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PATENTS ACT 1990

PATENT REQUEST : STANDARD PATENT

I/We being the person(s) identified below as the Applicant(s), request the grant of a patent to the person(s) identified below as the Nominated Person(s), for an invention described in the accompanying standard complete specification.

Full application details follow:

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[54] Invention Title:

Process for the preparation of granules of active principles by extrusion

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PROCESS FOR THE PREPARATION OF GRANULES OF ACTIVE PRINCIPLES BY EXTRUSION

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(56) Prior Art Documents
EP 204596
EP 276781
EP 208144

(57) Claim

1. Process for the granulation of an alimentary or therapeutic active principle containing 75% by weight or more of active principle, which comprises extruding a mass of the said active principle in the presence of a meltable binder in an amount such that it permits the passage of the mass through the die.

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COMPLETE SPECIFICATION

643037

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INVENTION TITLE:

Process for the preparation of granules of active principles by extrusion

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

The present invention relates to the preparation of granules of active principles, and more particularly to the preparation of granules of active principles for the feeding or treatment of ruminants.

5 It is known, for example according to US Patents 4,181,708, 4,181,709 and 4,181,710, to prepare granules, suitable for administration to ruminants, composed of a core of active substance and a coating based on a hydrophobic substance and a polymer resistant to the
10 neutral pH of the rumen and degradable at the more acid pH of the abomasum.

The core of these granules, composed of the active principle, is in granular form. It is obtained by dry mixing the active substances and one or more binders, if
15 appropriate with neutralizing agents. The mixture obtained is then wetted by adding 10 to 20 % of water and converted into a pasty mass, which is granulated by extrusion at ambient temperature and converted into spheres. The moist granules are dried in an oven or a fluidised bed.

20 When the moist mass is used as described in the abovementioned patents, the granules obtained after extrusion and conversion into spheres never have a perfectly spherical form after drying but always have surface roughness or irregularities and a high porosity,
25 which make the subsequent coating operation more difficult.

This coating operation is carried out, again in accordance with the abovementioned patents, directly on the granules obtained after drying using a mixture of polymer and hydrophobic substances. This coating mixture is
 5 dissolved in an organic solvent and then spray on the granules.

In order to obtain a correct protection of the active principle, it is necessary to spray at least 25 g of the polymer and fatty acid mixture per 100 g of granulated
 10 active substance, and the coating layer has a thickness of about 150 μm (see Example 1 of US Patent 4,181,710).

The present invention provides a means for avoiding the extrusion of a moist mixture to prepare the cores of active principle. This objective has been achieved by using
 15 as the core containing the active principle which is to be coated a granule prepared by extrusion of a mixture containing a binder in the molten state. This active principle core is obtained by extrusion of a mixture
 75% by weight of more of
 containing the active principle, preferably in the solid
 20 state, and a meltable binder in an amount sufficient to allow passage through a die. This amount is preferably less than 25 % by weight of the granules.

The meltable binder used is preferably a polyethylene wax, a paraffin, an oil or an optionally
 25 hydrogenated animal fat, a fatty acid containing 10 to 32 carbon atoms, or a corresponding ester or alcohol, and very



particularly stearic acid. In fact, the latter has the advantage of being a foodstuffs product and one of the preferred constituents of the coating layer.

In order to prevent exudation of the binder during the extrusion, it is frequently advantageous to add a polymer to the mass, and this polymer is preferably soluble in the binder, such as polymers based on vinylpyridine and styrene, alkylcellulose (ethylcellulose), hydroxyalkylcellulose (hydroxypropylcellulose), polyvinylpyrrolidone or a polyethylene. It is very particularly preferred to use a copolymer based on vinylpyridine and styrene, which also serves as the coating layer, or ethylcellulose.

In order to increase the density of the granule, it is sometimes advantageous to add a filler, especially an inorganic filler (e.g. silica or talc).

