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FREE-FLOWING INTRINSIC FACTOR CONCENTRATE

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This invention relates to novel therapeutic compositions of matter and, more particularly, to intrinsic factor concentrate prepared as dry powders by intermixing it with certain siliceous materials whereby a substantially dry, free-flowing intrinsic factor concentrate is obtained.

Intrinsic factor is a heat labile component of normal human gastric juice. Evidence presently indicates that intrinsic factor is involved in the utilization of vitamin B₁₂. In the classical condition in which a deficiency of intrinsic factor is found, namely pernicious anemia, small oral doses of vitamin B₁₂ are ineffective unless a source of intrinsic factor is administered simultaneously. The study of gastric intestinal absorption with radioactive vitamin B₁₂ in pernicious anemia patients and healthy individuals has proven that intrinsic factor is essential for this absorption. Although hematopoietic responses in pernicious anemia may follow the oral administration of massive doses of vitamin B₁₂ given without the intrinsic factor, the absorption of the vitamin, when amounts comparable to those found in an average diet are ingested, involves a participation of intrinsic factor.

Intrinsic factor concentrate is usually prepared from animal stomach and/or intestines, particularly hog duodenum or pyloric mucosa. The intrinsic factor concentrate produced by the known methods is a lumpy amorphous product usually dried by lyophilizing or spray-drying, which cannot be milled and has a very strong inherent odor. The aggregate nature of this concentrate is due to a residual moisture content which cannot be removed without destroying its therapeutic activity. It is also difficult to prepare homogeneous blends of the concentrate because of its heterogeneous lumpy consistency, its lack of mobility, and its adherence to container walls.

Usually, patients who need intrinsic factor concentrate in large doses are seriously ill with pernicious anemia. Such patients are made even more ill upon oral administration of intrinsic factor concentrate by reason of its repulsive consistency and nauseating odor. Furthermore, these undesirable properties make it difficult to incorporate intrinsic factor concentrate into elegant pharmaceutical formulations. Also, because of its lumpy amorphous nature, intrinsic factor concentrate cannot be milled nor reduced in particle size to less than 80 mesh.

My invention is based upon the discovery that the lumpy foul-smelling intrinsic factor concentrate produced by the known methods is transformed into a dry powder of more agreeable odor by intermixing, in proper proportions, the intrinsic factor concentrate with certain siliceous materials. The resulting product is free-flowing and does not tend to adhere to the walls of the container in which it is prepared, and is readily millable to any desired particle size.

In practicing this invention, one part of the siliceous material is mixed with from about 16 parts to about 32 parts of intrinsic factor concentrate and dry-blended by barrel-rolling, followed by milling through a comminuting apparatus equipped with a number 80 mesh screen. The final product is a cream-colored, free-flowing intrinsic factor concentrate of more agreeable odor.

Siliceous materials which may be used in accordance

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with the present invention are finely divided pulverulent materials containing in excess of about 85 to 98 percent siliceous material by weight on the water-free basis and having an average ultimate particle size below 0.1 micron, preferably in the range of 0.01 to 0.05 micron. Typical materials of this character are finely divided silica, calcium silicate, magnesium silicate, sodium aluminum silicate, sodium calcium aluminum silicate, aluminum silicate, and the like.

Siliceous materials particularly suitable for the present invention may be prepared in several ways. Pyrogenic silica, for example, is prepared by the vapor phase flame pyrolysis of silicon tetrachloride and has an average ultimate particle size of from about 0.01 micron to about 0.03 micron.

Finely divided silica having a surface area in the range of 25 to 250 square meters per gram and an average ultimate particle size below 0.1 micron may also be prepared by a precipitation method which involves reacting an aqueous solution of an alkali metal silicate such as sodium silicate with an acid. By carefully controlling the concentration of the reactants, the temperature conditions, rate of addition of acid, etc., it is possible to precipitate a product having finely-divided, discrete particles as compared to the gel resulting from processes commonly known in the art.

This precipitation method consists, more particularly, in adding an acid to an alkali metal silicate having a predetermined concentration. The acid is added to the silicate solution since the rate of neutralization of the alkali metal silicate is important. For instance, were the silicate solution to be added to an excess of acid, the former would be neutralized too rapidly and the conventional gel would be produced.

