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NONAGGLOMERATING BLENDING PROCESS

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ABSTRACT OF THE DISCLOSURE

This application relates to a process for uniformly blending a plurality of particulate materials wherein the finely divided materials are mixed with an inert carrier to form a slurry, blended for a period of time sufficient to achieve a homogenous mixture of materials throughout the slurry, and removing the carrier without adversely affecting the chemical activity of the mixture or disturbing the uniformity of blend.

BACKGROUND OF THE INVENTION

This application relates to a process for mixing particulate materials and, more particularly, relates to a process for the uniform slurry blending of two or more particulate materials to provide a final homogenous composition. The process is particularly suitable for producing a homogenous mixture of chemicals, portions of which may be utilized as reagents in analytical processes.

In microchemical analysis, a technique which is finding greater usage each day, not only are small quantities of samples required, but also smaller quantities of reagents as well. When more than one reagent is necessary, it is often desirable to mix the reagents together to form a powdered or tableted reagent composition which can be added at the desired point in time in the analytical process. In certain instances, it may be necessary to mix the particular ingredients in the formulation in quantities which radically differ from an equal mixture; in the most extreme cases, less than 1% of a first ingredient. Notwithstanding the diverse quantities of the respective materials being blended, it is absolutely essential to achieve a uniform blend so that even minute portions of the mixture correspond to the formulation desired. This is particularly essential when batches of analytical reagents are being prepared because lack of uniformity in the preparation will necessitate that the batch preparation be discarded or, if the discrepancy is not immediately found, the analytical data obtained therewith will be inaccurate and, therefore, of no value.

To obtain such uniform blends, it has been attempted in the past to reduce the respective ingredients to a suitable particle size such that uniform blending can be achieved. Unfortunately, when solid materials are ground to the particle size necessary for such blending, they normally take on sufficient electrostatic charge such that blending is extremely difficult, agglomeration problems are evident, or the material cannot be blended to the uniformity of blend desired.

OBJECTS OF THE INVENTION

It is therefore, an object of this invention to provide a process for uniformly blending a plurality of finely divided patriculate materials.

It is an object of the present invention to provide a process for the uniform blending of finely divided particulate materials which is not subject to the aforementioned deficiency relating to electrostatic charge.

It is an object of the present invention to provide a process for blending a plurality of finely divided particulate materials wherein an inert organic liquid is utilized to form a slurry of the materials to be blended.

It is a further object of the present invention to provide a process for uniformly blending dry materials, such as proteinaceous materials, without denaturing said materials or otherwise adversely affecting the chemical activity thereof.

Yet a still further object of the present invention is to provide a process for mixing at least two finely divided particulate materials wherein an inert organic liquid is utilized to form a slurry of the materials to be blended, said liquid leaving little or no residue upon subsequent removal thereof after uniformity of blend has been achieved.

The above and still further objects, features and advantages of the present invention will become apparent upon consideration of the following detailed disclosure of specific exemplary embodiments thereof.

BRIEF SUMMARY OF THE INVENTION

The above and still further objects of the present invention are achieved, in accordance with the present invention, by reducing the respective materials to be blended to a desired finely divided particulate size; forming a slurry of the finely divided materials in an inert organic carrier, said carrier being easily removed after uniformity of blend has been achieved with little or no residue remaining after removal; blending the slurried mixture until a homogenous dispersion of all particles throughout the slurried material is attained; and, thereafter, removing the carrier without affecting the chemical activity of the materials or disturbing the uniformity or blend. This process has been found satisfactory for uniformly blending rather minute quantities of a first particulate material with a much larger quantity of at least one other particulate material. Thus the process has been satisfactory for blending less than 1% of a first material with more than 99% of a second material(s) without denaturing or otherwise adversely affecting the chemical activity of the final formulation.

