestion-active compounds and compounds in gynaecology and obstetrics.

The preparation according to the invention preferably has an overall size of 0.1 to 15 mm, preferably 0.3 to 2 mm. Its shape may be varied but is preferably spherical.

The preparation is mainly characterized in that the ratio of active substance to other substances increases towards the centre of the body from the surface thereof (see Figs. 1 a—d, in which 1 denotes a core and 2 denotes the outer layer applied thereto). The total concentration of active substances in the body may vary within very wide limits, for example, from 0.01 to 99% by weight. The outer layer may have a continuous or discontinuous concentration gradient depending on which active component is used and which profile of release is desired.

The concentration gradient may also be varied to a great extent. For example, the concentration of active substance at a certain point near the centre of the body may be 100 to 0.1% and it may decrease to around 20—0.01% towards the surface of the body, depending on which active component and which type of release-controlling substance are used.

In Fig. 1a is shown schematically a core consisting of inactive substance, on which is applied a composition comprising an active component with a continuous concentration gradient. Each of Figs. 1 a—d shows a diagram having its origin at the centre of the body, and concentration along the ordinate has been plotted against the radius along the abscissa. The concentration of active component is shown by an uninterrupted line and the concentration of inactive substance is shown by a broken line. In Fig. 1b, a body is shown in which a core

comprising an active component is coated with a composition comprising an active component having a continuous concentration gradient. In Fig. 1c is shown a core of inactive material onto which a composition is applied comprising an active component with discontinuous gradient of concentration. In Fig. 1d is shown a core of active component on which a composition is applied comprising an active component with discontinuous concentration gradient.

The non-active substances which make up part of the preparation have the object of controlling the release rate of the active component. One or more such release controlling substances may make part of the same body. Both water-soluble and water-insoluble substances may thereby be employed. The choice of release-controlling agents depends on the type of active component, the amount thereof, and on the rate of release desired. Preferably lipophilic substances for example, waxes, fatty-acids or their esters or fatty-acid alcohols are used. Examples of such lipophilic substances are stearic acid, glycerylmonostearate, and cetyl alcohol (cetanol). In the same manner polymers such as polyethylene glycols, polyvinylpyrrolidones, polyvinylacetates, acrylates, or methacrylates or cellulose derivatives, such as ethyl cellulose and hydroxypropyl cellulose may be used. In certain cases, water-insoluble dispersible additives, such as talcum or Aerosil (silicic acid) may be used.

The preparation may be built up by one of the usual coating procedures e.g. in a coating pan such as apparatus known as Accela Cota or sprayed in for example a fluid bed apparatus, to form a body. A solution or suspension of the active substance in combination with one or more of the above mentioned auxiliary substances is applied to a core. In this manner an outer layer is built up round the core. Decreasing concentration of the active substance in said outer layer is achieved by variation of the concentration of active agents in the solution applied to the core; this may be by continuous variation to achieve a continuous concentration gradient or by use of at least two different solutions of different concentrations to achieve a discontinuous concentration gradient.

The particle employed as a core may, for example, consist of the active agent alone or mixed with other active or inactive agents. Alternatively, the core may consist of one or more inactive substances, e.g. sugar, lactose or starch. Preparation of the core material may be advantageously be carried out through a normal granulation procedure. The core may also comprise inert materials

such as most plastic materials or other polymers. The size and shape may vary substantially, but preferably spherical granules having a size of at least 0.05 mm, preferably 0.1 to 1 mm are used.

The rate of release of the active agent, besides depending on the conditions of release employed, depends on the solubility of the active agent in the medium employed, the type and amount of release controlling substances and the geometry and dimensions of the bodies. The desired profile of release is obtained through a suitable adjustment of the concentration gradient and a choice of type and amount of release-controlling substance.

In order to direct the release of the active component to a predetermined location, e.g. release in the stomach or to control the release rate, it is further possible to apply a suitable polymer film on the body. This may be done in the ordinary manner in e.g. a coating pan or a fluid bed apparatus.

Suitable polymers to be used in this case are of the type used in the pharmaceutical industry to coat tablets or granules, e.g. cellulose derivatives, derivatives of acrylic or methacrylic acid, and polyvinylacetate.

Suitable softening agents, such as phthalates, may be added to polymers employed.

The following Examples serve to illustrate the invention.

