This invention relates to an improved, free flowing citric acid powder, a method of preparing it and pharmaceutical preparations including it.

Citric acid is used extensively for various compositions, pharmaceutical and otherwise. This, for example, citric acid powder may be admixed with a carbonate or bicarbonate in order to produce an effervescence composition which may or may not have further constituents, such as asparin. Another important type of pharmaceutical preparation containing citric acid is potentiater crystalline. When admixed with citric acid, the tetracycline is potentiated and better blood levels are obtained. Other uses of citric acid with acid sensitive or moisture sensitive products are known. A very important class of product is the citric acid composition in gelatin capsules. For example, citric acid tetracycline compositions are frequently put in gelatin capsules.

A serious problem has resulted from the citric acid because it attacks moist gelatin and also reacts with other medicaments; for example, it reduces the effectiveness of tetracyclines on storage by formation of relatively inactive anhydro compounds. In the case of tetracyclines material exposed to a humid atmosphere, deterioration also takes place. Another problem, although not so serious, is the strongly acid taste of ordinary citric acid powders which sometimes is disagreeable in compositions containing them.

Attempts to solve the above problem were made by granulating citric acid powders with hydrophobic barriers. These attempts were not satisfactory as apparently the coatings were not continuous.

According to the present invention, the problem of coating citric acid particles so as to render them non-corrosive to gelatin is effected by a plurality of thin coatings of waxy hydrophobic material by alternately spraying the waxy material dissolved in a suitable inert volatile solvent onto sifted citric acid powder in a rotating tablet coating pan, evaporating the solvent, for example by blowing warm air over the stirred particles, and repeating the procedure until the desired thickness of coating is obtained. It is not known why the present process succeeds whereas the same weight of waxy material applied in a single coating is not satisfactory. It is possible that if there are occasional minute discontinuities in the coating, they will not line up in a plurality of thin coatings. It is also possible that successive thin coatings may plug up discontinuities in the first coat and produce finally coats which have no discontinuities or holes. It is not intended to limit the invention to any particular theory of why the plurality of thin coatings solved the problem whereas the same amount of wax in a single coating does not.

The number of coats, which is usually measured by the percentage of the waxy material based on the citric acid, is not sharply critical and the range that is useful is not identical for all purposes. Thus, for example, when the problem is to prevent corrosion of gelatin capsules, a number of coats which put less than 5% of waxy material on the citric acid are not sufficient. 5% represents about the irreducible minimum which can be used in a gelatin capsule. With 5%, some pitting does take place but there was no disintegration to an extent which would render capsules unuseable. When the amount of waxy material reaches 6%, gelatin is substantially unattacked. As a safety factor, it is usually preferable to apply a minimum of about 7.5% of wax. Strictly speaking, there is no upper limit of the amount of wax. However, no improvement is obtained beyond 20% and so for practical purposes, this represents a useful upper limit. Larger amounts are not excluded from the invention, but as they have no practical advantage over 20%, they will normally not be used.

When a coated citric acid powder is used in compositions containing tetracyclines, the requirements are somewhat more severe. With 6% of wax, there is no useful protection against formation of anhydrotetracycline. The amount formed is slightly reduced, but is still so high as to present no real advantage. A worthwhile protection is obtained with about 9% of wax which reduces anhydrotetracycline formation to one fourth, with 20% wax, the protection is complete. Therefore, for compositions containing tetracycline, the range is narrower than with gelatin capsules where the corrosive effect on gelatin is the only factor and may be considered as ranging from 9% to unlimited.

The particular waxy material is not too sharply critical but it should, in general, involve a major portion of a glyceride wax, such as glyceryl monostearate or dioleate, with a minor proportion of a plasticizing wax, such as beeswax. For practical purposes, proportions of the order of magnitude of 90% and 10% give optimum results. The particular combination of high melting fat and wax described above is not the only one that can be used. In fact, in general high melting fats can be used with either beeswax or waxy higher alcohols. Carnauba wax is not satisfactory alone, but in blends it permits an accurate degree of hardening.

The solvent to be used presents primarily a physical problem. Of course, it must be inert to citric acid. Also, it must not be highly toxic or at least any minute residue left should not be highly toxic since the citric acid is normally ingested. Volatility is important. Theoretically, even only moderately volatile solvents for the wax composition could be used. However, it is not practical to dry or evaporate the solvent at an excessive temperature. If the temperature is too high, the wax will soften to the extent that coated particles of the citric acid will stick together and they will no longer be free flowing. For practical purposes, it is desirable to effect the drying at temperatures not substantially in excess of 50° C. It should be noted that the temperature of the warm air used in drying may be somewhat higher than the actual temperature on the surface of the particles, as the evaporation of the solvent exerts a cooling effect. It is true that if there is sufficient time, even a fairly high boiling solvent could be evaporated at the moderate temperature. However, the time would be excessive and therefore it is desirable to use an inert solvent which has a boiling point not greatly in excess of 100° C. and preferably below 120° C. A simple, cheap and very satisfactory solvent is 1,1,1-trichloroethane, which is inert, boils at about 74° C., is cheap and does not leave a toxic residue. Other suitable inert solvents are the following: chloroform, carbon tetrachloride, other volatile halogenated hydrocarbons, petroleum ether, etc.

The amount of solvent is, of course, not critical. Naturally, the solution must be thin enough so that it can be satisfactorily sprayed to form a thin coating, but this is a purely physical problem and represents no critical factor.

The invention will be described in connection with the following specific examples in which the effect of a coated citric acid on gelatin and other medicaments is illus-
trated as well as the process of coating. The examples are typical only and do not limit the invention to the use of a coated citric acid in the particular formulation set forth. The parts are by weight unless otherwise specified.