This process is particularly suitable for the blending and formulation of analytical reagents necessary for microchemical analysis, though it is not necessarily limited thereto. When considering analytical reagents, the materials being formulated generally can be categorized into the following three broad categories: organic materials, inorganic materials, and biological materials, such as enzymes, albumins, etc. Obviously, this categorization covers a broad range of materials, few of which have similar properties or problems related thereto from a mixing or blending point of view. That is, the categories are so broad that individual members thereof, or groups of members, will have their own related blending problems. Blending a diverse mixture of chemicals further complicates an already complex situation, since it may be difficult to find a common blending technique suitable for all the ingredients. For example, some of the materials may be heat sensitive whereas other materials may be carrier or solvent sensitive, such that particular carrier or solvents for blending are automatically excluded, other carriers may be excluded because heat may be necessary to effect removal thereof, etc. The provision, therefore, of a process generally applicable to the blending of substantially all particulate materials would be highly desirable. The process of the present invention has been found suitable for a wide range of materials falling within each category.

Prior to slurry formation, the particles are reduced in size to a finely divided state, normally finer than 200 mesh. Where smaller quantities of a particular ingredient are to be uniformly blended throughout a much larger mass, the particles can be reduced even further, normally to a size on the order of 300–400 mesh. Since the materials are normally ground in a very dry environment

to prevent either short or long term degradation problems from ambient moisture, the finely divided particles are subject to severe electrostatic charge problems. That is, in the dry environment, the dry particles readily pick up electrostatic charge such that subsequent blending, in a dry mode, is for all intents and purposes impractical.

After the respective materials have been reduced to the finely divided state, a thick slurry of the materials is formed. If too little liquid is added, the electrostatic charge problems are not totally overcome wherefore uniform blending is not satisfactorily achieved. On the other hand, if excess liquid is added, a stratification effect will be achieved and the particles will separate rather than being blended uniformly. Thus, by slurry formation it is meant the mixing of the finely divided particles with the liquid material in proper quantities such that electrostatic charge problems are eliminated, very little or no excess liquid is utilized, and separation or stratification of the respective particles does not take place.

Generally X grams of solid material are blended with about 0.75X to about 2X milliliters of the liquid carrier. For many mixtures to be blended, an approximate blend of X grams of solids with X milliliters of carrier has been found to be quite suitable. It should be understood, however, that the amount of liquid necessary for slurry formation varies from batch to batch and that, as additional liquid is added, care should be taken to avoid solid particle separation or stratification.

The liquid carrier which is added to the finely divided particulate materials to form the slurry desirably has a particular set of unique characteristics. Initially, it is inert so that it will not affect the chemical activity of the final formulation. It should have a high boiling point, i.e. above about room temperature such that it will not be undesirably removed during subsequent blending operations. Optionally, a material with a lower boiling point can be utilized if the blending apparatus is suitably refrigerated during blending. The carrier should, on the other hand, have a sufficiently high vapor pressure at a temperature which does not adversely affect the blended mixture, preferably at a low temperature, so that it can be easily removed, such as by vacuum evaporation. Preferably, the material is free of water, and upon removal, leaves little or no residue which might adversely affect the chemical properties of the formulation. One particular material which has been used with great success in the practice of the present invention is the halogenated hydrocarbon 1,1,2 - trichloro - 1,2,2-trifluoroethane, also known as Freon TF (a trademark of E. I. du Pont de Nemours & Co., Inc.). Other typical liquid halogenated hydrocarbons include 1,1,2,2 - tetrachloro-1,2-difluoroethane; 1,1,2,2 - tetrafluoro - 1,2 - dibromoethane; trichloromonofluromethane; and azeotropes or blends of the aforementioned halogenated hydrocarbon liquids provided the liquid mixture does not affect the chemical activity of the blended formulation and blending conditions are controlled to prevent denaturation, etc.

The slurry, after formation, is blended on appropriate equipment, such as a ball mill, a high speed blender, such as a Waring Blendor, etc., for a sufficient period of time to obtain a homogenous mixture. The actual blending time which will be employed varies from composition to composition, batch size, etc., though, on the average, the blending time is on the order of about one to about six hours. With high speed (e.g., greater than 10,000–12,000 r.p.m.) blending of very small batches, blending times can be reduced to as little as three minutes or so. Because in many instances heat sensitive materials are being blended, it is desirable in such circumstances to maintain the temperature of the composition as close to room temperature as possible. This will avoid deleterious denaturing of heat sensitive materials such that the activity of the final formulation can be more appropriately regulated.

