METHOD FOR PRODUCING EXTENDED-RELEASE POTASSIUM CITRATE WAX MATRIX TABLET

BACKGROUND OF THE INVENTION

Potassium citrate is used clinically to treat kidney stones by alkalizing the urinary pH and increasing urinary citrate concentration. However, its therapeutic efficacy is limited by its gastrointestinal complications such as irritation and ulcerations. Extended-release tablets of potassium citrate could minimize these side effects and have been shown to lead to sustained elevation of urinary pH and citrate concentration (Pak et al., 1984).

Considerable difficulties have been encountered in the preparation of extended-release matrix tablets containing potassium citrate. Potassium citrate is very soluble in water and the dosage required is very high. The only way to extend the release of potassium citrate tablet while keeping the tablet size acceptable for swallowing is to use a hydrophobic wax matrix, wherein the total amount of inactive ingredients is below 25% w/w.

Mission Pharmacal (San Antonio, TX, USA) sells an extended-release potassium citrate tablet, Urocit-K, in three strengths: 5-meq, 10-meq, and 15-meq tablets. The daily dose of Urocit-K is 30-60 meq, which requires 6-12 tablets of the 5-meq, 3-6 tablets of the 10-meq, and 2-4 tablets of the 15-meq. Urocit-K is a wax matrix tablet containing potassium citrate, carnauba wax as extended-release agent, and magnesium stearate as lubricant.

When the drug content is low, the carnauba wax can be dry mixed with the drug and other inactive ingredients prior to compression. For example, US

4,904,478 teaches an extended-release wax matrix tablet of a highly water-soluble drug, sodium fluoride, wherein the carnauba wax, present at 35-70% w/w of the tablet weight, is dry mixed with the drug and other inactive ingredients prior to compression.

In the case of potassium citrate, because the drug dosage is high, the inactive ingredients including the extended-release agent(s) must be kept below 25% w/w to keep the tablet size acceptable for swallowing. If carnauba wax is used at less than 25% w/w, prior art teaches that the drug and carnauba wax should be heated until the carnauba wax liquefies, as described in Example 1 of US 2008/0131504 A1, to give an acceptable extended-release profile and abrasion. Abrasion is a measure of the durability of the tablet from the time it is compressed, to packaging, and to the time of use.

The process for making extended-release potassium citrate tablet containing carnauba wax is difficult. Heating until the carnauba wax liquefies requires a lot of time and then there is the problem of discharging the molten potassium citrate-carnauba wax mixture from the mixer. The cooled mass is extremely hard; therefore the molten mass must be poured into molds so that the cooled mixture is of appropriate size for feeding into a comminuting machine. There is a need for a simpler process to make extended-release potassium citrate wax matrix tablet.

SUMMARY OF THE INVENTION

We have surprisingly found that extended-release potassium citrate tablets containing carnauba wax can be produced without melting the wax. The potassium citrate-carnauba wax mixture is heated to a temperature below the temperature at which carnauba wax liquefies, and then discharged from the

mixer as granules. The temperature is preferably higher than 55°C, and most preferably higher than 60 °C. The cooled granulate can then be fed directly into a comminuting machine for size reduction. The tablet of this instant invention has the same dissolution profile as prior art tablet produced by totally melting the wax. This instant invention reduces the production time and eliminates the complexities related to melting and cooling the wax.

DETAILED DESCRIPTION OF THE INVENTION

Extended-release potassium citrate tablet must comply with USP 35. Dissolution is performed in 900 ml water, apparatus 2 at 50 rpm, and must comply with the following dissolution specifications:

Table 1 (dissolution, 12 units)

Time	All Units	Average
30 min	30-60%	35-55%
1 hour	45-75%	50-70%
3 hour	$\geq$ 75%	$\geq$ 80%

Abrasion was measured in an Erweka TAR20. Briefly, ten tablets were placed inside a baffled 190 mm ID drum. The drum was rotated at 25 rpm for 4 minutes. The difference in the total tablet weight before and after rotating the drum divided by the initial tablet weight is the abrasion. The desired abrasion for extended-release potassium citrate tablet is not more than 1.5%.