The preferred composition by weight for forming the core of the granules is as follows:

20	Active principle	95 to 80 %
	Meltable binder	5 to 20 %
	Polymer less than or equal to	2 %.

An even more preferred composition consists of:

25	Active principle	90 to 84 %
	Meltable binder	10 to 16 %
	Polymer less than or equal to	1 %.

The granules obtained by the process of the invention are in a matrix form, that is to say the active principle particles are joined to one another via the binder, and these particles are thus in the pendulous and
5 funicular state and at the limit of a capillary state (Granulation Sherrington & R. Oliver, Heyden & Son, p. 7-18, 1981).

According to one method of implementation, the mass to be extruded is forced, after heating to above the
10 melting point of the binder, through an extruder fitted with one or more dies having the diameter of the desired final granule. The extruded products at the outlet from the die are cut if necessary by means of a rotary cutter.

Extrusion by the molten route has the advantage
15 over the processes of the prior art of preventing the at least partial solubility of the active principle in water, which solubility tends to modify the behaviour of the mass during extrusion. The conversion of the granules obtained by the process according to the invention to spheres is
20 also facilitated, because the surface of the granule has plasticity characteristics owing to the surface melting of the binder, which characteristics did not exist in the granules obtained by the moist route. The granules obtained
25 have, after conversion into spheres, a regular and smooth surface and thus require a much smaller amount of coating polymer for an equivalent effectiveness.

In comparison with the prior art, which uses moist route processes, the process of the present invention also has the advantage of avoiding the drying operations which lower the density of the granule (1.0 to 1.1 g/ml as compared with 1.2 g/ml for the granules of the present invention) by the formation of microporosity. The increase in density is important because it has been demonstrated that it is advantageous to have a minimum density of 1.2 in order to avoid losses of active principles during mastication.

The moist route process is also highly sensitive to the mixing operation prior to the extrusion, in particular to the temperature and to the mixing time, but the molten route process according to the invention does not have this disadvantage.

The active principles may be amino acids, such as methionine, lysine or its salts, phenylalanine, histidine, arginine, tyrosine and tryptophan, medicaments such as vitamins, antibiotics, and anti-parasitic agents, or proteins.

The granules obtained after conversion into spheres, if necessary, are sieved to preserve a granule distribution of between 200 and 4000 μm and preferably between 500 μm and 2500 μm .

The coating layer, which provides protection in the rumen, is then sprayed in accordance with the technique

described in the abovementioned US patents.

The coating contains at least one element which is chosen from polymers, copolymers or basic mixtures in which the proportion of nitrogen is between 2 and 14 % and the
5 molecular weight is between 50,000 and 500,000.

For the definition of the polymers and copolymers reference will be made to their definition in column 7 of US Patent 4,181,710.

Amongst the copolymers, it is preferred to use the
10 styrene/2-vinylpyridine copolymer (containing 50 to 80 % by weight of 2-vinylpyridine and 20 to 50 % of styrene).

The coating also contains a hydrophobic substance chosen from the fatty acids having 12 to 32 carbon atoms. They are also described in US Patent 4,181,710. The
15 preferred hydrophobic substance is stearic acid.

The preferred coating according to the invention has the following composition by weight:

10-30 % of 2-vinylpyridine/styrene copolymer

70-90 % of stearic acid.

20 The coating mixture containing the copolymer and the hydrophobic substance is dissolved in a halogenated solvent, an alcohol, an ether, a ketone or a mixture of these solvents. It is very particularly advantageous to use an ethanol/1,2-dichloroethane, ethanol/methylene chloride
25 or ethanol/acetone mixture.

The solution of coating mixture is sprayed on the

active principle cores, obtained by the process of the present invention, with the aid of a fluidized bed or any other spraying apparatus. For spraying, it is preferred to use an apparatus known under the name of spray-coating, for example of UNIGLATT type fitted with a WURSTER cell.

The amount of coating agent used, expressed as solids relative to the granule core, is in particular between 10 and 30 %, and preferably between 15 and 25 %, this representing a coating thickness of between 20 and 70 μm for granules having an average diameter of between 500 μm and 1,600 μm .