When a ball mill is utilized as the blending equipment, it is highly desirable to reduce the components of the mixture prior to the slurry formation. Prior reduction drastically reduces the amount of blending time within the ball mill. This prevents particles of the porcelain balls from contaminating the final formulation which further eliminates an adverse effect upon the optical-affecting properties of formulated reagents when they are used in an analytical mode.

After the finely divided mixture has been slurry blended for a sufficient period of time to achieve substantial and uniform homogeneity, the liquid carrier is removed, normally by vacuum evaporation. If non-heat sensitive, materials are being blended, the liquid can be boiled off, though for most materials to be utilized in a reagent mode vacuum evaporation assures against loss of chemical activity. Vacuum evaporation is most easily achieved by taking the jar containing the now uniformly blended material and placing it with the top removed, in a vacuum cabinet. After removal of the carrier, the uniformly mixed material is separated from the grinding media used in the blending process. The uniform mixture can be utilized as the powdered material thus obtained or tableted, as desired.

DESCRIPTION OF SPECIFIC EMBODIMENTS

The following examples are given to enable those skilled in the art to more clearly understand and practice the invention. They should not be considered as a limitation upon the scope of the invention but merely as being illustrative thereof.

Example I

This example describes the blending and preparation of a reagent formulation suitable for use, along with the formulation of Example II, in the determination of glucose in body fluids.

The formulation contains the following ingredients in substantially the proportions as given:

	Milligrams
Glucose oxidase	0.790
Peroxidase	0.159
Sodium phosphate, dibasic	5.520
Sodium phosphate, monobasic	2.736
Potassium chloride	9.795
Polyethylene glycol-4000	1.000
	20.000

Sufficient chemicals for a 20,000 tablet batch are weighed out in a dry room and placed in a dark brown, ball milling bottle, or other suitable porcelain ball milling jar. The bottle should be large enough to be filled to about 60% of its total capacity with the dry powder added thereto. Sufficient grinding media, in the form of Coors HD balls, are added in an amount equal to about 40% of the remaining volume of the bottle. The size and quantity of the grinding media can be varied as desired. Sufficient Freon TF carrier is added to make a thick slurry; in this particular example, about 400 milliliters of liquid is added. A sufficiently thick unplasticized polyethylene sheet is placed between the bottle and the cap placed thereon to prevent contamination of metallic particles from the metallic cap. The slurry is blended on a ball mill for about 4 hours at approximately 90 r.p.m. The cap is removed and replaced with a lint-free porous cover secured by a rubber band and the bottle is placed at a 30-degree angle in a vacuum chamber equipped with a Dry Ice-acetone trap. Vacuum is slowly applied, at room temperature, to prevent flash boiling of the Freon TF carrier. The vacuum evaporation is continued for a sufficient period of time, normally about two hours, to remove excess carrier. The blended powder is then passed through a 10 mesh screen to remove the grinding media. Optionally,

the powder can be further vacuum dried until a powder blend having less than 1% moisture content is obtained. The powder is stored under dark, dry nitrogen conditions and, if desired, can be formed into reagent tablets having the desired uniform blend of components.

Analysis of the powder prior to tablet formation and of the tablets themselves indicate that the mixture is uniformly blended as desired, the materials are of sufficient activity, and no residue from the carrier adversely affects any of the mixture's chemical properties such that it would not be suitable for its intended use.

Example II

The procedure of Example I is repeated to uniformly blend the following chromogen formulation suitable for use, along with the formulation of Example I, in the determination of glucose in body fluids:

	Milligrams
o-Dianisidine-dihydrochloride	0.033
Mannitol	14.007
Polyethylene glycol-4000	0.960
	15.000

With this formulation, about 330 milliliters of Freon TF is sufficient to make the desired thick slurry.