Example 1

500 g granules (diameter 0.5—0.75 mm) constituting core material, and consisting of 50% alprenolol×HCl, 25% lactose and 25% starch are sprayed in a fluid-bed apparatus with an alprenolol-cetanol solution for 75 min. 300 g of each substance alprenolol and cetanol are employed. The starting solution consisting of alprenolol×HCl in methylene chloride/methanol solution is first sprayed during 11 minutes, then the concentration of alprenolol×HCl in the solution is decreased continuously during spraying, by adding cetanol in methylene chloride/methanol solution during the last 64 minutes at a rate of 4.7 g/min. The final size is 0.75—1.0 mm.

According to the so-called beaker method described by Levy, alprenolol is released from the product in water at a temperature of 37°C at the following rate:

0—5 min=4.8%/min
5—10 min=5.2%/min
10—20 min=4.7%/min

The granules obtained may thereafter be coated to control further the release. The above mentioned technique is employed and the following film composition is used:

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Etocel N-10 (ethyl cellulose) 50 g
+ "Citroflex" (Registered Trade Mark) A-4
(acetyltributyl citrate) 10 g.

The release according to the beaker
method is then

1-6 h=0.18%/min
6-9 h=0.14%/min

Example 2

500 g metoprolol tartrate granules
(diameter 0.5-0.75 mm), constituting core
material, are sprayed during 91 minutes in a
fluid-bed apparatus with a solution
consisting of metoprolol tartrate 90 g,
talcum 40 g, Aerosil 10 g, cetanol 10 g and
solvents. Into this solution is dropped during
the 30-89th minute a solution comprising
300 g cetanol at a rate of 5.1 g/min. The size
at final coating is 0.75-1.0 mm.

Release in water according to the beaker
method is 2.3%/min.

Example 3

250 g sugar granules (diameter 0.5-0.7
mm) are sprayed with a solution comprising
250 g alprenolol·HCl in methylene
chloride/methanol. Thereafter the spraying
is continued with a second solution
comprising 160 g cetanol and 40 g
alprenolol·HCl. The granules obtained
are coated with a film consisting of Etocel
N-10 (ethyl cellulose) 50 g and "Citroflex"
(acetyltributyl citrate) 10 g. The size at final
coating is 0.75-1.00 mm.

Release according to the beaker method
is 6.3%/h.

Example 4

250 g of sugar K4 were sprayed with 250 g
of quinidine bisulphate solution in a
fluid-bed apparatus. 500 g of the granules
thus obtained were sprayed in a fluid-bed
apparatus with a quinidine solution
containing 300 g of quinidine bisulphate
during 73 minutes. To this solution was
continuously added during the course of
spraying in the first 56 min. a solution
containing 200 g of cetanol at a rate of 3.6 g
cetanol/min.

Release according to the beaker method
1.8%/min.

Example 5

500 g of alprenolol granules (75%) were
sprayed with a solution comprising 300 g of
alprenolol during 66 min. To this alprenolol
solution was continuously added during the
first 60 minutes a solution comprising 300 g
of cetanol at a rate of 5 g cetanol/min.

The release rate in percent of the
concentration found according to the

beaker method after a specified period of
time was as shown below.

Minutes	%
10	11
20	26
30	38
40	48
50	57
60	66
90	87

In solution, 500 g of the granules
prepared were film coated with a copolymer
of methylmethacrylate and ethylacrylate 60
g and Triacetin 5 g. The release rate in % of
concentration found according to the
beaker method after a specified period of
time was as shown below

hours	%
1	21
2	44
3	58
4	69
5	77
6	83
8	90

Eudragit (Registered Trade Mark) RS is
an acrylic resin (a copolymer of acrylic and
methacrylic acid esters). Citroflex A-4 is an
acetyl tributyl citrate. Triacetin is a glycerol
triacetate.

It is considered especially advantageous
to employ the present invention in
preparation of granules containing
quinidine as an active substance. The best
method according to the present invention,
for preparing such granules is shown in
Example 4 above. It is further considered
advantageous to provide granules thus
prepared with a film coating and to fill them
into gelatine capsules.

