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"Method for preparing an effervescent granulate comprising iron gluconate, granulate thus obtained and tablets containing the same"

5 The present invention relates to a method for preparing an effervescent granulate comprising ferrous gluconate, to the granulate thus obtained and to tablets containing the same.

Effervescent pharmaceutical forms containing ferrous gluconate are known.

10 So far, the suggested methods for preparing them such as, for example, the method described in patent EP-0 673 644-A, do not solve all the problems associated with the manufacture of effervescent granulates containing divalent iron, since it has been found that, in a number of cases, the granulate does not form and/or the divalent iron has a tendency to become oxidized to trivalent iron.

15 Apparently, these drawbacks are not encountered in processes based on so-called "passivation", such as the process described in European patent EP-B-0 076 340, which involves the thermal treatment at 30-100°C of a mixture in powder or granule form formed from an acid and from an acid carbonate and/or from a carbonate, as effervescent
20 components, in a closed system under vacuum. According to this process, after optionally pretreating the acid at high temperature, it is mixed with the required amount of acid carbonate and/or carbonate and this mixture is then subjected to a treatment under vacuum and at a temperature of from 30 to 100°C, and preferably from 40 to 80°C, at
25 which temperature the mixture is mixed with a polar solvent such as water, methanol, ethanol or mixtures thereof. After this step, the aggregates thus obtained are fragmented into particles of the desired size, the desired additives can be added and the resulting mixture can optionally be converted into tablets. This process is characterized in
30 that, in order to passivate the surface of at least one of the components

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of the reaction and thus to reduce the components to a state of high inertia with respect to the reaction, a precise amount of polar solvent, of up to 7% of the mass considered as mass to be treated, is added to the mixture during the treatment under vacuum. The pressure difference
5 caused by the evolvement of carbon dioxide by means of the addition of solvent during the reaction is set at up to a maximum of 1000 mbar, the volume and mass of carbon dioxide released are determined from this difference in pressure, and the thermal treatment is repeated, after quick drying of the mixture, as many times as necessary to obtain a
10 passivation of the surface as indicated by an appreciable deceleration of the reaction and of the evolvement of gas.

However, it is easy to observe that this process is particularly complicated when it is desired to strictly monitor all of the numerous parameters involved in the reaction and that, when the polar solvent is
15 water, the amount thereof is quite considerable. Moreover, if water is not used, the problem arises of recovering the organic polar solvent used.

The object of the present invention is to develop a process for preparing an effervescent granulate based on ferrous gluconate in
20 which oxidation of the divalent iron and "passivation" of the granulate are substantially prevented. It is thus necessary for this process to involve the smallest possible amount of water and to have few critical parameters, which can easily be kept under control.

According to a first aspect of the present invention, this object is
25 achieved by means of a method for preparing an effervescent granulate comprising ferrous gluconate as pharmacologically active ingredient, and citric acid and sodium bicarbonate as effervescent system, by means of wet granulation in a fluid-bed granulator, characterized in that it comprises the following steps of:

- I. feeding a mixture comprising ferrous gluconate, citric acid and sodium bicarbonate into the said granulator which is simultaneously fed with a flow of air heated to about 70°C and having a moisture content of < 1.0 g/kg;
- 5 II. wetting the said mixture with nebulized water when this mixture has reached a temperature of about 35°C;
- III. evaporating off the nebulizing water, while keeping the temperature of the said mixture substantially constant at 35°C;
- 10 IV. repeating steps II and III until a granulate with the desired features is obtained; and
- V. drying the said granulate with air heated to about 80°C until its moisture content is $\leq 0.5\%$ by weight.

Throughout the present description and the claims

- 15 – the expression "substantially constant" indicates that the temperature is maintained within a narrow range (about $\pm 3^\circ\text{C}$); the reason for this is that it has been found that above 38°C the granulate has a tendency not to form, while below 32°C the water has a tendency to be deposited on the surface of the granulate, thus triggering effervescence;
- 20 – the expression "desired features" of the granulate indicates a residual moisture content of $\leq 0.5\%$; an average particle size of between 100 and 500 μ ; a run-out time of the granulate (100 g) from a glass funnel (walls inclined at 60° and outlet diameter of 9 mm) of < 20 sec., preferably < 18 sec., a tangent of the angle of rest of ≤ 1 ;
- 25 a Carr index of ≤ 20 ; and an apparent specific weight of between 0.7 and 1.0 g/ml.

Preferably, the magnitude of the air flow rate in step I is between 3200 and 3800 m³/hour for each batch of about 265 kg of mixture to be granulated.