The surface areas mentioned herein are measured by the Brunauer-Emmett-Teller (B.E.T.) method which is described in the Journal of the American Chemical Society, volume 60, page 309 (1938).

When the alkali metal silicate used in preparing a finely divided silica is sodium silicate, it should normally have the composition Na₂O(SiO₂)_x where x is at least 2, usually 2 to 4, including fractional numbers, preferably in the range of 3 to 4. The silicate solution generally contains 10 to 100 grams of SiO₂ per liter.

Precipitated silica having the properties set forth above may be prepared by still another method. Thus, by reacting a finely divided alkaline earth metal silicate, such as calcium silicate, having an average ultimate particle size below 0.1 micron, with an acid having an anion which forms a water soluble salt with the alkaline earth metal, a siliceous material particularly useful for the present invention is prepared.

Calcium silicates having a surface area in the range of 25 to 250 square meters per gram and an average ultimate particle size below 0.1 micron are best prepared by reacting calcium chloride with an alkali metal silicate in aqueous medium containing sodium chloride or like alkali metal chloride. The sodium chloride conveniently may be in the calcium chloride solution although it may also be in the sodium silicate solution. It has been found that the presence of sodium chloride materially improves the character of the siliceous material.

The amount of calcium chloride is generally in stoichiometric excess of the sodium silicate. Although a slight excess of sodium silicate is tolerable, it is best to have at least a stoichiometric amount of calcium chloride present during the reaction.

To insure production of the calcium silicate in a finely divided state, sodium silicate having the composition Na₂O(SiO₂)_x where x is a number not less than 2 nor more than 4, is preferably used. This results in the

production of a calcium silicate having a composition $\text{CaO}(\text{SiO}_2)_x$, where x is as defined above. When calcium silicate prepared in the fashion just described is treated with a mineral acid, in the manner disclosed above, a dry, powdered silica in extremely fine state of division is produced.

On a weight/weight basis the proportion of intrinsic factor concentrate to siliceous material may be as high as about 98% intrinsic factor concentrate to about 2% siliceous material and as low as about 93% intrinsic factor concentrate to about 7% siliceous material. Above about 7% by weight of siliceous material the final product tends to dust into the atmosphere, whereas below about 2% by weight of siliceous material the final product is still lumpy and amorphous. However, for optimum results, we prefer to employ from about 3% to about 6% by weight of the siliceous material based on the weight of the intrinsic factor concentrate.

The following examples will serve to illustrate my invention:

Example 1

Five parts of silicon dioxide having an average ultimate particle size of from 0.01 to 0.10 micron was mixed with 95 parts of intrinsic factor concentrate and dry-blended by barrel-rolling, followed by milling through a comminuting apparatus equipped with a number 80 mesh screen. The final product was a cream-colored, free-flowing powder which was readily incorporated in dry vitamin preparations.

Example 2

Five parts of calcium silicate having an average ultimate particle size of from 0.01 to 0.10 micron was mixed with 95 parts of intrinsic factor concentrate and dry-blended by barrel-rolling, followed by milling through a

comminuting apparatus equipped with a number 80 mesh screen. The final product was a cream-colored, free-flowing powder which was readily acceptable for market distribution.

What is claimed is:

1. A stable, substantially dry, free-flowing powder comprising intrinsic factor concentrate and a siliceous material, said powder containing not substantially less than 93% intrinsic factor concentrate by weight, and said siliceous material having a surface area of from about 25 to about 250 square meters/gram and being present in an amount not substantially more than about 7% by weight.

2. A stable, substantially dry, free-flowing powder as in claim 1 wherein the average ultimate particle size of said siliceous material is between about 0.01 micron and about 0.10 micron.

3. A process for the production of a stable, substantially dry, free-flowing powder containing a major amount of intrinsic factor concentrate, which comprises adding an amount, not substantially less than 93 parts by weight, of intrinsic factor concentrate to not substantially more than 7 parts by weight of a siliceous material having an average ultimate particle size of from about 0.01 micron to about 0.10 micron and a surface area of from about 25 to 250 square meters/gram and thoroughly blending the mixture so obtained.

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