COMPARATIVE EXAMPLE 1

10-meq tablets of Urocit-K (Mission Pharmacal, lot 9L038) were purchased. The tablet hardness was 9 kp, and abrasion was 0.3%. The dissolution was performed according to USP 35. The result is as follows:

Table 2 (dissolution, 12 units)

Time	Range	Average
30 min	43.6-47.6 %	45.2 %
1 hour	57.9-61.1 %	60.4 %
3 hour	87.9-97.4%	91.7 %

The product complies with the USP 35 requirement for extended-release potassium citrate tablet.

EXAMPLE 2

A 10-meq tablet was prepared by dry mixing potassium citrate and carnauba wax. The formulation is given in Table 3.

Table 3

Ingredient	mg/tablet	% w/w
Tripotassium citrate monohydrate	1080	85
Carnauba wax	177	14
Magnesium stearate	13	1

Potassium citrate was sieved through mesh 18, and then mixed with carnauba wax for 5 minutes in a sigma mixer. Magnesium stearate was

passed through mesh 30, added to the potassium citrate-carnauba wax mixture, and mixed for 1 minute. The granule was compressed into 18.9 x 8.6 mm elliptical tablet in a Stokes-Pennwalt rotary tablet press model 900. Tablet hardness was 7 kp, and the abrasion of the tablet was 1.8%, which is not acceptable. The dissolution profile is as follows:

Table 4 (dissolution, 12 units)

Time	Range	Average
30 min	47.8-62.0 %	53.7 %
1 hour	66.9-74.9 %	68.5 %
3 hour	89.7-95.6%	92.7 %

The product fails the dissolution requirement of USP 35. This example illustrates that dry mixing carnauba wax at 14% w/w to produce granules for direct compression does not produce tablet that complies with the USP requirements for potassium citrate extended-release tablet. Further, the abrasion is not acceptable.

EXAMPLE 3

A 10-meq tablet was prepared by dry mixing potassium citrate and carnauba wax. The formulation is given in Table 5.

Table 5

Ingredient	mg/tablet	% w/w
Tripotassium citrate monohydrate	1080	79
Carnauba wax	272	20
Magnesium stearate	14	1

Potassium citrate was sieved through mesh 18, and then mixed with carnauba wax for 5 minutes in a sigma mixer. Magnesium stearate was passed through mesh 30, added to the potassium citrate-carnauba wax mixture, and mixed for 1 minute. The granule was compressed into 18.9 x 8.6 mm elliptical tablet in a Stokes-Pennwalt rotary tablet press model 900. Tablet hardness was 7 kp, and the abrasion of the tablet was 2%, which is not acceptable. The dissolution profile is as follows:

Table 6 (dissolution, 12 units)

Time	Range	Average
30 min	49.4-54.5 %	52.5 %
1 hour	64.3-69.1 %	67.1 %
3 hour	90.2-94.5 %	92.4 %

This example illustrates that dry mixing carnauba wax at 20% w/w to produce granules for direct compression, while passing the compendial dissolution requirement, does not produce tablet of acceptable abrasion.

EXAMPLE 4

A 10-meq tablet with the same formulation as Example 2 was prepared by fully melting the carnauba wax. The procedure is as follows:

1. The potassium citrate was comminuted in a Fitzmill D6, knives forward, using perforated screen mesh 8.
2. The comminuted potassium citrate from #1 was mixed with carnauba wax in a sigma mixer for 20 minutes.

3. The granule from #2 was comminuted in a Fitzmill D6, knives forward, using perforated screen mesh 12.
4. The granule from #3 was heated in a jacketed sigma mixer, with continued mixing. Heating was continued until the carnauba wax was fully melted (above 80°C), and for an additional 10 minutes thereafter.
5. The liquid mass from #4 was poured into 2" x 2" x 2" molds, and allowed to cool to room temperature.
6. The blocks from #5 were comminuted in a Fitzmill D6, knives forward, using perforated screen mesh 16.
7. Magnesium stearate was passed through mesh 30 and mixed with the comminuted granule of #6 in a sigma mixer for 2 minutes.
8. The granule from #7 was compressed into 18.9 x 8.6 mm elliptical tablet in a Stokes-Pennwalt rotary tablet press model 900.