The flow rate of nebulized water in step II is preferably between 500 and 2000 ml/min, and even more preferably it is about 1000 ml/min. The pressure of the said flow is, in turn, preferably about 3 atmospheres.

5 Advantageously, the amount of water used for the granulation does not exceed about 2% by weight of the mass to be granulated. This is because using a small amount of water makes it possible to minimize not only any oxidation of the divalent iron, but also the trigger of the effervescence on the surface of the granulate (passivation). Moreover, it
10 is important to note that, according to the present invention, the water is nebulized and evaporated in several steps, such that, under the abovementioned conditions of temperature, flow rate of air and flow rate of water, the maximum quantity of nebulized water in contact with the granulate is not great and does not exceed, in each step, 0.5% by
15 weight of the mass being processed.

The effervescent granulate thus prepared is then mixed in a rotating-body mixer with lubricants such as, for example, L-leucine, and flavourings, and is then used for preparing tablets.

20 Typical features of the mixture thus obtained are, before tableting, as follows:
residual moisture content $\leq 1.0\%$;
run-out (flow) time of the granulate from a glass funnel (walls inclined at 60° and outlet diameter of 9 mm) < 20 sec.;
tangent of the angle of rest ≤ 1 ; and
25 Carr index ≤ 20 .

In a second aspect, the present invention relates to an effervescent granulate comprising from 7 to 35% by weight of ferrous gluconate, from 25 to 45% by weight of citric acid and from 15 to 25% by weight of sodium bicarbonate. Preferably, the said granulate also comprises from

5 to 18% by weight of sorbitol, about 2% by weight of L-leucine and from 5 to 11% by weight of flavourings.

Typically, the ferrous gluconate is in the form of the dihydrate and the citric acid is in anhydrous form.

5 In a third aspect, the present invention relates to a tablet obtained by tableting an effervescent granulate, the said tablet being characterized in that it comprises from 7 to 35% by weight of ferrous gluconate, from 25 to 45% by weight of citric acid, from 15 to 25% by weight of sodium bicarbonate, from 5 to 18% by weight of sorbitol, about 2% by weight of
10 L-leucine and from 5 to 11% by weight of flavourings.

Depending on the content of active principle, the punch used to produce the said tablet will be one with or without reliefs capable of impressing suitable pre-splitting incisions in the form, for example, of a mid-line incision or a T-shaped incision.

15 Typically, the tablet according to the present invention has a hardness of between 90 and 180 N, a force of expulsion from the die < 400 N (which indicates good lubrication), a disintegration time $\leq$ 5 minutes, a divalent iron titre equal to 95-105% of the declared value and a trivalent iron content $\leq$ 1.25% (relative to the content of ferrous
20 gluconate).

The examples which follow are intended to illustrate the present invention without, however, limiting it in any way.

EXAMPLE 1

Effervescent tablet comprising 37.5 mg of iron

25 a) Preparation of the effervescent granulate

A mixture of ferrous gluconate dihydrate (32.50 kg), anhydrous citric acid (119.00 kg), sodium bicarbonate (70.00 kg), sorbitol (50.25 kg) and sodium saccharin (2.25 kg) was screened using a vibrating pneumatic screen with a mesh aperture size of 3 mm.

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The screened mixture was placed in a fluid-bed granulator (1200 litre capacity) and maintained in suspension by means of a stream of dried air (residual moisture content < 1.0 g/kg; temperature = 70°C; throughput = 3000 m³/hour).

5 Once the said mixture reached a temperature of 35°C, granulation was started by means of nebulizing purified water. The said nebulizing was stopped when the temperature fell to about 32°C and restarted when the temperature approached 38°C. These steps were repeated until the granulating water (6 kg) was used up. The
10 nebulizing was carried out by passing the water (throughput of 1 litre/min.) through nebulizer nozzles (1.0 mm in diameter), at a pressure of 3 atmospheres.

The granulate was then dried by means of a flow of air heated to 80°C, until the residual moisture content, measured by the Karl
15 Fischer method, of the granulate was ≤ 0.5%. The granules thus obtained were then cooled and removed from the granulator in an environment with a residual moisture content ≤ 20 g/kg and at a temperature of 21-22°C.

The granulate thus obtained had the following features:

20 Residual moisture content: 0.30%
Average particle size: 213 μ
Flow time^(*): 17 sec.

^(*)The flow time was measured as the run-out time of the granulate (100 g) from a glass funnel with walls inclined at 60° and with an
25 outlet diameter of 9 mm.