**Example 1**

Citic acid powder sifted through No. 30 mesh screen is placed in a conventional rotating tablet coating pan and sprayed with a 30% solution of a wax mixture comprising 9 parts glyceryl monostearate and 1 part beeswax in 1,1,1-trichloroethane. After a thin coating, the spray is interrupted and warm air is blown over the swirling coated citric acid particles. As soon as the solvent has been substantially evaporated, another spraying cycle follows and this is repeated until 7.5% of wax coating was achieved. Gelatin capsules are filled with the above coated citric acid after the latter had been passed through a No. 30 mesh screen. A control run of soft gelatin capsules of the same gelatin composition were likewise filled with uncoated citric acid. The capsules were sealed in air-tight bottles and stored for 24 hours. At the end of the 24 hours, the control capsules showed gelatin which was pitted, mottled and partially liquefied. The capsules with the coated citric acid were generally unaffected. The procedure was repeated but both batches of capsules were carefully dried after filling. After 24 hours, the controls had leaked some solution, were pitted, mottled and chewed up and, of course, the coated citric acid capsules were unaffected.

**Example 2**

The citric acid, coated as described in Example 1, was mixed with an equal proportion of tetracycline hydrochloride. Controls were prepared using uncoated citric acid. On storing, the gelatin capsules containing uncoated citric acid were mottled and pitted and were unsuitable for sale. The gelatin capsules with the coated citric acid were unaffected and were saleable.

**Example 3**

The procedure of Example 1 was repeated with different amounts of wax coating, namely, 6%, 10% and 20% by weight. Citric acid with each thickness of coating was mixed with an equal amount of tetracycline hydrochloride and incorporated into soft gelatin capsules. The capsules were then set in a 5–10% relative humidity atmosphere to dry for about 24 hours, washed with isopropanol in a conventional manner and air dried. They were then bottled and stored for about 7 months. On opening, there were no mottled capsules. Some of the capsules containing 6% wax showed a little evidence of pitting inside the capsule when cut open. All, however, were saleable.

**Example 4**

The procedure of Example 3 was followed in order to test the effect of the citric acid on tetracycline and a control was also made up. The formulations were then stored for 3 days and assayed for anhydrotetracycline formation. The results appear in the following table:

<table>
<thead>
<tr>
<th>Anhydro formed per 250 mg. tetracycline HCl</th>
<th>mg. anhydro-</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg. tetracycline HCl</td>
<td>1.3</td>
</tr>
<tr>
<td>As in 1, with 250 mg. citric acid (anhydrous)</td>
<td>13.6</td>
</tr>
<tr>
<td>As in 1, with 250 mg. citric acid coated with 6.2% wax</td>
<td>11.0</td>
</tr>
<tr>
<td>As in 1, with 250 mg. citric acid coated with 9.2% wax</td>
<td>7.0</td>
</tr>
<tr>
<td>As in 1, with 250 mg. citric acid coated with 20% wax</td>
<td>1.3</td>
</tr>
</tbody>
</table>

It will be noted that even tetracycline HCl alone shows a small amount, 1.3 milligrams of anhydrotetracycline. The figures for the various mixtures with citric acid must therefore be compared with this figure. In other words, 1.3 milligrams of anhydrotetracycline must be subtracted from each figure in order to get the net increase. It will be noted that while there was some reduction in anhydro tetracycline formation with approximately 6% wax coating, namely about 21%, there was still an extensive formation of anhydrotetracycline and therefore this degree of coating is not quite sufficient. Coating with a little more than 9% wax showed a reduction of about 41% and is of practical significance. The 20% coating showed no anhydro tetracycline formation at all over and above that which is present in the base to start with.

I claim:

1. Free flowing powdered citric acid having a particle size at least as fine as 30 mesh having a plurality of thin coats of a predominantly glyceride wax, the coats being sufficient in number so that the total wax coating is in excess of 5%.

2. A gelatin capsule filled with a free flowing powder composition comprising the free flowing citric acid of claim 1.

3. A product according to claim 1 in which the wax is predominantly glyceride monostearate.

4. A gelatin capsule filled with powdered material comprising the coated citric acid of claim 3.

5. Free flowing powdered citric acid having a particle size at least as fine as 30 mesh having a plurality of thin coats of a predominantly glyceride wax, the coats being sufficient in number so that the total wax coating is in excess of 9%.

6. A gelatin capsule filled with a mixture of free flowing tetracycline HCl and coated citric acid powder of claim 5.

7. A product according to claim 5 in which the wax is predominantly glyceride monostearate.

8. A gelatin capsule filled with a mixture of tetracycline HCl powder and coated citric acid powder according to claim 7.

9. A process of coating citric acid powder having a particle size at least as fine as 30 mesh which comprises agitating the powder, spraying it while agitated with a solution of a wax in a volatile inert solvent, evaporating the solvent and repeating until sufficient coatings are formed so that the wax coating is at least 5% by weight of the citric acid particle.

10. A process according to claim 9 in which the wax is predominantly glyceride monostearate.

11. A process according to claim 10 in which the solvent is 1,1,1-trichloroethane.

12. A process of coating citric acid powder having a particle size at least as fine as 30 mesh which comprises agitating the powder, spraying it while agitated with a solution of a wax in a volatile inert solvent, evaporating the solvent and repeating until sufficient coatings are formed so that the wax coating is at least 5% by weight of the citric acid particle.

13. A process according to claim 12 in which the wax is predominantly glyceride monostearate.

14. A process according to claim 13 in which the solvent is 1,1,1-trichloroethane.

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