Example III

The procedure of Example I is repeated to uniformly blend the following chromogen formulation suitable for use, along with the formulation of Example IV, in a total protein analysis by the biuret method:

	Milligrams
Cupric tartrate	0.663
Sodium tartrate	1.779
Potassium chloride	10.558
Polyethylene glycol-4000	1.000
	14.000

Example IV

The procedure of Example I is repeated to uniformly blend the following alkalyzing formulation which is suitable for use, along with the formulation of Example III, in a total protein analysis by the biuret method:

	Milligrams
Lithium hydroxide	9.000
Potassium chloride	4.000
Polyethylene glycol-4000	1.000
	14.000

Example V

The procedure of Example I is repeated to uniformly blend the following formulation which is suitable for use, along with the formulations given in Examples VI and VIII, in the determination of uric acid in body fluids:

	Milligrams
Copper sulfate	0.055
Potassium chloride	9.945
	10.000

Example VI

The procedure of Example I is repeated to uniformly blend the following alkalyzing formulation suitable for use, along the formulations given in Examples V and VII, in the determination of uric acid in body fluids:

	Milligrams
Lithium hydroxide	0.0737
Potassium chloride	9.9263
	10.0000

Example VII

The procedure of Example I is repeated to uniformly blend the following chromogen formulation suitable for use, along with the formulations given in Examples V and VI, in the determination of uric acid in body fluids:

	Milligrams
2-amino-2-methyl-1-propanol hydrochloride	4.228
Neocuproine hydrochloride	0.143
Potassium chloride	5.029
Polyethylene glycol-4000	0.600
	10.000

Example VIII

The procedure of Example I is repeated to uniformly blend the following enzyme formulation suitable for use, along with the formulations of Examples IX and X, in the determination of blood urea nitrogen:

	Milligrams
Urease	0.01
Ethylene-diamine tetraacetic acid, disodium salt	0.10
Mannitol	20.00
	20.11

In this particular example, sufficient chemicals for a 1000 tablet batch are mixed with 32 milliliters of Freon TF to form the slurry which is then blended on the ball mill for 1½ hours.

Example IX

The procedure of Example I is repeated to uniformly blend the following formulation suitable for use, along with the formulations of Examples VIII and X, in the determination of blood urea nitrogen:

	Milligrams
Calcium hypochlorite	0.028
Lithium hydroxide	0.375
Sodium sulfate	0.875
Mannitol	19.000
	20.278

In this particular example, sufficient chemicals for a 1000 tablet batch are mixed with 40 milliliters of Freon TF to form the slurry which is then blended on the ball mill for 1½ hours.

Example X

The procedure of Example I is repeated to uniformly blend the following formulation suitable for use, along with the formulations of Examples VIII and IX, in the determination of blood urea nitrogen:

	Milligrams
Sodium salicylate	4.2000
Sodium nitroferricyanide	0.0125
Mannitol	15.8000
	20.0125

In this particular example, sufficient chemicals for a 1000 tablet batch are mixed with 35 milliliters of Freon TF to form the slurry which is then blended on the ball mill for one and one-half hours.

Example XI

The procedure of Example I is repeated to uniformly blend the following formulation suitable for use in a total protein determination by the biuret method:

	Milligrams
Trisodium phosphate	38.0
Sodium tartrate	2.5
Copper sulfate	0.5
	41.0

In this particular example, sufficient chemicals for a 50,000 tablet batch are mixed with two liters of Freon TF to form the slurry which is then blended for twenty minutes under liquid nitrogen cooling. The blended powder is vacuum dried for four hours at room temperature and for one hour at 100° C.

The preceding examples show the wide range of materials which can be uniformly blended with the process of the present invention. Biological materials, such as the enzymes glucose oxidase, peroxidase and urease have been satisfactorily blended as can be seen in Examples I and VIII. Organic materials have been satisfactorily blended as can be seen in Examples II, VII, X, etc. Satisfactory blends of inorganic materials are disclosed throughout the examples. Mixtures of materials from different classes are also blended. Nonetheless, it should be clearly understood that the materials described herein are merely representative examples and that the materials which can be blended in accordance with the teachings of the present invention are virtually unlimited.