Tangent of the angle of rest: 0.686
Carr index: 13.64
Apparent specific weight: 0.909 g/ml

b) Preparation of the mixture before tableting

L-leucine (6.00 kg), lemon flavouring (10.00 kg) and orange flavouring (10.00 kg) were added to the granulate (274.00 kg) obtained as described in point a) above. This mixture was kept stirring in a rotating-body mixer until a uniform mixture was obtained.

5 c) Tabletting

The abovementioned mixture was tabletted using steel punches (force = 50 kN) to form tablets of 3.0 g each.

The tablets thus obtained had the following features:

10	Colour:	green-grey
	Shape:	circular, flat
	Iron content:	37.5 mg
	Residual moisture content:	0.324%
	Hardness:	152.7 N
	Disintegration time:	80 seconds
15	Force of extraction from the die:	200 N
	Divalent iron titre:	100.6%
	Trivalent iron titre:	0.83%

The said tablets were packaged in rooms with a residual moisture content ≤ 20 g/kg and at a temperature of 21-22°C.

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EXAMPLE 2

Effervescent tablet containing 40.0 mg of iron

a) Preparation of the effervescent granulate

The process was performed in a manner similar to that described in Example 1 above, except that the mixture placed in the fluid-bed granulator had the following composition: ferrous gluconate dihydrate (34.75 kg), anhydrous citric acid (119.00 kg), sodium bicarbonate (70.00 kg), sorbitol (48.00 kg) and sodium saccharin (2.25 kg).

The granulate thus obtained had the following features:

25	Residual moisture content:	0.34%
30	Average particle size:	278 μ

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Flow time: 10 sec.
Tangent of the angle of rest: 0.500
Carr index: 19.23
Apparent specific weight: 0.769 g/ml

5 **b) Preparation of the mixture before tableting**

The process was performed as in Example 1 above.

c) Tabletting

The process was performed as in Example 1 above.

The tablets thus obtained had the following features:

10 Colour: green-grey
Shape: circular, flat
Iron content: 40.0 mg
Residual moisture content: 0.270%
Hardness: 128 N
15 Disintegration time: 85 seconds
Force of extraction from the die: 230 N
Divalent iron titre: 99.9%
Trivalent iron titre: 0.10%

EXAMPLE 3

20 **Effervescent tablet containing 75.0 mg of iron**

a) Preparation of the effervescent granulate

The process was performed in a manner similar to that described in Example 1 above, except that the mixture placed in the fluid-bed granulator had the following composition: ferrous gluconate dihydrate
25 (65.00 kg), anhydrous citric acid (98.50 kg), sodium bicarbonate (58.50 kg), sorbitol (38.00 kg) and sodium saccharin (4.00 kg).

The granulate thus obtained had the following features:

Residual moisture content: 0.40%
Average particle size: 331 μ
30 Flow time: 9 sec.

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Tangent of the angle of rest: 0.552
Carr index: 14.62
Apparent specific weight: 0.769 g/ml

b) Preparation of the mixture before tableting

5 L-leucine (6.00 kg), lemon flavouring (15.00 kg) and orange flavouring (15.00 kg) were added to the granulate (264.00 kg) obtained as described in the abovementioned point a).

c) Tableting

10 The process was performed in a manner similar to that in Example 1 above, except that the abovementioned mixture was tableted using a steel punch capable of impressing a mid-line pre-splitting incision on one face.

The tablets thus obtained had the following features:

15 Colour: green-grey
Shape: circular, flat with mid-line pre-splitting incision
Iron content: 75.0 mg
Residual moisture content: 0.301%
Hardness: 100.2 N
Disintegration time: 93 seconds
20 Force of extraction from the die: 210 N
Divalent iron titre: 102.9%
Trivalent iron titre: 0.55%

EXAMPLE 4

Effervescent tablet containing 80.0 mg of iron

25 a) Preparation of the effervescent granulate

The process was performed in a manner similar to that described in Example 1 above, except that the mixture placed in the fluid-bed granulator had the following composition: ferrous gluconate dihydrate (69.50 kg), anhydrous citric acid (98.50 kg), sodium bicarbonate (58.50 kg), sorbitol (33.50 kg) and sodium saccharin (4.00 kg).
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The granulate thus obtained had the following features:

	Residual moisture content:	0.18%
	Average particle size:	286 μ
	Flow time:	6 sec.
5	Tangent of the angle of rest:	0.550
	Carr index:	15.38
	Apparent specific weight:	0.769 g/ml

b) Preparation of the mixture before tableting

10 L-leucine (6.00 kg), lemon flavouring (15.00 kg) and orange flavouring (15.00 kg) were added to the granulate (264.0 kg) obtained as described in the abovementioned point a).

c) Tableting

The process was performed in as in Example 3 above.