The present invention is illustrated by the following Examples.

EXAMPLE 1

- 1) Equipment used
- DITO SAMA planetary mixer
- WYSS monoscrew extruder, diameter 35 mm,
- PHARMEX 35 T
- feeding of the extruder via K TRON screw
- variable speed granulator cutter having four flexible blades which rub against the die plate and the axis of which is on the axis of the screw
- WYSS spheroniser, diameter 300 mm, SPHAEROMAT 300

2) Operating conditions

Extrusion: temperature of the double wall 130°C

speed of rotation of the screw 150 rev/min

die: diameter of the orifice 1.5 mm

5 inlet chamfer angle 60°

length of the cylindrical

channel 3.5 mm

total thickness 5 mm

number of orifices 84

10 Feed: delivery from the K-Tron screw adjusted to the
extrusion delivery

Cutting: axial, four-blade rotary cutter

speed of rotation 500 rev/min

Conversion to spheres: temperature of the

15 double wall 120°C

speed of rotation

of the plate 1150 rev/min

3) Preparation of the mixtures

20 The binder is made up of pure stearic acid
(UNICHEMA Prifrac 2981) and ethylcellulose (DOW 100). The
initial mixtures are prepared by stirring for 15 minutes
at ambient temperature by charging one kilo into a
planetary mixer (DITO SAMA). The various constituents,
methionine and binder, are introduced separately.

25 The average extrusion delivery is 6.25 kg/h and
the particle size distribution of the product after

converting to spheres is as follows:

diameter > 1,6 mm	1 %
1.6 > diameter > 1	92 %
diameter < 1 mm	7 %

5 4) Variation in the proportion of binder

The proportion of binder in the final granule is varied between 10 and 11 %, the binder consisting of a (94/6) stearic acid/ethylcellulose mixture. The results are given in Table I.

TABLE I

Proportion of binder % of the granule	11	10	10.5	11
Average extrusion delivery kg/h	6.31	6.45	6.00	6.25
Particle size distribution of the core				
diameter > 1.6 mm	0	28	3	1
1.6 > diameter > 1 mm	90	41	71	92
1 > diameter	9	31	26	7
Density	1.24	1.23	1.22	1.24

5) Variation of the binder composition

The relative proportion of stearic acid relative to ethylcellulose is varied, keeping the proportion of binder at 11 % by weight relative to the methionine. The results are given in Table II.

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TABLE II

Proportion of polymer % of the binder	6	5	4	3	2	1	0
Average extrusion delivery kg/h	6.25	6.38	6.25	6.25	6.00	6.38	6.50
Particle size dis- tribution of the core							
diameter > 1.6 mm	1	1	71	1	12	4	11
1.6 > diameter > 1 mm	92	89	25	86	80	86	82
1 > diameter	7	10	4	13	8	10	7
Density	1.24	1.23	1.23	1.23	1.23	1.23	1.20
Observation					Exudation and fouling of the die		

6) Conversion to spheres

Experiments on conversion to spheres were carried out on methionine granulated with a proportion of 11 % of binder consisting of 95 % of stearic acid and 5 % of ethylcellulose; the results are given in Table III.

TABLE III

Time for conversion to spheres	5 sec	5 min	10 min	14 min
Particle size distribution of the core				
diameter > 1.6 μ m	1	2	2	3
1.6 > diameter > 1 μ m	64	78	79	81
1 > diameter	35	20	19	16
Density	1.22	1.23	1.25	1.25

EXAMPLE 2

Example 1 is repeated using the same equipment, the same operating conditions and the same binder, stearic acid/ethylcellulose in proportions by weight of 94/6, but using several mixtures of methionine and lysine in variable proportions as active material. The results of the experiments are given in Table IV.