More importantly, however, these examples illustrate the uniform blending of minute quantities of a first substance with relatively major quantities of a second substance. For example, in Example II, minute quantities of ortho-dianisidine-dihydrochloride have been uniformly blended with major quantities of mannitol in the approximate ratio of one part of ortho-dianisidine to about 420 parts mannitol. In Example V, minute quantities of copper sulfate have been uniformly blended with a major quantity of potassium chloride in the approximate ratio of about one part copper sulfate per 180 parts potassium chloride. Since the material described in the preceding examples are stated to be useful in analytical chemistry and, more particularly, in blood chemistry analysis, it is essential that the preceding formulations be properly and uniformly blended so that accurate and reliable analytical results can be obtained. If, for example, insufficient chromogen is dispersed through out a particular chromogen formulation, then the desired colorimetric endpoint may not be properly achieved during analysis. This is obviously unacceptable. The same undesirable result, of improper blending, can be alternatively reflected in increased cost to the manufacturer, who must discard improperly formulated reagents, a cost which is eventually passed on to the final consumer. Obviously, then, any process which is capable of uniformly and repeatedly blending a plurality of particulate materials to the desired uniformity of blend is of great use and benefits, directly or indirectly, all concerned. The process of the present invention has been found to achieve such results, as indicated above, even though the ratio of ingredients in different formulations varies widely.

While the invention has been described with reference to specific embodiments thereof, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the true spirit and scope of the invention. For example, other techniques can be utilized to remove the carrier after uniformity of blend has been achieved, provided the removal technique does not adversely affect the chemical activity of the final formulation. In addition, many modifications may be made to adapt a particular situation, material or formulation, to the teaching of the present invention without departing from its essential teachings.

What is claimed is:

1. A process for blending a plurality of particulate materials which comprises reducing a minute quantity of a first particulate material to a finely-divided state, reducing a major quantity of a second particulate material to a finely divided state, admixing said finely divided first and second particulate materials with only a sufficient amount of an inert organic carrier to form a thick slurry, blending said slurried mixture for a period of time sufficient to uniformly disperse said first particulate material throughout said major quantity of said second particulate material and, thereafter, returning said particles to a dry unagglomerated condition by removing said carrier material without adversely affecting the chemical activity of said blended materials or disturbing the uniformity of blend.

2. A process for blending a plurality of particulate materials comprising forming a slurry by mixing finely-divided, dry particles of a plurality of different materials with an inert non-aqueous carrier, blending said slurried mixture for a period of time sufficient to achieve a homogeneous distribution of said finely-divided particles throughout said slurry, and returning said particles to a dry, unagglomerated condition by removing said inert, non-aqueous carrier without affecting the chemical activity of said mixture or disturbing the uniformity of blend.

3. The process of claim 2 wherein said inert carrier is an organic material having a boiling point at least as high as room temperature and having a sufficient vapor pressure at low temperatures to permit removal by vacuum evaporation.

4. The process of claim 2 wherein said inert carrier is an organic material.

5. The process of claim 2 wherein said inert carrier is a liquid halogenated hydrocarbon.

6. The process of claim 2 wherein said inert carrier is trichlorotrifluoroethane.

7. The process of claim 2 wherein about 0.75X to about 2X milliliters of inert carrier is added to about X grams of solids to form said slurry.

8. The process of claim 2 wherein about X milliliters of inert carrier is added to about X grams of solids to form said slurry.

9. The process of claim 2 wherein a minor proportion of a first particulate material is uniformly blended with a major proportion of at least one additional particulate material.

10. The process of claim 2 wherein less than 1% of a first particulate material is uniformly blended with more than 9% of at least one additional particulate material.

11. The process of claim 2 wherein said inert carrier material is removed by low temperature, vacuum evaporation.

12. The process of claim 2 wherein said inert carrier material is removed by vacuum evaporation at room temperature.

13. The process of claim 2 wherein said blending is achieved in the absence of agglomeration of said finely-divided particles.

14. The process of claim 2 further including the step of reducing each of said plurality of particulate materials to the finely-divided state prior to the mixing thereof with said inert, non-aqueous carrier.

15. The process of claim 14 wherein said plurality of particulate materials are initially reduced to a particulate size finer than 200 mesh.

16. The process of claim 14 wherein at least one particulate material is initially reduced to a particulate size on the order of about 300 to 400 mesh.

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