The tablets thus obtained had the following features:

15	Colour:	green-grey
	Shape:	circular, flat with mid-line pre-splitting incision
	Iron content:	80.0 mg
	Residual moisture content:	0.459%
	Hardness:	108 N
20	Disintegration time:	90 seconds
	Force of extraction from the die:	200 N
	Divalent iron titre:	100.6%
	Trivalent iron titre:	0.48%

EXAMPLE 5

25 Effervescent tablet containing 112.5 mg of iron

a) Preparation of the effervescent granulate

The process was performed in a manner similar to that described in Example 1 above, except that the mixture placed in the fluid-bed granulator had the following composition: ferrous gluconate dihydrate

(97.50 kg), anhydrous citric acid (89.00 kg), sodium bicarbonate (53.50 kg), sorbitol (20.00 kg) and sodium saccharin (4.00 kg).

The granulate thus obtained had the following features:

	Residual moisture content:	0.34%
5	Average particle size:	280 μ
	Flow time:	6 sec.
	Tangent of the angle of rest:	0.552
	Carr index:	15.33
	Apparent specific weight:	0.909 g/ml

10 b) Preparation of the mixture before tableting

L-leucine (6.00 kg), lemon flavouring (15.00 kg) and orange flavouring (15.00 kg) were added to the granulate (264.00 kg) obtained as described in the abovementioned point a).

c) Tableting

15 The process was performed as in Example 3 above, except that the abovementioned mixture was tableted using a steel punch capable of impressing a T-shaped pre-splitting incision on one face.

The tablets thus obtained had the following features:

	Colour:	green-grey
20	Shape:	circular, flat with T-shaped pre-splitting incision
	Iron content:	112.5 mg
	Residual moisture content:	0.290%
	Hardness:	107 N
	Disintegration time:	120 seconds
25	Force of extraction from the die:	280 N
	Divalent iron titre:	101.0%
	Trivalent iron titre:	0.87%



CLAIMS

1. A method for preparing an effervescent granulate comprising ferrous gluconate as pharmacologically active ingredient, and citric acid and sodium bicarbonate as effervescent system, by means of wet granulation in a fluid-bed granulator, characterized in that it comprises the following steps of:
- I. feeding a mixture comprising ferrous gluconate, citric acid and sodium bicarbonate into the said granulator which is simultaneously fed with a flow of air heated to about 70°C and having a moisture content of < 1.0 g/kg;
- II. wetting the said mixture with nebulized water when this mixture has reached a temperature of about 35°C;
- III. evaporating off the nebulizing water, while keeping the temperature of the said mixture substantially constant at 35°C;
- IV. repeating steps II and III until a granulate with the desired features is obtained; and
- V. drying the said granulate with air heated to about 80°C until its moisture content is $\leq 0.5\%$ by weight.
2. A method according to claim 1, characterized in that, in step I, the magnitude of the air flow rate is between 3200 and 3800 m³/hour for each batch of about 265 kg of mixture to be granulated.
3. A method according to claim 1 or 2, characterized in that, in step II, the flow rate of nebulized water is preferably between 500 and 2000 ml/min.
4. A method according to any one of the preceding claims 1 to 3, characterized in that, in step II, the pressure of the flow of nebulized water is about 3 atmospheres.
5. An effervescent granulate obtained according to any one of the preceding claims 1 to 4, comprising from 7 to 35% by weight of

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ferrous gluconate, from 25 to 45% by weight of citric acid and from 15 to 25% by weight of sodium bicarbonate.

- 5 6. An effervescent granulate according to claim 5, characterized in that it also comprises from 5 to 18% by weight of sorbitol, about 2% by weight of L-leucine and from 5 to 11% by weight of flavourings.
7. A granulate according to claim 5, characterized in that the ferrous gluconate is in the form of the dihydrate.
- 10 8. A tablet obtained by tableting an effervescent granulate which is itself obtained according to any one of the preceding claims 1 to 4, the said tablet comprising from 7 to 35% by weight of ferrous gluconate, from 25 to 45% by weight of citric acid, from 15 to 25% by weight of sodium bicarbonate, from 5 to 18% by weight of sorbitol, about 2% by weight of L-leucine and from 5 to 11% by weight of flavourings.