Tablet hardness was 12 kp, and the abrasion of the tablet was 0.5%. The dissolution profile is as follows:

Table 7 (dissolution, 12 units)

Time	Range	Average
30 min	46.8-53.3 %	48.2 %
1 hour	61.7-69.1 %	63.1 %
3 hour	91.3-98.3 %	92.7 %

This tablet produced according to prior art method has good abrasion and passes the dissolution requirement of USP 35.

EXAMPLE 5

A 10-meq tablet of this instant invention was prepared. The formulation is the same as Example 2. The procedure is as follows:

1. The potassium citrate was comminuted in a Fitzmill D6, knives forward, using perforated screen mesh 8.
2. The comminuted potassium citrate from #1 was mixed with carnauba wax in a sigma mixer for 20 minutes.
3. The granule from #2 was comminuted in a Fitzmill D6, knives forward, using perforated screen mesh 12.
4. The granule from #3 was heated in a jacketed sigma mixer, with continued mixing. Heating was continued until the temperature reached 70°C, which is below the melting point of carnauba wax.
5. The granule from #4 was discharged into plastic drums and allowed to cool to room temperature.
6. The cooled granule from #5 was comminuted in a Fitzmill D6, knives forward, using perforated screen mesh 16.
7. Magnesium stearate was passed through mesh 30 and mixed with the comminuted granule of #6 in a sigma mixer for 2 minutes.
8. The granule from #7 was compressed into 18.9 x 8.6 mm elliptical tablet in a Stokes-Pennwalt rotary tablet press model 900.

Tablet hardness was 12 kp, and the abrasion of the tablet was 0.6%. The dissolution profile is as follows:

Table 8 (dissolution, 12 units)

Time	Range	Average
30 min	43.5-48.7 %	46.8 %
1 hour	59.6-63.8 %	61.9 %
3 hour	89.9-94.7 %	92.8 %

The tablet produced according to this instant invention has good abrasion and similar dissolution profile with tablets produced using prior art method whereby the carnauba wax is fully melted (Example 4). This is surprising because it was previously believed that extended-release potassium citrate tablet containing carnauba wax can only be produced by fully melting the carnauba wax. The method of this instant invention significantly simplifies the production of extended-release potassium citrate tablet, with reduction in production time and elimination of manufacturing complexities related to melting and cooling the wax.

COMPARATIVE EXAMPLE 6

15-meq tablets of Urocit-K (Mission Pharmacal, lot 2A012) were purchased. The tablet hardness was 12 kp, and abrasion was 1%. The dissolution was performed according to USP 35. The result is as follows:

Table 9 (dissolution, 12 units)

Time	Range	Average
30 min	35.2-40.2 %	38.0 %
1 hour	49.9-61.0 %	53.1 %
3 hour	79.7-82.8 %	81.1 %

The product complies with the USP 35 requirement for extended-release potassium citrate tablet.

EXAMPLE 7

A 15-meq tablet was prepared by fully melting the carnauba wax. The formulation is given in Table 10.

Table 10

Ingredient	mg/tablet	% w/w
Tripotassium citrate monohydrate	1620	84
Carnauba wax	289	15
Magnesium stearate	19	1

The tablets were made as described in Example 4 except that the granule was compressed into 22.5 x 9.3 mm elliptical tablets with a hardness of 13 kp and abrasion of 0.3%. The dissolution is as follows:

Table 11 (dissolution, 12 units)

Time	Range	Average
30 min	35.9-41.2 %	38.5 %
1 hour	48.9-62.0 %	53.5 %
3 hour	79.5-84.6 %	82.2 %

This tablet produced according to prior art method has good abrasion and passes the dissolution requirement of USP 35.