TABLE IV

Lysine hydrochloride (g)	59	60	67
Methionine (g)	25.3	25.8	17
Stearic acid (g)	14.7	13.3	15
Ethylcellulose (g)	0.9	0.8	0.9
Die in mm	1.5	1	1.5
Actual density	1.21	1.22	1.21
Particle size distribution			
diameter > 2 mm	23	1	33
1.6 < diameter < 2	22	0	16
1.4 < diameter < 1.6	30	7	23
1.25 < diameter < 1.4	15	36	13
1 < diameter < 1.25	3	8	3
diameter < 1	7	48	2

EXAMPLE 3

Example 1 is repeated changing the nature of the meltable binder. The nature of the compositions which were the subject of extrusion is indicated in Table V. All of the products obtained underwent conversion to spheres without any problem.

TABLE V

Constituents	Fraction by weight			
Lysine.HCl	63.75	63.75	63.75	63.75
Methionine	21.25	21.25	21.25	21.25
Ethylcellulose	1.05	1.05	1.05	1.05
Stearic acid (1)	8.37			
Palmitic acid (1)	5.58			
Glycerol monostearate		13.95		
Glycerol distearate			13.95	
Hydrogenated tallow				13.95

The claims defining the invention are as follows:

1. Process for the granulation of an alimentary or therapeutic active principle containing 75% by weight or more of active principle, which comprises extruding a mass of the said active principle in the presence of a meltable binder in an amount such that it permits the passage of the mass through the die.
2. Process according to claim 1, in which the active principle is a medicament or amino acid for feeding to ruminants.
3. Process according to claim 1, in which the active principle is methionine or lysine hydrochloride.
4. Process according to any one of the preceding claims, in which the meltable binder is a polyethylene wax, a paraffin, an oil or a fat, which may be hydrogenated, a fatty acid having 10 to 32 carbon atoms, or a corresponding ester or alcohol, or a mixture thereof.
5. Process according to claim 4, in which the meltable binder is stearic acid.
6. Process according to any one of the preceding claims, in which a polymer is added in sufficient amount to produce a mass permitting correct passage through the die and not causing exudation phenomena during extrusion.
7. Process according to claim 6, in which the polymer used is a copolymer of styrene with a vinylpyridine, an alkylcellulose, a hydroxyalkylcellulose, a polyvinylpyrrolidone or a polyethylene.
8. Process according to claim 7, in which the polymer is a styrene/vinylpyridine copolymer.
9. Process according to claim 7, in which the polymer is ethylcellulose.
10. A granule consisting of a matrix mixture of 75% by weight or more of one or more amino acids, a meltable binder in an amount of less than 25% by weight and, optionally, a polymer.



11. Granule according to claim 10, consisting of by weight:

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- 95 to 80% of one or more active principles,
- 5 to 20% of meltable binder, and
- at most 2% of polymer.

12. Granule according to claim 11, consisting of by weight:

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- 90 to 84% of one or more active principles,
- 10 to 16% of meltable binder, and
- at most 1% of polymer.

13. Granule according to claim 10, 11 or 12, consisting of a matrix mixture of methionine and/or lysine hydrochloride, stearic acid and styrene/vinylpyridine copolymer.

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14. Granule according to claim 10, 11 or 12, consisting of a matrix mixture of methionine and/or lysine hydrochloride, stearic acid and ethylcellulose.

15. Granule according to any one of claims 10 to 14 having a density of at least 1.2 g/cm³.

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16. Process according to claim 1 substantially as described in any one of the foregoing Examples.

17. A granule according to claim 10 when produced by a process of any of claims 1 to 9 or 16

25 DATED this Twenty Sixth day of AUGUST 1993

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ABSTRACT

PROCESS FOR THE PREPARATION OF GRANULES OF
ACTIVE PRINCIPLES BY EXTRUSION

Granules are obtained by extrusion of a mixture
5 containing an active principle and a meltable binder in an
amount such that it permits the passage of the mixture
through a die. The granules obtained may then be coated
with a polymer permitting their trans-rumen passage
without degradation. After coating, the granules are used
10 for animal feeding of ruminants.