WHAT WE CLAIM IS:-

1. In a controlled release, pharmaceutical
or agricultural chemical preparation having
a core and an outer layer and containing at
least one active component and at least one
release-controlling inactive component,
which on disintegration, releases at least
one active component at a controlled rate,
the improvement which comprises
providing around a core of active and/or
inactive material, an outer layer comprising
at least one active component and at least
one inactive release-controlling substance,
in which outer layer the concentration of
said active component decreases in a
direction outwards from the core, the outer
layer having been applied to the core in a

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+ "Citroflex" (Registered Trade Mark) A-4
(acetyltributyl citrate) 10 g.

beaker method after a specified period of
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prepared were film coated with a copolymer
of methylmethacrylate and ethylacrylate 60
g and Triacetin 5 g. The release rate in % of
concentration found according to the
beaker method after a specified period of
time was as shown below

Release in water according to the beaker
method is 2.3%/min.

hours	%
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2	44
3	58
4	69
5	77
6	83
8	90

75

Example 3

250 g sugar granules (diameter 0.5-0.7
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250 g alprenolol x HCl in methylene
chloride/methanol. Thereafter the spraying
is continued with a second solution
comprising 160 g cetanol and 40 g
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are coated with a film consisting of Etocel
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Release according to the beaker method
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containing 300 g of quinidine bisulphate
during 73 minutes. To this solution was
continuously added during the course of
spraying in the first 56 min. a solution
containing 200 g of cetanol at a rate of 3.6 g
cetanol/min.

It is considered especially advantageous
to employ the present invention in
preparation of granules containing
quinidine as an active substance. The best
method according to the present invention,
for preparing such granules is shown in
Example 4 above. It is further considered
advantageous to provide granules thus
prepared with a film coating and to fill them
into gelatine capsules.

Release according to the beaker method
1.8%/min.

Example 5

500 g of alprenolol granules (75%) were
sprayed with a solution comprising 300 g of
alprenolol during 66 min. To this alprenolol
solution was continuously added during the
first 60 minutes a solution comprising 300 g
of cetanol at a rate of 5 g cetanol/min.

The release rate in percent of the
concentration found according to the

WHAT WE CLAIM IS:-

1. In a controlled release, pharmaceutical
or agricultural chemical preparation having
a core and an outer layer and containing at
least one active component and at least one
release-controlling inactive component,
which on disintegration, releases at least
one active component at a controlled rate,
the improvement which comprises
providing around a core of active and/or
inactive material, an outer layer comprising
at least one active component and at least
one inactive release-controlling substance,
in which outer layer the concentration of
said active component decreases in a
direction outwards from the core, the outer
layer having been applied to the core in a

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- coating operation uninterrupted by other process steps.
2. A preparation according to claim 1 wherein the outer layer has a continuous concentration gradient.
3. A preparation according to claim 1 wherein the outer layer has a discontinuous concentration gradient.
4. A preparation according to any one of the preceding claims wherein the inactive, release-controlling substance consists of a substance having lipophilic properties.
5. A preparation according to any one of claims 1 to 3 wherein the inactive release-controlling substance consists of a water-soluble polymer.
6. A preparation according to any one of claims 1 to 3 wherein the inactive release-controlling substance is a water-insoluble dispersible substance.
7. A preparation according to any one of the preceding claims wherein the active component is a therapeutically active component.
8. A preparation according to any one of claims 1 to 6 wherein the active component is a pesticide.
9. A preparation according to any one of claims 1 to 6 wherein the active component is a herbicide.
10. A preparation according to any one of claims 1 to 6 wherein the active component is a growth-promoting component for a plant.
11. A preparation according to any one of the preceding claims wherein the core has a size of at least 0.05 mm.
12. A preparation according to any one of the preceding claims wherein the overall size is 0.1 to 15 mm.
13. A preparation according to claim 12 wherein the size is 0.3 to 2 mm.
14. A preparation according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.
15. A dosage unit comprising a plurality of granules, each granule being a preparation as claimed in any one of the preceding claims.

16. A dosage unit according to claim 15 in the form of a tablet.
17. A dosage unit according to claim 15 in the form of a capsule.
18. A process for producing a preparation as claimed in any one of claims 1 to 14 wherein a particle comprising active and/or inactive material is provided with an outer layer having a decreasing concentration of said active component in a direction outwards from the particle, by coating it, in a coating operation uninterrupted by other process steps, with a composition comprising at least said active component and at least one inactive release-controlling substance, to form a body in which the particle forms a core.
19. A process according to claim 18 wherein the coating operation is carried out by spraying.
20. A process according to claim 18 or 19 wherein the active component is applied by a fluid bed technique.
21. A process according to claim 18 wherein the active component is applied by a coating pan technique.
22. A process according to any one of claims 18 to 21 wherein the concentration of the active component in the coating composition is decreased continuously during the coating operation such that the resulting outer layer has a continuous concentration gradient.
23. A process according to any one of claims 18 to 21 wherein at least two compositions having different concentrations of active component are used in the coating operation such that the outer layer has a discontinuous concentration gradient.
24. A process according to claim 18 substantially as hereinbefore described with reference to any one of the Examples.

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