EXAMPLE 8

A 15-meq tablet of this instant invention was prepared. The formulation is the same as Example 7. The procedure is as follows:

1. The potassium citrate was comminuted in a Fitzmill D6, knives forward, using perforated screen mesh 8.
2. The comminuted potassium citrate from #1 was mixed with carnauba wax in a sigma mixer for 20 minutes.
3. The granule from #2 was comminuted in a Fitzmill D6, knives forward, using perforated screen mesh 12.
4. The granule from #3 was heated in a jacketed sigma mixer, with continued mixing. Heating was continued until the temperature reached 60 °C, which is below the melting point of carnauba wax.
5. The granule from #4 was discharged into plastic drums and allowed to cool to room temperature.
6. The cooled granule from #5 was comminuted in a Fitzmill D6, knives forward, using perforated screen mesh 16.
7. Magnesium stearate was passed through mesh 30 and mixed with the comminuted granule of #6 in a sigma mixer for 2 minutes.
8. The granule from #7 was compressed into 22.5 x 9.3 mm elliptical tablet in a Stokes-Pennwalt rotary tablet press model 900.

Tablet hardness was 12 kp, and the abrasion of the tablet was 0.8%. The dissolution profile is as follows:

Table 12 (dissolution, 12 units)

Time	Range	Average
30 min	38.8-41.0 %	40.1 %
1 hour	53.1-56.3 %	55.0 %
3 hour	84.7-90.9 %	87.6 %

The tablet produced according to this instant invention has good abrasion and passes the USP 35 dissolution specs. This is surprising because it was previously believed that extended-release potassium citrate tablet containing carnauba wax can only be produced by fully melting the carnauba wax. The method of this instant invention significantly simplifies the production of extended-release potassium citrate tablet, with reduction in production time and elimination of manufacturing complexities related to melting and cooling the wax.

CLAIMS

1. A method for preparing extended-release potassium citrate tablet containing carnauba wax, wherein the potassium citrate and carnauba wax are mixed and heated to 55°C or higher, but below the temperature at which carnauba wax liquefies, and wherein the carnauba wax is less than 25% w/w of the tablet weight.

2. The method according to Claim 1, wherein the potassium citrate and carnauba wax are mixed and heated to 60°C or higher, but below the temperature at which carnauba wax liquefies.

3. The method according to claim 2, wherein the potassium citrate and carnauba wax are mixed and heated to 65 °C or higher, but below the temperature at which carnauba wax liquefies.

4. The method according to any one of the preceding claims, wherein the heated granule is cooled, comminuted, and mixed with other inactive ingredients prior to tableting.

5. The method according to any one of the preceding claims, wherein the carnauba wax is less than 20% w/w of the tablet weight.

6. The method according to claim 5, wherein the carnauba wax is less than 15% w/w of the tablet weight.

7. The method according to any one of the preceding claims, wherein the abrasion of the tablet is less than 1.5%.

8. The method according to claim 7, wherein the abrasion of the tablet is less than 1%.

9. A method of making extended-release potassium citrate tablet containing carnauba wax, comprising the following steps:

a). Mixing and heating potassium citrate and carnauba wax to 55 °C or higher, but below the temperature at which carnauba wax liquefies;

b). Cooling and comminuting the above granule;

c). Mixing other inactive ingredients into the comminuted granule;

d). Compressing the mixed granule into tablets;

wherein the amount of the carnauba wax is less than 25% w/w of the tablet weight, and the abrasion is less than 1.5%.

10. The method according to claim 9, wherein the potassium citrate and carnauba wax are mixed and heated to 60 °C or higher, but below the temperature at which carnauba wax liquefies.

11. The method according to claim 11, wherein the potassium citrate and carnauba wax are mixed and heated to 65 °C or higher, but below the temperature at which carnauba wax liquefies.

12. The method according to any one of claims 9 to 11, wherein the carnauba wax is less than 20% w/w of the tablet weight.

13. The method according to claim 12, wherein the carnauba wax is less than 15% w/w of the tablet weight.